FERNANDO CAMPOS GOMES PINTO

**TRATAMENTO CIRÚRGICO DA HIDROCEFALIA DE PRESSÃO
NORMAL**

Texto sistematizado elaborado de forma crítica apresentado à Faculdade de Medicina da Universidade de São Paulo, para obtenção do Título de Professor Livre-docente junto ao Departamento de Neurologia (Disciplina de Neurocirurgia)

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Descritores: 1.Hidrocefalia 2.Hidrocefalia de pressão normal 3.Transtornos
neurológicos da marcha 4.Demência 5.Incontinência urinária 6.Derivação do
líquido cefalorraquidiano 7.Ventriculostomia 8.Neuroendoscopia 9.Neurocirurgia

Dedicatória

À minha família, que me apoia, me nutre e me inspira.

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Operar é divertido, é uma arte, é
ciência e faz bem aos outros.

Prof. Dr. Euryclides de Jesus
Zerbini (1912 - 1993)

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Lista de Abreviaturas, Siglas e Símbolos

%	Porcentagem
°	Graus
μL	Microlitro
<	Menor
≥	Maior igual
>	Maior
±	Mais ou menos
®	Marca registrada
AVE	Acidente vascular encefálico
BAAR	Bacilos álcool-acido resistentes
cm	Centímetro
DA	Doença de Alzheimer
DGI	<i>Dinamic gait index</i>
DLP	Derivação lomboperitonal
DVP	Derivação ventrículoperitoneal
EUA	Estados Unidos da América
FSCr	Fluxo sanguíneo cerebral regional
FSH	Hormônio folículo-estimulante
GHC	Grupo de Hidrodinâmica Cerebral
H ₂ O	Água
HAS	Hipertensão arterial sistêmica
HC/FMUSP	Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo
HPN	Hidrocefalia de pressão normal
HPNi	Hidrocefalia de pressão normal idiopática
HSA	Hemorragia subaracnóidea
LCR	Líquido cefalorraquidiano
LH	Hormônio luteinizante
MIF	Medida de independência funcional
min	Minutos
mL	Mililitro
mm	Milímetro
MM	Minimental
mmHg	Milímetros de mercúrio
p. ex.	Por exemplo
PH	Pressão hidrostática
PIA	Pressão intra-abdominal
PIC	Pressão intracraniana
PP	Pressão de perfusão
RM	Ressonância magnética

SPECT	Tomografia computadorizada com emissão de fóton único
SR	Seio reto
SSS	Seio sagital superior
TC	Tomografia computadorizada
TCE	Traumatismo craniencefálico
TFP	Testes funcionais preditivos
TT	Tap Test
TUG	<i>Time up and Go</i>
Vit.	Vitamina

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Resumo

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A Hidrocefalia de Pressão Normal (HPN) é uma doença neurológica caracterizada por um quadro progressivo de apraxia de marcha, alterações cognitivas e incontinência urinária (síndrome de Hakim-Adams), associada a hidrocefalia comunicante (comprovada por tomografia de crânio ou ressonância magnética de encéfalo) e com a pressão do líquido cefalorraquidiano (LCR) dentro de valores normais ($< 24\text{cm H}_2\text{O}$). O tratamento da HPN visa restaurar a capacidade funcional do paciente. Como a HPN acomete principalmente idosos, a decisão sobre quando uma intervenção cirúrgica deve ser realizada requer a ciência da probabilidade de melhora, através da utilização de ferramentas preditoras do resultado pós-cirúrgico: tap test, teste da infusão lombar e drenagem lombar externa contínua por 72 horas com monitorização constante da pressão. Atualmente, para o tratamento da HPN, existem duas principais opções terapêuticas: a derivação ventrículooperitoneal (DVP) e a terceiro-ventriculostomia endoscópica (TVE). A opção mais aceita e realizada é a DVP, principalmente com o implante de válvula programável. Oitenta e um pacientes, portadores de HPN idiopática (HPNi) com tap test positivo e capacidade de deambular preservada, foram operados de 2007 a 2011 no Hospital das Clínicas e no Hospital do Servidor Público Estadual Francisco Morato de Oliveira. Estes pacientes foram distribuídos em 3 diferentes pesquisas prospectivas. Os tratamentos cirúrgicos adotados foram: 15 DVP com válvula de baixa pressão fixa com mecanismo antissifão de membrana (Sphera®, HpBio), 16 TVE (Minop®, lente de 30°, Aesculap), 24 DVP com válvula programável (Strata®, Medtronic), 26 DVP com válvula de pressão fixa (PS Medical, Medtronic). A melhora clínica foi observada em 93% dos pacientes submetidos à DVP com a válvula Sphera® em 24 meses de seguimento, 75% com a TVE em 12 meses de seguimento, 76,9% com a DVP com a válvula PS Medical em 12 meses de seguimento e 83% com a DVP com válvula programável Strata® em 12 meses de seguimento. Conclui-se que tratar cirurgicamente os pacientes portadores de HPNi implica em melhora clínica em pelo menos 75% dos pacientes no período de 1 ano, independente do tratamento escolhido. A escolha personalizada do tratamento cirúrgico para cada paciente (válvula de pressão fixa, válvula de pressão fixa com mecanismo antisifão, válvula autorregulável, válvula programável ou neuroendoscopia) pode promover os melhores resultados funcionais e o menor custo operacional.

Descritores: 1.Hidrocefalia 2.Hidrocefalia de pressão normal 3.Transtornos neurológicos da marcha 4.Demência 5.Incontinência urinária 6.Derivação

do líquido cefalorraquidiano
9.Neurocirurgia

7.Ventriculostomia

8.Neuroendoscopia

Summary

Surgical Treatment of Normal Pressure Hydrocephalus. São Paulo, Faculty of Medicine, University of São Paulo, 2012.

Normal pressure hydrocephalus (NPH) is a neurological disease characterized by progressive gait apraxia, cognitive dysfunction and urinary incontinence (Hakim-Adams syndrome) associated with communicating hydrocephalus (confirmed by brain CT or MRI) and normal cerebrospinal fluid (CSF) pressure (< 24 cm H₂O). The treatment for NPH aims at restoring the patient's functional ability. As NPH typically affects the elderly, the decision as to when to perform surgery requires expertise on the likelihood of improvement based on the following predictive tools of postsurgery results: tap test, lumbar infusion test, and continuous 72-hour external lumbar drainage and pressure monitoring. Currently, there are two therapeutic options for NPH treatment, the ventriculoperitoneal shunt (VPS) and endoscopic third ventriculostomy (ETV). The former is the more accepted and performed option, especially with a programmable valve implant. Eighty-one idiopathic normal pressure hydrocephalus (iNPH) patients, with a positive tap test and intact walking ability underwent surgery between 2007 and 2011 at the Hospital das Clínicas and the Hospital do Servidor Público Estadual Francisco Morato de Oliveira. The patients were allocated to 3 different prospective studies. The surgical treatments were as follows: 15 VPS with a fixed low pressure valve with a membrane-controlled antisiphon device (Sphera®, HpBio), 16 ETV (Minop®, 30° lens, Aesculap), 24 VPS with a programmable valve (Strata®, Medtronic), and 26 VPS with a fixed pressure valve (PS Medical®, Medtronic). Clinical improvement was observed in 24 months of follow-up in 93% of the patients who underwent VPS with the Sphera® valve, in 12 months of follow-up in 75% who underwent ETV, in 12 months of follow-up in 76.9% who underwent VPS with the PS Medical® valve, and in 12 months of follow-up in 83% who underwent VPS with the Strata® programmable valve. The conclusion to be drawn is that surgical treatment of iNPH patients results in clinical improvement in 75% of the patients in 12 months of follow-up regardless of the choice of treatment. A case by case choice of surgical treatment (fixed pressure valve, fixed pressure valve with an antisiphon device, flow-regulated valve, programmable valve, or neuroendoscopy) may lead to the best functional results and lowest operational costs.

1. Hydrocephalus
2. Normal pressure hydrocephalus
3. Gait disorders, Neurologic
4. Dementia
5. Urinary incontinence
6. Cerebrospinal fluid shunt
7. Ventriculostomy
8. Neuroendoscopy
9. Neurosurgery

1 Introdução

1.1 Conceito

A hidrocefalia de pressão normal (HPN) é uma doença neurológica caracterizada por quadro progressivo de apraxia de marcha, alterações cognitivas e incontinência urinária (síndrome de Hakim-Adams), associada à hidrocefalia comunicante (comprovada por tomografia de crânio ou ressonância magnética de encéfalo) e com a pressão do líquido cefalorraquidiano (LCR) dentro de valores normais ($< 24 \text{ cm H}_2\text{O}$). A tríade clínica da síndrome de Hakim-Adams está presente simultaneamente em cerca de 50% dos casos. Porém, apenas um ou a associação de dois dos sintomas devem ser igualmente considerados para investigação diagnóstica¹⁻⁷.

1.2 História da hidrocefalia de pressão normal

Em 1957, no Hospital San Juan de Dios (Bogotá, Colômbia), o neurocirurgião latino-americano Salomón Hakim identificou seu primeiro caso de HPN, a princípio chamada de *hidrocefalia sintomática oculta*. O

Figura 1 - Pneumoencefalografia do primeiro paciente de Salomón Hakim, com HPN, que apresentou ventriculomegalia e, no entanto, PIC normal. Estas imagens foram publicadas em sua tese, intitulada: *Some observations on C.S.F. pressure. Hydrocephalic syndrome in adults with "normal" C.S.F. pressure.* [Tese]. Universidade Javeriana da Faculdade de Medicina, Bogotá, Colômbia, S.A. em 1964, pág. 7¹.

paciente era um menino de 16 anos de idade, vítima de traumatismo cranioencefálico (TCE) resultante de um acidente automobilístico. Foi realizada a drenagem de um hematoma subdural no hemisfério direito, porém o paciente

permaneceu em estado semicomatoso e foi diagnosticado como tendo danos cerebrais irreversíveis. Após uma pneumoencefalografia (Figura 1), identificou-se ventriculomegalia, porém a pressão intracraniana (PIC) apresentava-se normal (150 mm H₂O), o que despertou o interesse de Hakim. Com objetivo de realizar análises laboratoriais, Hakim fez uma punção lombar e retirou 15 mL de LCR. De maneira inesperada, o paciente apresentou melhora no dia seguinte e, inclusive, falou pela primeira vez, após meses sem falar. Mostrou piora do quadro poucos dias depois, porém voltou a melhorar após uma nova drenagem lombar. A partir dessas observações, Hakim foi impelido a implantar uma derivação ventrículo-atricul, apesar da ausência de evidências comprovando sua eficácia diante de portadores de ventriculomegalia com PIC normal. Para sua surpresa, o paciente melhorou consideravelmente e retornou à escola depois de três meses do tratamento¹.

Este caso foi relatado por Hakim em sua tese em 1964 e publicado no *Journal of the Neurological Sciences*, em 1965, junto com outros dois casos de HPN cujos sintomas foram revertidos totalmente após a implantação de um sistema de derivação liquórica¹⁻².

As primeiras hipóteses para explicar os mecanismos da hidrocefalia com PIC normal surgiram a partir do momento em que Salomón Hakim lançou mão de princípios da física, se valendo da lei de Pascal para exemplificar e, sobretudo, reproduzir situações que lhe permitissem demonstrar como o aumento progressivo da área ventricular poderia se instalar mesmo sem aumento concomitante da pressão³.

A lei de Pascal abrange as interações entre força, pressão e área, no interior de um sistema hidráulico, e Hakim utilizou estes princípios como base de seu raciocínio (Figura 2). De acordo com esta lei, quando duas colunas de água, com áreas diferentes, são submetidas a uma mesma pressão, a força exercida pela água na parede da coluna de maior área é maior do que na coluna de área menor, visto que a força é o produto da multiplicação de pressão por área, como demonstrado pela equação a, onde

F, P e A representam força, pressão e área, respectivamente¹⁻². Logo, diante de mesma P, o aumento da A resulta em aumento da F (equação 2).

Equação 1 $F = P \times A$

Equação 2 $\uparrow F = P \times \uparrow A$

Figura 2 - Dr. Salomón Hakim descrevendo as propriedades físicas da HPN envolvendo pressão, força e área. Esta fotografia encontra-se no artigo *Salomón Hakim and the discovery of normal-pressure hydrocephalus*, *Neurosurgery*, 67(1):156⁶.

Figura 3 - Demonstração do efeito da prensa hidráulica, com aplicação da Lei de Pascal. Hakim demonstrou que a pressão permanece constante em estágios diferentes de enchimento das bexigas (ponta de seta cinza). No entanto, a força elástica no interior das bexigas mais infladas era maior do que em bexigas menos infladas (ponta de seta preta). Desta forma, conseguiu comprovar como era possível a coexistência entre áreas diferentes e pressões semelhantes no interior de um sistema hidráulico. Estas imagens foram publicadas na tese de Hakim, em 1964, intitulada *Some observations on C.S.F. pressure. Hydrocephalic syndrome in adults with "normal" C.S.F. pressure*. [Tese]. Universidade Javeriana da Faculdade de Medicina, Bogotá, Colômbia, S.A. em 1964, págs. 30, 33¹ (Modificado).

Hakim demonstrou, com a utilização de bexigas elásticas em vários estágios de enchimento - cuja força elástica e pressão foram constantemente mensuradas - que a pressão obtida tanto com bexigas totalmente quanto parcialmente infladas poderia ser a mesma em alguns estágios de enchimento, porém quando as forças elásticas de tais bexigas eram comparadas, as bexigas mais infladas apresentavam maior força elástica devido à maior área de superfície onde esta era aplicada (Figura 3). Após confirmar, com seu experimento, que pressões iguais poderiam coexistir com estágios de dilatação diferentes, Hakim associou seus conceitos referentes às interações entre força, pressão e área aos resultados e, a partir disso, comparou seu sistema com o sistema ventricular e com a dinâmica liquórica (Figura 4)¹⁻².

Figura 4 - Comparação entre o sistema ventricular e as propriedades hidrodinâmicas da Lei de Pascal. A comparação demonstra que tanto em sistemas hidráulicos quanto em sistemas ventriculares que possuem áreas diferentes, sob a mesma pressão, os sistemas de área maior exercem forças maiores sobre suas paredes. Desta forma, Hakim atribui as lesões neurológicas da HPN a este aumento de força exercida sobre neurônios periventriculares. Esta imagem foi publicada no artigo *The special clinical problem of symptomatic hydrocephalus with normal cerebrospinal fluid pressure*, no Journal of the Neurological Sciences, 2(4): 325, em 1965².

Desta forma, Salomón Hakim concluiu que os pacientes apresentavam ventriculomegalia e PIC normal porque a existência de

ventrículos alargados (aumento da área) resultava em neutralização relativa dos aumentos pressóricos. No entanto, percebeu que, em tais condições, a força exercida nas paredes ventriculares era consideravelmente elevada, e que era esse aumento o causador da lesão hidráulica cerebral e, consequentemente das manifestações clínicas da doença^{1,6}. A partir dos estudos de Hakim, grandes esforços foram feitos a fim de melhor caracterizar e diagnosticar a HPN, bem como prever a probabilidade de melhora após o implante de um sistema de derivação liquórica^{5,7-13}.

1.3 Epidemiologia

Incidência e prevalência da HPN ainda não são precisas e muitos estudos relatam valores diferentes. Tal fato se deve, grande parte, à ausência de um consenso universal sobre as etapas referentes ao diagnóstico da doença, que resulta tanto em subdiagnósticos quanto em diagnósticos errados, visto que, muitas vezes, a HPN pode ser “confundida” com outras etiologias de apresentação semelhante, sobretudo em seus estágios iniciais e quando as características da tríade não se manifestam ao mesmo tempo.

Brean e Eide, em estudo que realizou uma busca ativa por meio de extensa campanha de mídia em uma população norueguesa estável de 220.000 habitantes atendidos por um único centro neurológico, a fim de recrutar possíveis casos de HPN, relataram incidência de HPN idiopática de 5,5/100.000 e prevalência de 21,9/100.000 habitantes⁸. Além disso, quando considerados apenas pacientes com idade acima de 65 anos, a prevalência foi de 117,9 por 100.000 habitantes.

Marmarou e colaboradores empreenderam estudo que investigou a incidência de HPN “possível” em idosos institucionalizados em casas de abrigo. Relataram encontrar distúrbios da marcha em pelo menos 21,2% dos pacientes. Ademais, 9,4% destes exibiram demência e, 14,7%, também incontinência urinária¹⁴.

A probabilidade de identificação da HPN tratável em pacientes que se apresentam com demência é muito baixa. De 560 casos de demência observados na Clínica Mayo entre 1990 e 1994, cinco (1%) tiveram suspeita de HPN, mas nenhum dos três tratados com derivação ventriculoperitoneal (DVP) melhorou¹⁵.

Hiraoka e colaboradores investigaram retrospectivamente a prevalência da HPN na população idosa de uma comunidade rural japonesa. Foram avaliados 170 idosos com idade maior que 65 anos, ou igual, por meio de ressonância magnética de encéfalo (RM), exame clínico, mini exame do estado mental (MM) e escala de avaliação de demência. Treze dos 170 idosos mostraram aumento dos ventrículos laterais acima de 0,3 no índice de Evans. Cinco idosos (2,9%) apresentaram tanto alargamento ventricular quanto estreitamento do espaço liquórico nas regiões cranianas de alta convexidade (na linha média). Todos os cinco indivíduos com esses sinais na RM manifestaram prejuízo cognitivo; um deles apresentou alterações na marcha e outro, incontinência urinária. Este estudo relatou que 2,9% dos idosos dessa comunidade demonstraram sinais radiológicos e características clínicas compatíveis com HPN idiopática¹⁶.

1.4 Classificação

A HPN pode ser dividida em duas categorias: secundária e idiopática (HPNi). A secundária ocorre em seguida a eventos neurológicos bem definidos, como hemorragia subaracnóidea (HSA), hemorragia intraventricular, traumatismo craniocéfálico (TCE), tumores no sistema nervoso central, infecções ou no pós-operatório de neurocirurgia. Em contrapartida, a HPNi geralmente aparece entre a sexta e a oitava década de vida e ainda não tem seus mecanismos fisiopatológicos completamente definidos⁴.

A HPNi é classificada em provável, possível e improvável. Esta classificação representa um esforço conjunto de um grupo de renomados autores (International NPH Consultant Group), e foi publicada em 2005 no suplemento do periódico *Neurosurgery*, em um extenso trabalho denominado *Guidelines for the Diagnosis and Management of Idiopathic NPH*¹⁷. O objetivo foi definir e relatar o consenso sobre HPN, facilitando a classificação para pesquisas e publicações futuras¹⁷⁻¹⁹.

A diretriz de 2005 sobre HPNi fornece critérios para o diagnóstico clínico da HPN, dividindo-o em três categorias: provável, possível e improvável. Essa classificação pode ser feita, frequentemente, na primeira visita clínica e leva em consideração história, neuroimagem, clínica e testes fisiológicos do paciente. Para ser classificada em *provável*, a história deve incluir: acometimento insidioso; origem após os 40 anos; duração mínima de 3 a 6 meses; nenhuma evidência de antecedentes como TCE, hemorragia intracerebral, meningite ou outra condição conhecida de hidrocefalia secundária; progressão no tempo e nenhuma outra condição neurológica/psiquiátrica que seja suficiente para explicar os sintomas. Exames de neuroimagem, realizados após o início dos sintomas, devem mostrar evidência de aumento ventricular não inteiramente atribuído à atrofia cerebral ou aumento congênito (índice de Evans ≥ 0.3); nenhuma obstrução macroscópica do fluxo liquórico e pelo menos uma das características de suporte, como aumento dos cornos temporais dos ventrículos laterais, não inteiramente atribuído à atrofia hipocampal; ângulo caloso igual ou maior que 40°; evidência de alteração no conteúdo de água no cérebro, incluindo alterações do sinal periventricular em TC e RM que não seja atribuída a alterações microvasculares isquêmicas ou de desmielinização e alteração do fluxo aquedutal ou do quarto ventrículo. Na clínica, achados de distúrbio de marcha devem estar presentes, pelo menos uma área de alteração na cognição e sintomas urinários, ou ambos. Quanto ao distúrbio de marcha, pelo menos dois dos seguintes devem estar presentes (e não serem totalmente atribuídos a outras condições): altura do passo diminuída, comprimento do passo diminuído, ritmo (velocidade da marcha) reduzido,

balanço do tronco aumentado, base alargada, dedos dos pés virados para fora ao andar, retropulsão (espontânea ou provocada), virar-se em bloco (virar-se requer três ou mais passos para volta de 180°) e equilíbrio alterado ao andar, evidenciado por duas ou mais correções em oito passos do teste do “pé ante pé”. Em relação à cognição, deve-se ter uma alteração documentada (ajustada à idade e educação) e/ou redução do desempenho em um teste cognitivo (como o minimal) ou evidência de pelo menos duas alterações não totalmente atribuídas a outras condições, como diminuição do desempenho psicomotor (aumento da latência de resposta); velocidade motora fina diminuída; precisão motora fina reduzida; dificuldade em dividir ou manter atenção; alteração de memória, principalmente para eventos recentes; disfunção executiva, como dificuldade em procedimentos de múltiplos passos, memória de trabalho, formulação de abstrações/similaridades, percepção e alterações de personalidade e comportamento. Para documentar os sintomas relacionados à incontinência urinária, um dos seguintes sintomas deve estar presente: incontinência urinária episódica ou persistente, não atribuída às doenças urológicas primárias; incontinência urinária persistente e incontinência urinária e fecal; ou dois dos seguintes devem estar presentes: urgência urinária (definida como percepção frequente de necessidade de urinar); frequência urinária (definida como mais de seis episódios de micção em uma média de 12 horas, apesar do volume normal) e noctúria (definida como a necessidade de urinar mais de duas vezes, em média, por noite)¹⁸.

Quanto à avaliação fisiológica, a pressão de abertura do LCR, determinada por punção lombar ou um procedimento comparável, deve estar em uma faixa de 105-190 mm H₂O, sendo que medidas apropriadas da pressão maiores ou menores que esta faixa não são compatíveis com o diagnóstico de HPNi provável.

Para ser classificada como possível, a história pode conter sintomas como início recente ou indeterminado, começo em qualquer idade depois da infância, duração de menos de três meses ou indeterminada, seguir eventos

como TCE, história remota de hemorragia intracerebral, meningite na infância ou na adolescência ou outras condições, coexistir com outra condição neurológica, psiquiátrica ou doenças gerais, mas que, na avaliação do clínico, não seja inteiramente atribuída a essas condições e que não seja progressiva ou claramente progressiva. A neuroimagem apresentando aumento dos ventrículos, mas associada à evidência de atrofia cerebral, com gravidade suficiente para explicar o tamanho do ventrículo e lesões estruturais que podem influenciar nesse tamanho. Sintomas de incontinência e/ou alteração cognitiva, na ausência de distúrbio de marcha ou equilíbrio. Avaliação fisiológica da pressão de abertura não disponível ou resultados nos extremos da taxa de variação esperada (60-104 ou 191-240 mm H₂O) são condizentes com HPNi possível^{9-10,20}.

A HPNi é considerada improvável quando: não há evidência de ventriculomegalia; há sinais de aumento da pressão intracraniana como papiledema; nenhum componente da tríade clínica da HPN está presente, os valores da pressão de abertura do LCR encontram-se fora das variações da HPNi “possível” (< 60 ou > 240 mm H₂O) e quando os sintomas são explicados por outras causas. Ao elucidar a história, o clínico deve dar atenção ao modo pelo qual os sintomas se iniciaram (agudo e subagudo), seu curso temporal (estático, progressivo) e sua intensidade (leve, moderada, grave). Deve-se dar ênfase, especialmente, aos sintomas envolvendo marcha, equilíbrio, cognição e incontinência urinária. Ocorrência familiar de HPN raramente é observada (em contraste com a hidrocefalia congênita). Porém, recomenda-se obter elementos da história familiar, com ênfase em doenças neurodegenerativas como doença de Parkinson, doença de Alzheimer e doença de Huntington, assim como outras condições neurológicas e psiquiátricas que tenham caráter hereditário e possam se assemelhar com a HPN¹⁸.

1.5 Fisiopatologia

Apesar de ter sido descrita há quase 50 anos, a fisiopatologia da HPN ainda permanece não totalmente definida. Grandes esforços foram feitos na tentativa de elucidar seus mecanismos de instalação e tais esforços originaram diversas hipóteses causais que têm servido de base para sua explicação, atualmente. Tais hipóteses variam amplamente entre si e incluem absorção líquórica deficiente, isquemia da substância branca profunda, redistribuição das pulsações vasculares e diminuição da complacência do parênquima cerebral, vasos sanguíneos e espaço subaracnóideo ^{13,21-22}.

Salomón Hakim descreveu o aumento da área ventricular como um requisito muito importante em HPN e afirmou que é devido a este aumento da área que se desenvolve uma força prejudicial aos circuitos neuronais periventriculares, mesmo com PIC normal ¹⁻³. Apesar de esta descrição ser um bom “ponto de partida” em relação à tentativa de se explicar a fisiopatologia da HPN, Hakim não esclareceu os motivos pelos quais o sistema ventricular aumenta, predispondo à exacerbação força exercida sobre suas paredes. A fim de responder tal questão originaram-se diversas hipóteses, sobretudo referentes à hemodinâmica cerebral e à hidrodinâmica líquórica cerebral ^{3,13,22}.

Alguns autores associam a hipoperfusão cerebral ao desenvolvimento da HPN ^{9,13,21}. Tal associação se deve, principalmente, à importante influência do ciclo cardíaco sobre a dinâmica líquórica. Durante a sístole ventricular ocorre aumento do espaço ocupado pelo parênquima cerebral, pela elevação do influxo sanguíneo intracraniano proveniente dos sistemas carotídeos e vertebrobasilar, gerando picos sistólicos intracranianos. Este aumento de espaço requerido pelo parênquima cerebral resulta em expansão cerebral que provoca uma contração ventricular, graças à sua menor resistência. Esta contração ventricular causa ejeção de pequena quantidade de LCR ao longo de todo o sistema ventricular (dos ventrículos laterais para o terceiro ventrículo através dos forâmens de Monro, deste para o quarto ventrículo, passando pelo aqueduto do mesencéfalo e, finalmente,

para o espaço subaracnóideo através dos forâmens de Lushka e Magendie). Um exemplo da influência do ciclo cardíaco sobre a dinâmica líquórica está demonstrado na Figura 5. Além disso, outra pequena quantidade de LCR entra no interior do canal espinhal, que atua como um reservatório durante a sístole²⁰. Durante a diástole o volume cerebral diminui, uma vez que ocorre um efluxo em sangue venoso e redução do influxo arterial. Essas alterações permitem a reentrada do LCR do canal espinhal no crânio, resultando em fluxo retrógrado (caudocranial) de LCR dentro do sistema ventricular²⁰. Como demonstrado na Figura 5, a força compressiva originada pela sístole deve ser progressiva e contínua ao longo do sistema ventricular, garantindo vazão adequada de LCR pelo aqueduto do mesencéfalo. Para que a dinâmica líquórica seja sempre unidirecional durante a sístole, o parênquima cerebral deve estar saudável e o sistema arterial deve estar íntegro bilateralmente, visto que a “força motriz” responsável pelo fluxo do LCR é a pulsação arterial. O comprometimento da “simetria sistólica” cerebral, causada por doenças como hipertensão arterial, aterosclerose e isquemia cerebral, pode resultar em fluxo líquórico alterado e multidirecional, causando estase do LCR e, principalmente, sua impactação sobre as paredes ventriculares durante os picos sistólicos. Este impacto líquórico causa tanto lesão mecânica (compressão do parênquima, capilares, vênulas

Figura 5 - Desenho simplificado do terceiro ventrículo e aqueduto do mesencéfalo. As setas maiores indicam as forças de compressão agindo de maneira coordenada sobre o ventrículo durante a sístole. As setas sólidas indicam o fluxo sistólico unidirecional de LCR resultando em sua vazão adequada. Situação normal. a-c: início, meio e final da sístole. Este desenho foi publicado no artigo *Idiopathic normal pressure hydrocephalus: Thoughts on etiology and pathophysiology*, Medical Hypotheses, 73:, 720²⁰.

e veias corticais superficiais) quanto tóxica/osmótica (redução do *clearance* de resíduos metabólicos e lesão endotelial, que resultam em aumento da carga osmótica) levando à dilatação ventricular e à lesão neuronal ainda maior, respectivamente (Figura 6)²⁰.

Takeuchi e colaboradores avaliaram 44 pacientes com possível HPNi¹³. Destes, 40 foram submetidos a algum sistema de derivação liquórica [derivação ventriculoperitoneal (DVP) e derivação lomboperitoneal (DLP)] e seu fluxo sanguíneo cerebral regional cortical e profundo (tálamo e núcleos da base) foi mensurado um mês antes e depois da cirurgia. Os 40 pacientes apresentaram fluxo sanguíneo cerebral diminuído antes da cirurgia e se observou relação positiva entre o aumento do fluxo sanguíneo cerebral médio após a implantação da derivação (de $32,1 \pm 2,74$ ml/100g/min antes da cirurgia para $39,8 \pm 3,02$ ml/100g/min após a cirurgia) e a eficácia do sistema de derivação¹³.

Figura 6 - Desenho simplificado do terceiro ventrículo em um plano transaxial com o aqueduto do mesencéfalo na região inferior. As setas maiores demonstram a influência da sístole sobre a compressão ventricular. As setas sólidas mostram o fluxo de LCR. A compressão inadequada simultânea (proximal e distal) do ventrículo resulta em compartimentalização ventricular, acúmulo de pressão e vazão reduzida de LCR. Este desenho foi publicado no artigo *Idiopathic normal pressure hydrocephalus: Thoughts on etiology and pathophysiology*, Medical Hypotheses, 73:720²⁰.

Takaya e colaboradores avaliaram o fluxo sanguíneo cerebral em 35 áreas por tomografia computadorizada com emissão de fóton único (SPECT) de 21 pacientes: sete com sintomas objetivos da tríade da HPN, sete sem sinais objetivos e sete pacientes-controle²³. Observaram que os pacientes sem sinais objetivos apresentavam hipoperfusão global comparados com o grupo-controle. Tal hipoperfusão era semelhante à dos pacientes com os sinais objetivos da tríade, exceto na substância branca frontal, onde não mostraram hipoperfusão²³. Portanto, os autores concluíram que outros fatores além da hipoperfusão cerebral são responsáveis pela fisiopatologia da HPN, visto que os pacientes sem sinais objetivos também já exibiam hipoperfusão global, assim como os pacientes em estágio clínico.

Bateman também discorda da hipótese da hipoperfusão cerebral como base fisiopatológica da HPN²¹. Ele selecionou 20 pacientes com diagnóstico de HPN e fluxo sanguíneo cerebral acima do normal (>700 ml/min), submetidos a exames de RM que avaliaram os seguintes itens: fluxo venoso no seio sagital superior (SSS) e no seio reto (SR); influxo arterial total e o volume médio de LCR que passava pelo aqueduto do mesencéfalo em direção aos quarto e terceiro ventrículos, durante sístole e diástole, respectivamente (*aqueduct stroke volume*). Os pacientes foram comparados com 12 controles. Observaram-se fluxo sanguíneo venoso profundo (SR) normal e fluxo sanguíneo superficial (SSS) diminuído (com efluxo reduzido em 9% comparado com influxo e complacência venosa diminuída em 50%). Desta forma, o autor afirma que a HPN pode ocorrer independentemente de perfusão arterial e fluxo venoso profundo e reconhece a redução do fluxo venoso superficial como potencial causadora da HPN.

1.6 Manifestações clínicas

A HPN manifesta-se, em geral, através da tríade clínica composta de apraxia de marcha, demência e incontinência urinária combinada com achados radiográficos de ventriculomegalia, e laboratoriais de pressão normal do LCR^{4,5}. Os sinais e sintomas tipicamente se desenvolvem de forma insidiosa, bilateralmente, mas podem aparecer lateralizados quando superpostos por condições coexistentes, como acidente vascular encefálico (AVE), radiculopatia e neuropatia periférica e, geralmente, ocorrem entre a sexta e a oitava década de vida^{20,22}.

A apresentação clínica da HPN pode, ainda assim, variar significativamente quanto à gravidade e progressão desses sintomas; portanto, não é necessário que toda a tríade esteja presente para ser considerado o diagnóstico de HPN¹⁰.

Quadro 1 - Diagnósticos diferenciais da HPN¹⁸

Distúrbios		
Neurodegenerativas	Demência vascular	Outras causas
Doença de Alzheimer	Infartos múltiplos	Hidrocefalia obstrutiva
Doença de Parkinson	Doença de pequenos vasos cerebrais	Hidrocefalia congênita
Corpos de Lewy	Doença de Binswanger	Tumor na coluna espinhal
Doença de Huntington	Acidente vascular cerebral	Deficiência de Vit. B12
Demência frontotemporal	Insuficiência vertebro-basilar	Estenose espinhal
Atrofia de múltiplos sistemas		Lesão cerebral traumática
Encefalopatia espongiforme		
Degeneração corticobasal		

Quanto aos elementos da tríade, a alteração de marcha usualmente aparece antes de demência e incontinência urinária, sendo, na maioria dos casos, o sinal clínico mais proeminente nos estágios iniciais da doença ⁴.

Devido à HPN ser uma doença, sobretudo, da população idosa, faixa etária em que dificuldade de marcha, demência e incontinência urinária são relativamente comuns, uma diversidade de diagnósticos de sintomas individuais deve ser considerada, incluindo doenças neurodegenerativas, etiologias vasculares e desordens urológicas. Uma relação de diagnósticos diferenciais da HPN é apresentada no Quadro 1, e diante de tais diagnósticos, torna-se evidente a importância de uma avaliação clínica adequada, tanto por parte dos clínicos gerais, quanto dos geriatras e, finalmente, dos neurologistas que estiverem assistindo os pacientes que apresentarem características da HPN, visto que o diagnóstico precoce e, sobretudo, correto, guarda estreita relação com o sucesso terapêutico^{4-5,10,18}.

1.6.1 Apraxia da marcha

Geralmente, o distúrbio de marcha e algum outro sintoma são necessários para realizar o diagnóstico, e tende a ser a característica mais reconhecível da HPN^{6,18}. Embora nenhuma característica seja patognomônica da alteração de marcha em HPN, esta se apresenta como uma marcha lenta, de base alargada, passos curtos com os pés arrastados pelo chão (como uma “marcha magnética”), dificuldade em se virar, realizar o teste do “pé ante pé” e iniciar os primeiros passos. Não há fraqueza motora e os pacientes frequentemente têm história de quedas. Desequilíbrio e redução da velocidade da marcha (devido aos passos curtos e apraxia da marcha) também são comuns¹⁸. Entretanto, o balanço dos braços ao andar está preservado, o que pode ajudar na distinção entre a marcha da doença de Parkinson^{6,18,24}.

A alteração de marcha pode surgir como dificuldade em subir ou descer escadas e andar no ritmo esperado. Os pacientes podem se queixar de dificuldade em levantar de uma cadeira, fraqueza das extremidades inferiores e fadiga ao andar. Além disso, muitas vezes mostram inabilidade em subir na mesa de exame ou em suas próprias camas^{5,18}.

A origem da alteração de marcha não é totalmente compreendida, porém algumas ideias foram sugeridas. As hipóteses iniciais sugeriam que a dilatação progressiva dos ventrículos provoca compressão e deformação das fibras neuronais motoras na porção superior e medial da coroa radiada. Entretanto, fraqueza nos membros inferiores, não costuma ser encontrada ao exame neurológico desses pacientes; de forma que a disfunção primária do trato piramidal não é considerada um sintoma comum em HPN. Por outro lado, o acometimento de fibras pré-motoras podem estar envolvidas nesse processo. Evidências eletromiográficas revelam contração de grupos musculares antagonistas e aumento anormal da atividade de músculos antigravitacionais nas articulações do quadril e dos joelhos²⁵⁻²⁷.

O acometimento da via dopaminérgica nigroestriatal pelo fluxo pulsátil anormal de LCR é uma possível explicação para o distúrbio no planejamento motor. Modelos experimentais de hidrocefalia criam sintomas parkinsonianos reversíveis, evidenciando uma explicação para associação entre HPN e doença de Parkinson em humanos²⁸⁻²⁹.

Outras condições que causam anormalidade de marcha devem ser consideradas ao realizar o diagnóstico da HPN, como estenose de canal lombar, neuropatia periférica, doença cerebrovascular, doença de Alzheimer (DA), tumores, trauma, doença de Parkinson, demência dos corpos de Lewy, depressão, alcoolismo crônico, deficiência de vitamina B12 e ácido fólico^{4,30}. Além disso, a anormalidade de marcha é o sinal mais responsivo ao tratamento com a implantação de um sistema de derivação liquórica^{4,22,31-32}.

1.6.2 Alterações cognitivas

A alteração cognitiva geralmente é a segunda manifestação da HPN após o distúrbio de marcha. É caracterizada por um progressivo déficit das funções das áreas subcortical e frontal, manifestado como retardo psicomotor, redução da atenção e concentração, disfunção executiva e visuoespacial e alteração de memória, sendo a função executiva danificada precocemente no curso da doença. Os déficits da área cortical como apraxia, agnosia e afasia são raros¹⁰. A gravidade de tais déficits em HPN pode variar de minimamente detectável a extremamente exuberante³³ e significativa melhora desses sintomas pode ser obtida depois da derivação, sendo, portanto, uma das poucas causas de demência reversível. Uma breve avaliação pode ajudar a determinar a causa do prejuízo da cognição. O minixame do estado mental (Minimental ou MM) pode mostrar déficits para realização de cálculos, concentração, escrita de frases, copiar a intersecção de pentágonos, e seguir um comando de três estágios. Processamento mental lentificado pode ser evidente devido ao aumento do tempo do teste. O desempenho no teste do relógio também pode estar

alterado, indicando dificuldade no planejamento espacial e organização³⁴. Relatam-se distúrbios de comportamento associados à HPN como depressão, mania, agressividade, distúrbio obsessivo-compulsivo, psicoses incluindo paranoia, alucinações e distúrbios do controle do impulso. O aparecimento de sintomas depressivos em pacientes com HPN pode ser uma consequência neuroquímica da desordem cerebral. Entretanto, pode ser resposta à incapacidade física e mental associada à HPN. O local de disfunção responsável pela demência em HPN permanece incerto, embora o sistema frontoestriatal tenha sido implicado por alguns investigadores. Outros enfatizam a importância de outras estruturas subcorticais, incluindo fibras de projeção passando próximo aos ventrículos laterais^{5,33}.

O diagnóstico diferencial pode ser particularmente difícil devido à similaridade das alterações cognitivas com doenças mais prevalentes como a DA. Geralmente a DA está mais associada à alteração de memória, aprendizado e orientação, enquanto a HPN se liga com maior frequência à diminuição psicomotora e da velocidade motora fina. As duas doenças podem levar à perda de função executiva, atenção e concentração, mas a HPN dificilmente causa alterações precoces de linguagem. A existência concomitante de DA e HPN não é incomum, e a probabilidade de cada uma aumenta com idade avançada e hipertensão arterial sistêmica (HAS)³⁵. Em casos coexistentes de HPN e DA, atrofia hipocampal pode-se observar à ressonância magnética (RM)³⁰.

1.6.3 Incontinência urinária

A incontinência urinária normalmente é observada nos estágios avançados da doença e parece ocorrer por interrupção das vias neuronais periventriculares que se direcionam ao centro sacral da bexiga urinária, levando à hiperatividade do músculo detrusor, que pode resultar primariamente em urgência urinária e polaciúria^{4,34}. Pode decorrer, também, do distúrbio da marcha, apraxia e bradicinesia que impedem o paciente de

chegar ao banheiro a tempo e, em casos extremamente avançados, pode resultar de falta de preocupação para micção, sugerindo que a incontinência é associada a uma disfunção executiva frontal^{4,5}.

Uma pesquisa realizada por Sakakibara e colaboradores³⁶, que avaliaram 42 pacientes com possível HPN, submetidos à exame de urodinâmica, revelou que 95% deles apresentaram evidência de hiperatividade do músculo detrusor, 93% exibiram sintomas do trato urinário inferior, que incluíam sintomas de armazenamento em 93% dos pacientes e de esvaziamento em 71%³⁶. Este estudo demonstrou que, em estágios iniciais a urgência urinária pode anteceder a incontinência em pacientes com HPN.

A incontinência não é um componente invariável da doença e pode ocorrer raramente ou apenas intermitentemente em alguns casos. A polaciúria apresenta tipicamente mais de seis episódios em 12 horas, sendo comum a noctúria¹⁰. A incontinência também pode ser causada por doenças que afetam o controle autonômico da bexiga, como a neuropatia diabética. Outras causas frequentes são uso de diuréticos e fármacos com efeito anticolinérgico e perda multifatorial do controle da bexiga como aumento da próstata e prolapso de órgãos pélvicos^{30,35}.

1.7 Diagnóstico

1.7.1 Exames de Imagem

O diagnóstico da HPN requer evidências convergentes de história clínica, exame físico e estudos de neuroimagem, que abrangem tomografia computadorizada do crânio (TC) e ressonância magnética de encéfalo (RM). A RM é superior à TC. A TC pode excluir a hipótese da HPN e é útil para a triagem inicial, enquanto a RM fornece informações mais precisas, permite a

identificação de anormalidades estruturais e a causa da HPN. Além disso, a RM pode ser utilizada para obtenção de informações fisiológicas adicionais, como a estimativa do fluxo de CSF por imagens ponderadas em T2⁴.

Aumento ventricular (índice de Evans $\geq 0,3$) aos exames de neuroimagem é necessária, porém não é suficiente para estabelecer o diagnóstico de HPN. Os resultados da neuroimagem (Figura 7) necessitam de interpretação associada aos dados da história clínica e achados físicos para que o diagnóstico correto da HPN seja obtido e para que se possa diferenciá-la de outras doenças^{5,18}.

Figura 7 - Imagem de ressonância magnética mostrando ventriculomegalia em um paciente com HPN. O índice de Evans é a largura máxima dos cornos anteriores (seta menor) dividida pela largura máxima da calvária (seta maior). Hidrocefalia é definida por um índice maior ou igual a 0,3. O índice deste paciente é de 0,4. Esta figura foi publicada no artigo *When do common symptoms indicate normal pressure hydrocephalus?* Cleveland Clinic Journal of Medicine, 73(5):452³⁰.

A HPN pode ser similar, ou ocorrer em associação a várias doenças que são prevalentes em idosos, como doença cerebrovascular, desordens neurodegenerativas, desordens urinárias primárias, estenose espinhal e outras condições¹⁸. Apesar da importância da avaliação clínica para o diagnóstico de HPNi, o grau de certeza fornecido apenas pelo diagnóstico clínico, relacionado à melhora do paciente após a implantação de um sistema de derivação líquórica varia de menos de 50% até 60%³⁷.

1.7.2 Testes funcionais preditivos

O tratamento cirúrgico é um procedimento invasivo que pode acarretar complicações, especialmente em pacientes de idade avançada, como os portadores da HPN. Os testes funcionais preditivos (TFP) têm duas finalidades: (1) confirmar o diagnóstico e (2) identificar quais pacientes

melhorarão após a intervenção cirúrgica e predizer com maior acurácia a probabilidade dessa melhora^{4,10,21}. Os TFP atualmente aceitos e que podem ser utilizados são os seguintes:

- Teste de punção lombar (*tap test*): realiza-se uma punção lombar e se removem cerca de 40 – 50 ml de LCR. O paciente é observado quanto às alterações na marcha e/ou função cognitiva em torno de 180 minutos depois. Resposta positiva ao teste tem um grau de certeza maior para uma resposta favorável à colocação de uma derivação liquórica do que pode ser obtido apenas pelo exame clínico. No entanto, o *tap test* não pode ser usado como um teste de exclusão devido à sua baixa sensibilidade (26-61%)^{4,21,22}.
- Testes de resistência de saída de LCR (teste de infusão): são vários métodos para avaliar a dinâmica liquórica, geralmente utilizando infusão de soro fisiológico, Ringer lactato, ou LCR artificial no espaço subaracnóideo. Quando surge um estado de equilíbrio entre o volume infundido e o volume absorvido, a pressão é mensurada. Este teste apresenta maior sensibilidade (57-100%) em comparação com o *tap test*, e valor preditivo positivo de 75-92%^{4,9,21,37}.
- Drenagem lombar externa (DLE): drenagem contínua de LCR, geralmente em uma taxa de 5 a 10 mL por hora, com observação da resposta por mais de 72 horas no hospital. DLE acima de 300 ml está associada à alta sensibilidade (50-100%) e a alto valor preditivo positivo (80-100%). Apesar de ser o TFP que possui maior acurácia, também é o que tem maior taxa de complicação, além de requerer internação hospitalar^{4,10,37}.

Outros exames que não fazem parte do consenso atual como teste funcional preditivo:

- Monitorização contínua da pressão intracraniana: pode ser considerada durante a fase de diagnóstico/prognóstico da HPNi por meio de

mensuração tanto da PIC estática (*ondas B de Lundberg*) quanto da pulsátil. Valores de PIC elevados devem levar a uma reavaliação para descartar uma causa secundária de HPN^{4,21}. Eide e colaboradores avaliaram a PIC estática e a pulsátil de 214 portadores de HPNi³³. Destes, 131 foram submetidos ao implante de um sistema de derivação liquórica e 101 (93%) apresentaram boa resposta após a cirurgia. Observou-se que em 109 pacientes as ondas médias da PIC pulsátil foram superiores a 4 mmHg. Dos 21 pacientes cujas ondas médias da PIC foram inferiores a 4 mmHg, apenas dois responderam favoravelmente à cirurgia, sugerindo relação positiva entre a PIC pulsátil e a melhora após derivação liquórica; no entanto, este exame não é comumente utilizado, visto se tratar de um procedimento invasivo.

- Cisternocintilografia: introduzir-se, um isótopo radioativo no espaço liquórico. A detecção de acúmulo do isótopo na convexidade, por uma câmara gama, é considerada normal³⁸. A estase do isótopo radioativo nos ventrículos por 48 horas ou mais, conhecida como padrão reverso, está associada ao diagnóstico de HPN^{39,40}. Apesar de inicialmente esta técnica ter sido considerada promissora, não mostrou ser capaz de melhorar a acurácia do diagnóstico⁴⁰⁻⁴².
- Medidas do fluxo sanguíneo e da taxa metabólica: muitos estudos de fluxo sanguíneo cerebral regional (FSCr) com SPECT, PET e tomografia com xenônio mostram diminuição do FSCr, mas a área com fluxo acometido difere entre os estudos. As medidas do fluxo sanguíneo cerebral não são consideradas úteis como teste preditivo do implante de DVP⁴³. Tedeschi e colaboradores, usando PET e 18F-2-fluorodeoxiglicose, mostraram diferentes padrões de redução da taxa metabólica da glicose e estabeleceram que este parâmetro não é capaz de predizer o resultado cirúrgico⁴⁴.
- Avaliação do volume de ejeção liquórica no aqueduto do mesencéfalo (*aqueduct stroke volume*): como já mencionado brevemente define-se o

Aqueduct stroke volume como o volume médio de LCR passando através do aqueduto do mesencéfalo em direção cranio-caudal durante a sístole cardíaca e em direção caudocranial durante a diástole cardíaca, num único ciclo cardíaco, geralmente avaliado pela RM, por meio das técnicas de *cine-RM* e *phase contrast*^{4,9-10,37,45}. Scollato *et al.*, em estudo que avaliou o volume de ejeção de LCR no aqueduto de 65 pacientes com HPN antes e após a implantação de DVP, observaram que nos 35 pacientes que melhoraram depois da cirurgia, sua média pré-operatória de 157,01 μ L diminuiu para 18% um mês após a DVP e 49% 12 meses depois da cirurgia⁴⁵. Em um grupo de 15 pacientes que não melhoraram, a menor média do volume de ejeção no aqueduto observada no pré-operatório (84,2 μ L) diminuiu para 14,3% um mês após a DVP, e 34% em 12 meses, sugerindo uma relação positiva entre melhora clínica e maiores quedas na taxa de volume de ejeção aquedutal pós-DVP. Bateman e Loiselle avaliaram o volume de ejeção aquedutal em 32 pacientes submetidos à derivação liquórica (antes e depois da cirurgia)³. Destes, 63% apresentaram melhora após a derivação; no entanto, em relação ao volume de ejeção aquedutal, não se observou diferença entre os responsivos e os irresponsivos, contra-indicando, assim a utilização deste exame como preditor de resposta pós-cirúrgica.

A Figura 8 mostra uma sequência de etapas, tanto referentes à avaliação clínica, quanto relacionadas aos TFP descritos, a fim de identificar quais pacientes provavelmente sejam mais beneficiados depois da implantação de um sistema de derivação liquórica. Tal algoritmo foi publicado na diretriz sobre HPNi de 2005 e inclui o grau de certeza de responsividade à derivação liquórica ofertado por cada procedimento^{37,46}.

Figura 8 - Esquema para prever a responsividade à derivação liquórica. A avaliação da indicação cirúrgica utilizando-se apenas os dados da avaliação clínica resultará em sensibilidade de 46 a 61% (escala à esquerda) em relação à melhora pós-cirúrgica. A resposta positiva ao *tap test* com retirada de 40 a 50 ml de LCR é altamente preditiva de resposta favorável à derivação liquórica (72-100%), porém, sua sensibilidade é baixa (26-61%). A mensuração da pressão de abertura do LCR durante o Tap Test é útil para que se possa excluir hidrocefalia secundária (PIC >18mmHg). O teste de resistência de saída do LCR (através do sistema de infusão) fornece alta sensibilidade, variando de 57 a 100%, e está associado a um valor preditivo positivo de 75 a 92%. A drenagem lombar externa é o teste suplementar que fornece a maior sensibilidade (50-100%) e o maior valor preditivo positivo (80-100%); no entanto, requer internação hospitalar e é o mais associado a complicações. RS, *resistência de saída* do LCR. Este esquema foi publicado no artigo: *The value of supplemental 'prognostic tests for the preoperative assessment of idiopathic normal pressure hydrocephalus'* Neurosurgery, 57(sup.3):27, 2005.³⁷ (Traduzido)

2 Tratamento cirúrgico

O tratamento da HPN visa, principalmente, restaurar a capacidade funcional do paciente. Desta forma, a decisão sobre quando uma intervenção cirúrgica deve ou não ser realizada requer que se leve em consideração a probabilidade de tal restauração, com emprego de algumas ferramentas preditoras do resultado pós-cirúrgico. Além dos testes suplementares abordados anteriormente, existem outros indicadores (favoráveis e desfavoráveis) que podem ser utilizados. Os indicadores favoráveis de melhora pós-cirúrgica incluem: início precoce do distúrbio de marcha (sendo o distúrbio de marcha a característica clínica mais proeminente); início dos sintomas em período inferior a 6 meses. Os indicadores desfavoráveis compreendem: ausência de distúrbio de marcha ou o seu surgimento após iniciada a demência; início precoce de demência; demência moderada a grave; demência há mais de dois anos; atrofia difusa e importante comprometimento da substância branca ao exame de RM^{12,47-48}.

2.1 Derivação ventricular

A implantação de um sistema de derivação liquórica mediante intervenção cirúrgica é a medida terapêutica mais utilizada para a HPN. É realizada para aliviar o excesso de LCR no interior do sistema ventricular e tem demonstrado significativos benefícios^{1-2,10-11,24,30-31,33-34,49-52}. Empregam-se diferentes tipos de derivação liquórica, porém o mais comum é a DVP, com um cateter delgado, cujo fluxo interior é unidirecional (craniocaudal), devido a um dispositivo valvulado acoplado ao sistema, que comunica os ventrículos cerebrais com a cavidade peritoneal, onde o excesso de LCR é drenado^{34,46}.

Outros exemplos de derivações que pouco são usadas atualmente incluem a derivação ventriculoatrial (DVA) e a derivação lomboperitoneal (DLP)^{4,9,33}.

A eficácia da DVP varia entre 33% e 90%⁴⁹⁻⁵³. Esta grande disparidade se deve à variação na seleção dos pacientes em diferentes estudos e ao fato de não existir uma escala única para análise de melhora do paciente que seja aceita universalmente²³. Há taxa de complicações significantes (hemorragia intraoperatória grave, hematomas subdurais, déficits neurológicos, epilepsia, arritmias cardíacas, disfunções hipotalâmicas, fístulas liquóricas, infecções) em cerca de 6% dos pacientes depois da cirurgia^{4,31}.

Pujari e colaboradores analisaram, retrospectivamente, 55 pacientes acompanhados por, pelo menos, três anos após cirurgia de DVP e relataram que em 53% deles foram necessárias revisões cirúrgicas³². No entanto, observaram que mesmo diante da necessidade de revisões, os pacientes em geral mantiveram melhora clínica a longo prazo, variando de 5 a 7 anos, sobretudo relacionada ao distúrbio de marcha e à incontinência urinária.

Kahlon e colaboradores realizaram um estudo prospectivo de pacientes com suspeita de HPN, submetidos à DVP, seguidos por 6 meses (54 pacientes) e 5 anos (23 pacientes)⁵¹. Relataram que a curto prazo (6 meses), 83% dos 54 pacientes operados melhoraram a marcha, 65% o tempo de reação, 46% melhoraram nos testes de memória e 96% relataram melhora subjetiva. A longo prazo (5 anos), os 23 pacientes apresentaram melhora pós-derivação de aproximadamente 40% na marcha, contudo, menos de 10% na cognição e no tempo de reação. Os pacientes com menos de 75 anos tiveram taxa de melhora maior (64%) que os com mais de 75 anos (11%). Os autores afirmaram que os benefícios da DVP podem ser obtidos até 5 anos após a cirurgia e fatores como taxa de mortalidade, idade e comorbidades devem ser levados em conta durante a seleção dos pacientes, visto que tais fatores alteram de maneira importante os resultados a curto e longo prazos.

2.2 Neuroendoscopia

A terceiro-ventriculostomia endoscópica (TVE) também tem sido utilizada para tratamento da HPN^{24,52,54}. Considerada uma derivação interna, tal técnica consiste na fenestração do assoalho do terceiro ventrículo e da membrana de Liliequist, permitindo que o LCR passe diretamente do terceiro ventrículo para o compartimento anterior da cisterna interpeduncular e cisterna pré-pontina, aumentando o fluxo sistólico de saída dos ventrículos (o que resulta em redução do excesso de LCR intraventricular) e diminuindo os efeitos deletérios do LCR sobre as paredes ventriculares durante as ondas sistólicas pulsáteis. Gangemi e colaboradores avaliaram retrospectivamente 110 pacientes com HPN submetidos à TVE¹⁰⁶. Os autores observaram melhora clínica pós-operatória em 76 (69,1%) pacientes. Não houve correlação entre a taxa de sucesso e a idade dos pacientes ou o tipo de aumento ventricular. Entretanto, a taxa de melhora neurológica foi maior naqueles com menor tempo de história clínica e distúrbios de marcha no início da doença. No intraoperatório, o reaparecimento das pulsações cerebrais normais e a observação de movimentos significativos do assoalho do terceiro ventrículo, para cima e para baixo, após a TVE, foram relacionados a bom resultado. Complicações ocorreram em 7 (6,4%) pacientes e houve necessidade de um segundo procedimento endoscópico em 4 (3,6%). Portanto, os autores concluíram que a TVE é uma opção eficaz e segura para o tratamento da HPN.

3 Contribuições pessoais ao tratamento cirúrgico da HPN

3.1 Criação de um grupo de trabalho multiprofissional

Hidrocefalia é uma doença neurológica que pode representar um modelo de resiliência cerebral, pela reversibilidade neurobiológica observável após tratamento adequado. Num artigo de revisão publicado na *Frontiers in Human Neuroscience* em janeiro de 2012, intitulado *Revisiting hydrocephalus as a model to study brain resilience*, apresentamos e discutimos esta questão. Assim, todos os esforços para melhorar o atendimento de portadores de HPN têm como objetivo final preservar o tecido cerebral viável, mas em estado de “penumbra”, e oferecer condições para seu restabelecimento metabólico, a fim de que a qualidade de vida do paciente seja melhorada e o envelhecimento seja digno⁵⁵ (Anexo 1).

Os pacientes com HPN são idosos e quase sempre seus cuidadores são principalmente familiares. Fornecer diagnóstico e tratamento em poucos retornos ao hospital facilita todo o processo, além de permitir que o tempo de evolução da doença sem tratamento seja reduzido, favorecendo o melhor prognóstico. Pacientes tratados em menos de 24 meses do início dos sintomas têm melhor prognóstico^{11-12,54,56}.

Desde 2007, participei ativamente da criação e da coordenação do Grupo de Hidrodinâmica Cerebral (GHC) da Divisão de Neurocirurgia Funcional do Instituto de Psiquiatria do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. Atualmente, é um grupo de trabalho multiprofissional. Para o diagnóstico e tratamento adequado, este modelo de funcionamento multidisciplinar mostra vantagens operacionais. Há também vantagens para elaboração e execução de projetos clínicos de pesquisa.

A equipe é composta de neurocirurgiões, neurologista, neuroanestesista, urologista, intensivista, neuropsicóloga, fisioterapeuta,

terapeuta-ocupacional, nutricionista, enfermeiros e voluntários. Realiza cerca de mil atendimentos ambulatoriais e duzentas cirurgias por ano. Todos os casos, com suas particularidades e exames, são discutidos e a conduta é decidida em reunião multidisciplinar. Desenvolvem-se pesquisas clínicas, cirúrgicas e tecnológicas sobre questões da hidrodinâmica cerebral.

O fruto do nosso trabalho contínuo de atender e entender o idoso portador de hidrocefalia de pressão normal (HPN) culminou na redação do livro *Hidrocefalia de pressão normal – do reconhecimento da doença ao tratamento multiprofissional* (Editora Segmento Farma, São Paulo, 2012; Anexo 2), cujo objetivo é transmitir a informação sobre essa doença aos profissionais da área da saúde e, aos próprios pacientes e seus familiares. Dessa forma, mais indivíduos portadores da HPN serão diagnosticados e conseqüentemente, tratados. A obra é dividida em três partes. A primeira apresenta a HPN, o processo diagnóstico e o tratamento neurocirúrgico. A segunda demonstra a reabilitação fisioterapêutica, a neuropsicológica e a urológica. Por fim, a terceira parte mostra os cuidados e dicas gerais que todo paciente portador de HPN e seu cuidador devem saber.

3.2 Normatização do Tap Test

Hakim e colaboradores, em 1965, descreveram o tap test (TT) em suas observações iniciais durante o reconhecimento da HPN. Retiraram, inicialmente, um volume de 15 mL e realizaram manometria inicial e final^{2,57}.

Wikkelsö e colaboradores, em 1982 e 1986, mostraram que o TT com a retirada de 40 - 50 mL de liquor lombar poderia ser utilizado como teste preditivo. Consideraram-no, positivo quando duas de quadro escalas utilizadas (sendo três psicométricas e um teste de marcha) melhoravam após o TT⁵⁸⁻⁵⁹.

Em 1995, Malm e colaboradores realizaram um estudo classe II, com retirada de liquor até que a pressão final fosse zero. Obtiveram 62% de sensibilidade e 33% de especificidade⁶⁰.

Em 2002, Walchenbach e colaboradores, com um estudo multicêntrico classe II, retirando 40 mL obtiveram 23% de sensibilidade e 100% de especificidade⁶¹.

Ainda hoje, no Brasil e no mundo, existem variações na realização deste importante teste preditivo funcional. É um exame de simples execução e permite esquema ambulatorial, evitando internações; porém, questões relacionadas à segurança do paciente são fundamentais.

Inicialmente, quando o GHC foi composto, alguns critérios foram adotados para realização do TT, principalmente porque, no nosso meio, não havia consenso de como deveria ser feito e interpretado.

O protocolo estabelecido e normatizado no GHC consiste na execução do TT no período pré-operatório, para determinação da pressão líquórica intrarraquidiana e do prognóstico terapêutico, com retirada de 40 mL de LCR. A avaliação clínica é feita por uma equipe multidisciplinar composta de neurocirurgião, neurologista e fisioterapeuta. São realizadas duas avaliações pré-TT, com intervalo de uma semana. Depois da punção lombar, outras duas avaliações são obtidas após 3 horas e 72 horas. A marcha do paciente sempre é filmada para considerações multiprofissionais futuras. Cada avaliação é composta de uma bateria de seis escalas clínicas, sendo o TT considerado positivo quando o paciente apresenta pontuação 10% maior em pelo menos duas das seis escalas, levando em conta sempre o melhor resultado das duas avaliações pré-TT e das duas avaliações pós-TT para comparação. Caso o TT seja tido como negativo, repetimos o TT nos mesmos moldes após 30 dias.

Com neste protocolo estabelecido e aplicado no GHC desde 2007, não houve paciente que tenha apresentado infecção ou sinais e sintomas de hiperdrenagem pós-punção.

ESCALAS UTILIZADAS:

1. Mini exame do Estado Mental – MM^{2,62}.

Objetivo: avaliar alterações cognitivas.

Pontuação: 0-30 (quanto maior, melhor).

2. Teste de Equilíbrio de Berg-BERG^{37,63}.

Objetivo: avaliar habilidade de equilíbrio funcional, em diferentes posturas: sentado, ortostatismo e apoio unipodal.

Pontuação: 0-56 (quanto maior, melhor).

3. Medida de Independência Funcional – MIF⁶⁴.

Objetivo: avaliar qual o grau de dependência para atividades funcionais diárias. Pontuação: 18-126 (quanto maior, melhor; 18-36 dependência total, 37-90 dependência moderada e 91-126 independente).

4. *Dinamic Gait Index* – DGI⁶⁵.

Objetivo: avaliar desordens na dinâmica da marcha. O indivíduo é submetido à caminhada pelo percurso de 6 metros, realizando alguns movimentos de aceleração e desaceleração, e passando por obstáculos.

Pontuação: 0-24 (quanto maior, melhor).

5. Escala Japonesa de NPH – NPH SCALE⁶⁶.

Objetivo: pontuar o paciente segundo suas características clínicas da tríade da HPN.

Pontuação: 0-12 (quanto maior, pior).

DISTÚRBIO DE MARCHA

- 0.....Ausente
- 1.....Marcha instável, mas independente
- 2.....Anda com 1 apoio
- 3.....Anda com 2 apoios ou andador
- 4.....Não é possível andar

DEMÊNCIA

- 0.....Ausente
- 1.....Sem demência aparente, mas apático
- 2.....Socialmente dependente, mas independente na residência
- 3.....Parcialmente dependente na residência
- 4.....Totalmente dependente

INCONTINÊNCIA URINÁRIA

- 0.....Ausente
- 1.....Ausente, mas com polaciúria ou urgência miccional
- 2.....Às vezes, apenas à noite
- 3.....Às vezes, mesmo durante o dia
- 4.....Frequente

6. *Timed Up and Go* – TUG ¹².

Objetivo: avaliar a mobilidade e o equilíbrio. O teste quantifica, em segundos a mobilidade funcional pelo tempo em que o indivíduo realiza a tarefa. O tempo é cronometrado desde o momento em que o indivíduo se levanta da cadeira caminha pelo percurso de 3 metros ate um ponto pré-determinado, regressa e torna a sentar-se.

Desempenho normal para adultos saudáveis: 10-12 segundos

Considera-se normal para adultos com deficiência: 12,01-20 segundos

Considera-se comprometimento funcional: acima de 20,01 segundos.

De julho de 2007 até abril de 2012, 139 TT foram realizados. Foram considerados positivos 98 TT, 41 foram inicialmente considerados negativos. Destes tidos como negativos, 23 TT foram repetidos e, então, 12 TT foram positivos.

As mesmas escalas foram utilizadas para seguimento ambulatorial. Nesse período, apenas foram operados pacientes com TT positivo. O valor preditivo positivo do TT normatizado foi 76,2%, levando em que 32 dos 42 portadores de HPNi manifestaram melhora após 12 meses da cirurgia. Estes dados foram apresentados no trabalho *Endoscopic Third Ventriculostomy and Ventriculo-peritoneal shunt in idiopathic normal pressure hydrocephalus: a preliminary report of a prospective study*, submetido à *Neurosurgery* em 18 de maio de 2012. (Anexo 3)

O TT oferece outras duas informações importantes: valores de pressão inicial e final; possibilidade de análise quimiocitológica, Gram, culturas, reação para sífilis e cisticercose, pesquisa para BAAR e fungos, além da dosagem de proteína β -amiloide, tau e fosfo-tau. Estes marcadores biológicos permitem identificar pacientes com doença mista (DA associada,

por exemplo), ao se detectarem valores reduzidos de proteína β -amiloide e elevados das proteínas tau e fosfo-tau⁶⁷⁻⁶⁹.

Como não há consenso sobre que pressão de abertura da válvula de derivação ventricular deva ser escolhida, estipulou-se na criação deste protocolo, que a faixa de pressão em que uma válvula funciona deva conter o valor final manométrico do TT. Considerando a válvula disponível para o SUS e utilizada pelo nosso grupo, a PS Medical (Medtronic), o seguinte critério foi adotado: a pressão da válvula escolhida é baseada no valor final da manometria pós-tap-teste, depois da retirada de 40 mL - Pressão final < 4 cm H₂O, seleciona-se a válvula de baixa pressão; pressão final entre 4 e 10 cm H₂O, seleciona-se a válvula de media pressão e pressão final > 10 cm H₂O, seleciona-se válvula de alta pressão. Neste trabalho (Anexo 3) e no trabalho intitulado *Performance of fixed-pressure valve with antisiphon device Sphera® in hydrocephalus treatment and overdrainage prevention*, aceito para publicação em Arquivos de Neuropsiquiatria em 1 de junho 2012 (Anexo 4), aplicamos este critério de escolha da válvula em 41 pacientes portadores de HPNi e observamos melhora clínica em pelo menos 77%, no período de 12 meses e em 93%, em 24 meses quando a válvula utilizada possuía mecanismo antissifão de membrana (Sphera®, HPBIO, Brasil).

3.3 Comparação entre DVP e terceiro-ventriculostomia endoscópica no tratamento da HPNi

Dandy e Blackfan, no início do século passado, com estudos experimentais em cães, trouxeram para a comunidade científica a classificação da hidrocefalia em dois tipos: comunicante e obstrutiva (não comunicante). Dandy atribuiu como causa principal da hidrocefalia comunicante um déficit de absorção do LCR no espaço subaracnóideo⁷⁰.

Hakim, na década de 1960, descreveu a HPN como um tipo de hidrocefalia comunicante¹⁻². Greitz, em 2007, publicou considerações

interessantes sobre mudança de paradigma na pesquisa sobre hidrocefalia: a hidrocefalia aguda sempre é uma doença obstrutiva do trânsito liquórico, mas a hidrocefalia crônica (HPN, por exemplo) é caracterizada por uma doença da complacência cerebral⁷¹.

Até 3 de junho de 2012, 246 trabalhos foram identificados no PUBMED quando simplesmente se buscava *surgical treatment of idiopathic normal pressure hydrocephalus*. Atualmente, para o tratamento da HPNi, existem duas principais opções terapêuticas: a derivação ventriculoperitoneal (DVP) e a terceiro-ventriculostomia endoscópica (TVE). A opção mais aceita e realizada é a DVP, principalmente com o implante de válvula programável. De qualquer forma, tratar cirurgicamente os pacientes com iNPH é um consenso, pois isto causa impacto positivo no curso da história natural da doença^{55,72}.

Entretanto, a DVP tem o inconveniente de ser uma prótese a ser implantada, e apresentar um risco de médio a longo prazo de complicações que necessitem de reoperação como infecção, mau funcionamento mecânico e hiperdrenagem. O registro do Reino Unido mostra taxas de reoperação de DVP para o tratamento de hidrocefalia, em adultos, de 22% em 5 anos⁷³. O efeito sifão, responsável pela hiperdrenagem, pode ser parcialmente controlado com dispositivos antissifão associados ao sistema de válvula, válvula autorregulável (Orbis-Sigma®) ou com a mudança da pressão de abertura da válvula programável assim que se detectem indícios de hiperdrenagem (coleções liquóricas subdurais, por exemplo)⁶³. Dessa forma, se os pacientes portadores de HPNi pudessem ser tratados por intermédio TVE com os mesmos resultados a longo prazo da DVP, seria um grande benefício para a redução de risco de complicações a médio e a longo prazos. Isto seria uma vantagem para o paciente idoso, muitas vezes com comorbidades.

O estudo retrospectivo multicêntrico italiano publicado em 2008 causou grande discussão no meio neurocirúrgico, ao mostrar taxa de melhora clínica de 69,1% da TVE no tratamento de 110 pacientes portadores

de HPNi por um período de pelo menos 2 anos de seguimento⁵⁴. Esta taxa de melhora clínica é compatível com os resultados obtidos com a DVP, que variam de 69 a 90%^{12,42,48,64,74-77}. Muitas das críticas a esse trabalho surgiram por questões metodológicas: falta de clara distinção entre os casos de HPN idiopática e HPN secundária, e pelo fato de o teste funcional preditivo realizado ter sido a monitorização da pressão intracraniana e não os testes que são consenso na literatura, como o TT, o teste da infusão lombar e a drenagem lombar externa monitorizada por 72 horas.

Assim, para responder estas questões que ficaram em aberto na literatura, melhoramos a metodologia e executamos um estudo em nosso meio, incluindo 42 pacientes com HPNi com resposta positiva ao TT e com capacidade de deambular preservada.

O desenho desse trabalho foi prospectivo e o tratamento cirúrgico foi randomizado na própria sala cirúrgica, imediatamente após a indução anestésica. O objetivo inicial foi comparar os resultados neurológicos funcionais no período de 1 ano da DVP com válvula de pressão fixa (PS Medical, Medtronic) e da TVE (Minop®, lente de 30°, Aesculap) no tratamento de pacientes portadores de HPNi. Não utilizamos a válvula programável porque tal prótese não está disponível no HC/FMUSP.

O TT mostrou ser um teste preditivo universal, com resultados semelhantes para TVE e DVP. Observamos que a porcentagem de pacientes que melhoraram neste primeiro ano de seguimento foi semelhante em ambos os grupos, com valores de 75 e 76,9% para TVE e DVP, respectivamente. Porém, os pacientes tratados com DVP apresentaram melhora neurológica funcional da marcha muito mais significativa após os 12 meses que os pacientes tratados com TVE.

Os pacientes que não melhoraram com a TVE nos primeiros 6 meses (4/16, 25%), tiveram a DVP implantada e 50% melhoraram depois dessa segunda cirurgia, conforme já citado em literatura. Esses pacientes não apresentaram pulsações (sinal da bandeira) no assoalho do III ventrículo

imediatamente após a TVE. Tal achado foi descrito também por Gangemi e colaboradores e representa a informação mais importante e preditiva do sucesso terapêutico do tratamento endoscópico¹¹.

Nossa hipótese para explicar porque a TVE promove melhora funcional nos pacientes com HPNi, considerada uma hidrocefalia comunicante, é que durante a sístole, quando há o pico de pressão intracraniana, o assoalho do terceiro ventrículo aberto cirurgicamente funcionaria como um caminho de escape dessa energia mecânica e, assim, os lobos frontais, gânglios da base e tálamos receberiam uma intensidade menor do pulso pressórico. Isso provocaria melhora da perfusão sanguínea nessas regiões específicas, viabilizando o restabelecimento funcional dos neurônios acometidos pela doença (HPN) em progressão^{71,78}.

Considerando os resultados preliminares deste primeiro ano de seguimento, frente à característica intraoperatória (ausência do sinal da bandeira) em comum de todos os casos de pacientes submetidos à TVE e que não melhoraram, sugerimos que, se a escolha terapêutica para o portador de HPNi for a TVE e no intraoperatório não se observar o sinal da bandeira; imediatamente, ele seja submetido à DVP da mesma trepanação, para se evitar um novo ato anestésico-cirúrgico no futuro.

Para sabermos a evolução da TVE e da DVP a longo prazo, os pacientes desta pesquisa permanecerão sob seguimento e vigilância. Demais pacientes recentemente incluídos na pesquisa, mas que ainda não completaram o período de seguimento para observação, aumentarão nossa casuística para considerações futuras.

Pelo observado até o momento, não podemos indicar a TVE como melhor opção para o tratamento inicial da HPNi, visto que a DVP apresentou melhores resultados neurológicos funcionais após 1 ano. Porém o neurocirurgião deve saber que a TVE pode ser considerada uma opção de tratamento com resultados clínicos mais discretos que a DVP. Este trabalho foi submetido para publicação na *Neurosurgery* em maio de 2012, com o

título de: *Endoscopic third ventriculostomy and ventriculo-peritoneal shunt in idiopathic normal pressure hydrocephalus: a preliminary report of a prospective study* (Anexo 3).

O neurocirurgião deve, portanto, estar familiarizado com a neuroendoscopia ventricular, porque a TVE representa uma opção importante para o tratamento da hidrocefalia. Publicamos, em 2009, na *Minim. Invas. Neurosurg.*, o trabalho intitulado *Simulation of endoscopic third ventriculostomy in fresh cadaveric specimens*, no qual estudamos principalmente a anatomia dos ventrículos laterais e do terceiro ventrículo, bem como pudemos realizar a TVE como simulação da cirurgia em 47 cadáveres frescos, com média de idades de 66 anos. Este estudo proporcionou uma nova visão do treinamento em neuroendoscopia em adultos, ao utilizar cérebros frescos (sem fixação) ainda dentro do crânio e sem sacramentos que poderiam ser observados *in vivo*⁷⁹ (Anexo 5).

3.4 Considerações sobre o papel da neuroendoscopia no tratamento da HPN secundária por causa obstrutiva

Há consenso sobre a indicação de procedimentos neuroendoscópicos, sobretudo a TVE, para tratamento da HPN secundária obstrutiva, como por exemplo, nos casos de estenose de aqueduto (congenita ou adquirida)^{24,52,54}.

Cistos de aracnoide, cisticercos intraventriculares obstruindo o trânsito liquórico e tumores cerebrais, como cisto coloide do terceiro ventrículo, glioma de teto mesencefálico, tumores da pineal, etc; podem causar hidrocefalia e sintomas de hidrocefalia aguda ou sintomas insidiosos semelhantes aos da tríade clínica da HPN. A TVE, a remoção neuroendoscópica do componente obstrutivo (tumor ou cisticerco), septostomia, fenestração de cistos leptomenígeos podem ser realizadas para o tratamento da HPN secundária^{24,52,54}.

Em 2009, publicamos em *Arquivos de Neuropsiquiatria* o trabalho intitulado *Treatment of colloid cysts of the third ventricle through neuroendoscopic Nd: YAG laser stereotaxis*. Foi apresentada a experiência com o tratamento neuroendoscópico com estereotaxia associada ao *laser* de alta potência em 11 pacientes com cisto coloide do terceiro ventrículo. Destes pacientes, uma portava apraxia de marcha secundária à hidrocefalia. Após o procedimento, a paciente teve o tumor totalmente removido, a hidrocefalia resolvida e a marcha voltou ao normal⁸⁰ (Anexo 6).

Em 2011, na *Childs Nerv System*, publicamos, num artigo revisão sobre hidrocefalia em neurocisticercose intitulado *Hydrocephalus in neurocysticercosis*, o protocolo de tratamento neuroendoscópico para cistos intraventriculares obstrutivos (Figura 9)⁸¹. Atualmente, dos 30 pacientes adultos operados desde 2007, cinco tinham cisticerco único nos ventrículos laterais ou no terceiro ventrículo e exibiam quadro clínico compatível com HPN secundária com sintomas insidiosos. Todos os pacientes melhoraram com a remoção do cisticerco que obstruía os forâmens interventriculares e/ou aqueduto⁸¹ (Anexo 7).

Figura 9 – Algoritmo para tratamento da hidrocefalia em neurocisticercose. (fig. 5, pg 1718)⁸¹

Em 2012, na *Pediatric Neurosurgery*, publicamos um relato de caso e revisão da literatura intitulado *Hypopituitarism due to hydrocephalus: case report and review of the literature*. A paciente de 20 anos apresentava sintomas neuroendócrinos; sobretudo amenorreia primária devido à hidrocefalia crônica por estenose congênita do aqueduto. Dois meses após a TVE com resolução da tensão hidrodinâmica no hipotálamo, a paciente passou a menstruar por normalização do pulso de GnRH e, conseqüentemente, dos ciclos de LH e FSH⁷⁸ (Anexo 8).

3.5 Desempenho da válvula de pressão fixa com mecanismo antissifão Sphera® (HpBio)

As principais complicações relacionadas à DVP são infecção (meningite, ventriculite, cisto abdominal), mau funcionamento mecânico (obstrução ou desconexão do sistema) e hiperdrenagem (coleções subdurais, síndrome dos ventrículos colabados, hematomas subdurais). Todas estas complicações são graves, necessitam de reoperação e podem acarretar óbito^{63,82-89}.

Atualmente é consenso, sempre que possível e indicado, evitar o implante de DVP frente a alta taxa de complicações identificadas no seguimento a longo prazo (média 60 meses) de até 51 % dos casos; da-se preferência aos procedimentos neuroendoscópicos ventriculares^{63,79-81}.

Para se evitar as complicações infecciosas, a adoção institucional de protocolos, como o descrito pioneiramente por Choux, é o que causa maior impacto positivo e controle deste tipo de complicação⁹⁰. Cateteres impregnados antibióticos ou prata também parecem reduzir as complicações infecciosas⁹¹⁻⁹².

A prevenção do mau funcionamento mecânico se relaciona à boa técnica cirúrgica e a escolha adequada do tipo de válvula e do sítio distal de implante da DVP. A trepanação frontal parece ser relacionada ao melhor

posicionamento do cateter proximal, pela maior facilidade da punção que este ponto oferece, por aceitar maior variedade de ângulo de introdução, através dos pontos no occipital ou parietal⁹³⁻⁹⁴.

Toda DVP implantada apresenta efeito sifão quando o paciente assume a posição vertical, porque surge entre as duas extremidades do sistema uma diferença de pressão que supera a pressão de abertura da válvula. O termo “efeito sifão” é mais utilizado para designar o fenômeno físico implicado, regido pela bem conhecida Lei de Stevin ($p_f = p_0 + d \cdot g \cdot h$).

O termo hiperdrenagem é comumente empregado para descrever o mecanismo fisiopatológico pelo qual uma derivação liquórica interna ou externa gera alterações radiológicas específicas ou uma das síndromes clínicas relacionadas: hipotensão liquórica, hipertensão intracraniana por efeito expansivo de hematoma ou por obstrução intermitente na síndrome dos ventrículos colabados. O grau de hiperdrenagem, e portanto o risco de manifestações clínicas, está ligado tanto à pressão intracraniana (negativa) quanto ao volume liquórico intracraniano (deficitário). Pacientes com pseudotumor, por exemplo, podem ter imagem de hiperdrenagem com pressão intracraniana normal ou pouco negativa. A hiperdrenagem está associada a alterações hemodinâmicas intracranianas e intrarraquianas compensatórias, principalmente venosas, num primeiro momento. Nem sempre há manifestação clínica, dependendo de elementos como turgor cerebral, grau de atrofia cerebral, sensibilidade à dor e velocidade da drenagem.

Para reduzir a hiperdrenagem, a escolha da pressão de abertura da válvula de pressão fixa deve ser adequada para o paciente, para que garanta o fluxo de CSF necessário para tratar o distúrbio hidrodinâmico, porém sem causar drenagem excessiva e hipotensão intracraniana sintomática^{82-83,95-97}.

As válvulas programáveis oferecem a possibilidade de ajuste após a cirurgia, sem a necessidade de reoperação. A válvula autorregulável (Orbis-

Sigma®) garante um fluxo estável e, em teoria, se ajustaria melhor a cada paciente; contudo grandes casuísticas não mostraram superioridade de performance desse sistema⁷⁶.

Por outro lado, o mecanismo antissifão pode ser implantado em série com qualquer tipo de válvula e tem a função de aumentar a resistência ao fluxo sempre que o diferencial de pressão (ventrículo = p_0 /sítio distal = p_f) aumentar, prevenindo a hiperdrenagem e reduzindo o efeito sifão. Basicamente, há dois tipos de mecanismo antissifão: gravitacional (esferas ou peças que se deslocam com a força da gravidade, dificultando e reduzindo o fluxo) e membrana (membrana delgada e flexível que oclui o sistema quando a diferença de pressão aumenta por queda da pressão distal)⁸².

São muitos os fatores que influenciam a dinâmica da drenagem líquórica e estes podem ser tanto hidrodinâmicos quanto relacionados a características fisiológicas individuais, tornando, portanto, imprescindível o conhecimento desses, para que seja possível escolher o sistema de drenagem mais apropriado a cada paciente e até mesmo identificar prováveis causas de hipo ou hiperdrenagem. As principais forças que atuam sobre o fluxo drenado através do sistema de DVP são pressão intracraniana (PIC), pressão intra-abdominal (PIA) e pressão hidrostática (PH), sendo que a relação entre tais forças resultam na pressão de perfusão (PP), que pode ser calculada pela seguinte fórmula: $PP = PH + (PIC - PIA)$ ⁹⁵.

Grandes aumentos, sobretudo nos gradientes de PH, ocorrem quando o paciente se senta ou levanta causando drenagem excessiva do LCR. Kajimoto e colaboradores avaliaram a relação das alterações posturais com a pressão líquórica em sistemas de derivação ventriculoperitoneal implantados em 13 pacientes com hidrocefalia, sem incidência de hiperdrenagem. Para tanto, mediu simultaneamente as pressões dos diversos compartimentos nas posições supina e sentada. Com os pacientes em posição supina PIC, PIA e PH foram $4,6 \pm 3$ mmHg, $5,7 \pm 3,3$ mmHg e $3,3 \pm 1$ mmHg, respectivamente. Como resultado, a PP foi somente $2,2 \pm 4,9$

mmHg. Porém, quando os pacientes se sentaram, a PIA aumentou para $14,7 \pm 4,8$ mmHg, e a PIC diminuiu para $-14,2 \pm 4,5$ mmHg. O aumento da PIA e redução da PIC compensou em 67% o PH ($42,9 \pm 3,5$ mmHg) e consequentemente, o PP ($14 \pm 6,3$ mmHg) correspondeu a 33% de PH. Demonstraram que PIA alta e PIC baixa têm efeitos preventivos e que a PH alta tem efeitos promotores sobre a hiperdrenagem. Além disso, observaram que apenas uma pequena parcela dos indivíduos com DVP se torna sintomática devido aos efeitos de hiperdrenagem do LCR⁹⁵.

O antissifão gravitacional reforça esse mecanismo protetor fisiológico, de forma que o peso das esferas simularia um aumento ainda maior da PIA. Entretanto, tal mecanismo deve ser rigorosamente implantado na posição vertical para que funcione adequadamente. Apresenta a taxa de complicações gerais identificadas no seguimento a longo prazo (média de 60 meses) de até 21% dos casos, 5% delas se relacionaram à hipodrenagem⁸⁸.

As características fisiológicas individuais também dificultam a determinação não só do nível vertical do LCR no compartimento cranioespinal, mas também do nível do fluido na cavidade onde este está sendo absorvido. Assim, é difícil calcular precisamente a diferença hidrostática vertical entre os dois compartimentos. Entre as principais características fisiológicas que influenciam gradiente hidrostático vertical estão: crescimento da criança, aumentos da complacência do compartimento cranioespinal (como crianças com amplas fontanelas abertas e adultos submetidos a craniectomias descompressivas), diminuição da complacência do compartimento craniospinal (como estenose do canal raquidiano, Chiari I, pseudotumor cerebral, presença de lesão expansiva intracraniana). Ademais, a perda de peso aumenta a complacência da cavidade peritoneal (favorecendo a hiperdrenagem) e constipação extrema pode diminuir a complacência intraperitoneal (resultando em aumento da PIA). Portanto, dois indivíduos de mesma altura podem ter diferenças de gradiente hidrostático vertical, seja por diferença no compartimento cranioespinal, seja por diferença no compartimento abdominal. É possível

que a prevenção da hiperdrenagem seja mais eficaz com um determinado dispositivo antissifão do que com outro. Mesmo durante o sono, e de maneira episódica, alterações vasogênicas encefálicas podem provocar aumento da pressão intracraniana e ocasionar hiperdrenagem (p.ex., ondas B de Lundberg)⁹⁵⁻⁹⁶.

Estas características fisiológicas podem explicar por que muitos pacientes com compartimento cranioespinhal e cavidade peritoneal saudáveis parecem tolerar uma derivação ventriculoperitoneal com ou sem um mecanismo antissifão, corroborando as conclusões de Kajimoto, enquanto em outros pacientes com complacências alteradas pode ser extremamente difícil tratar a hidrocefalia por DVP (sem incidência de hiperdrenagem), apesar do emprego concomitante de diversos mecanismos antissifão⁹⁵.

No trabalho intitulado *Performance of fixed-pressure valve with antisiphon device Sphera® in hydrocephalus treatment and overdrainage prevention*, aceito para publicação em *Arquivos de Neuropsiquiatria* em 1 de junho 2012 (Anexo 4), 35 pacientes com distúrbio hidrodinâmico cerebral (hidrocefalia ou pseudotumor cerebral) foram estudados, sendo selecionados propositadamente portadores de hiperdrenagem ou pacientes com hidrocefalia e com alta suscetibilidade para hiperdrenagem para testar o desempenho da válvula de pressão fixa com antissifão Sphera®. O mecanismo antissifão de membrana promoveu melhora clínica, detectada e sustentada em 94,3% dos pacientes no período de 2 anos, sem indícios tomográficos de hipo ou hiperdrenagem e sem complicações significativas imediatas, precoces ou tardias. A única complicação detectada nessa casuística foi infecciosa, não relacionada ao desempenho funcional da válvula.

A escolha da válvula de pressão média para os casos de pseudotumor (6 dos 35 pacientes) e de pressão baixa para HPNi (15 dos 35 pacientes) foi adequada para tratar esses distúrbios hidrodinâmicos. O

processo cicatricial não atrapalhou o funcionamento do mecanismo antissifão de membrana. O caso de HPN que apresentou discreta piora da marcha após o primeiro ano de melhora, não exibiu sinais radiológicos de hipo ou hiperdrenagem; parece que a piora decorreu de progressão da doença sem relação com a hidrocefalia por alteração funcional da DVP.

O mecanismo antissifão de membrana tem duas vantagens. A vantagem técnica existe porque a válvula pode ser colocada em qualquer posição, no crânio que funcionará com adequação, diferentemente do mecanismo gravitacional no qual o posicionamento vertical das esferas é fundamental para o funcionamento adequado do sistema. Outra vantagem implica na proteção antissifão independentemente da postura (decúbito ou ortostase). O mecanismo antissifão de membrana pode ser utilizado em derivação ventricular para a pleura, situação na qual os gradientes de pressão inspiratórios, mesmo em pacientes deitados, podem produzir hiperdrenagem.

3.6 Protocolo de ajuste da válvula de pressão programável Strata® (Medtronic)

A possibilidade de se programar a pressão de funcionamento da válvula depois de implantada no paciente tem duas potenciais vantagens: evitar os efeitos nocivos da hiperdrenagem, como hematoma subdural e síndrome dos ventrículos colabados; e possibilitar incremento do resultado terapêutico, uma vez que é possível drenar mais liquor reduzindo a pressão de funcionamento da válvula e, conseqüentemente, dos ventrículos, sem necessidade de troca cruenta do dispositivo, mas apenas utilizando um campo magnético local⁹⁸⁻¹⁰⁰. Obviamente, isto implica num cuidado em especial com exames de ressonância magnética, que podem desprogramar a válvula. Para evitar tal inconveniente, certas próteses suportam até 3 teslas de campo eletromagnético e possuem trava mecânica (Sophy Polaris®, Sophisa e Progav®, Aesculap)¹⁰¹⁻¹⁰².

O emprego dessas válvulas programáveis mudam o paradigma de seguimento clínico dos pacientes com HPN. É preciso um acompanhamento médico ainda mais próximo, principalmente no primeiro ano, pois reajustes podem representar melhora clínica e evitar complicações sem necessidade de reoperação. A utilização desse tipo de prótese para tratar pacientes com HPN é cada vez mais respaldada pela literatura¹⁰³⁻¹⁰⁴. Entretanto, não existe orientação formal, apenas sugestões baseadas em experiências locais de como lidar com os ajustes de pressão, possíveis com essas válvulas, bem como na escolha da pressão a ser utilizada inicialmente no implante da DVP^{102-103,105}.

A partir da elaboração de um protocolo de ajuste e seguimento para portadores de HPN submetidos a implante da válvula programável Strata® (Medtronic, EUA), 24 pacientes com HPNi, com tap test positivo e sem outras demências associadas foram prospectivamente tratados e acompanhados. Este trabalho, intitulado *A protocol for pressure adjustment of Strata® programmable valve in the follow-up of idiopathic normal-pressure hydrocephalus patients: a prospective study*, foi submetido para publicação em 16 de junho de 2012 em *Fluids and Barriers of the CNS*. (Anexo 9)

Os possíveis níveis de ajuste da Strata® são: 2,5, 2,0, 1,5, 1,0 e 0,5. Respectivamente, equivalem à seguinte pressão de abertura: 140, 110, 80, 40 e 20 mmHg. O protocolo consiste no implante da válvula regulada na sua pressão mais alta possível (nível 2,5, que equivale a 140 mmHg). Através de retornos mensais, seguidos de tomografia de crânio após a cirurgia e após o primeiro mês e, depois, sempre que ajustes fossem realizados, todos os pacientes foram acompanhados por 1 ano. Os ajustes de redução da pressão foram feitos até se atingir o máximo grau de melhora clínica, porém sem indícios de hiperdrenagem, sobretudo por observação tomográfica da formação de coleções subdurais. O número médio de ajustes da pressão da válvula foi 3 (variando de único ajuste em quatro pacientes a 6 ajustes em outros quatro pacientes). O nível final dos ajustes variou de 1,0 a 2,0, sendo 1,5 o nível final médio nessa casuística. A melhora clínica, comprovada por

três testes (MM, TUG e escala de HPN) e pela opinião subjetiva dos familiares, foi observada em 83% (20/24) dos pacientes em 1 ano de seguimento. Com este protocolo, a taxa de complicações foi de 20,8%, compatível com os menores valores assinalados na literatura (19,7 a 40%)^{64,98,103-106}.

4 Considerações Finais

A HPN é uma doença insidiosa que acomete, principalmente, idosos. É uma das poucas causas reversíveis de demência, respondendo por cerca de 5% dos casos. As hipóteses referentes à sua fisiopatologia baseiam-se, sobretudo, nas alterações da hemodinâmica cerebral e dinâmica liquórica. É fundamental que o diagnóstico da HPN seja realizado precocemente, com conhecimento sobre a doença e seus diferenciais, por parte dos clínicos, geriatras e neurologistas e que os pacientes com boas chances de responder ao tratamento sejam identificados com os testes preditivos funcionais adequados. Os critérios diagnósticos padronizados devem ser divulgados e difundidos, métodos universais de avaliação pós-cirúrgica devem ser estabelecidos, a fim de se definirem quais métodos terapêuticos são mais eficazes e seguros para o manejo cirúrgico da HPN.

Atualmente, o tratamento cirúrgico da HPN pode ser realizado por intermédio de procedimentos neuroendoscópicos ou do implante de prótese (derivação ventricular). Métodos menos invasivos e mais eficientes devem ser investigados para incrementar a qualidade de vida desses pacientes.

Nos 81 pacientes, portadores de HPNi com *tap test* positivo, operados desde 2007, distribuídos em três diferentes publicações (Anexos 3, 4 e 9), os tratamentos adotados foram: 15 DVP com válvula de baixa pressão fixa com mecanismo antissifão de membrana (Sphera®, HpBio), 16 TVE (Minop®, lente de 30°, Aesculap), 24 DVP com válvula programável (Strata®, Medtronic), 26 DVP com válvula de pressão fixa (PS Medical, Medtronic). A melhora clínica foi observada em 93% dos pacientes submetidos à DVP com a válvula Sphera® em 24 meses de seguimento; 75% com a TVE em 12 meses de seguimento; 76,9% com a DVP com a válvula PS Medical em 12 meses de seguimento e 83% com a DVP com válvula programável Strata®.

Conclui-se que tratar cirurgicamente os pacientes com HPNi implica em melhora clínica em pelo menos 75% deles no período de 1 ano, independentemente do tratamento escolhido.

Atualmente, existem quatro empresas que fabricam válvulas programáveis para tratamento neurocirúrgico da hidrocefalia: Medtronic (EUA), Sophisa (França), Aesculap (Alemanha) e Johnson&Johnson (EUA). O custo desse dispositivo no Brasil chega a ser 10 vezes mais caro que uma válvula de pressão fixa. Frente à superioridade de tratamento que este tipo de prótese pode assegurar em certos casos de HPN, três soluções são possíveis para redução do preço da cirurgia: a) desenvolvimento e fabricação de uma válvula programável nacional, com menor custo; b) redução de taxas e impostos para importação das válvulas programáveis já existentes no mercado; e/ou c) aplicação do melhor tratamento para cada paciente em particular, diante das opções atualmente existentes: válvula de pressão fixa, válvula de pressão fixa com mecanismo antissifão, válvula autorregulável (Orbis-Sigma®), válvula programável ou neuroendoscopia. Em especial, a última alternativa (c) tem sido a preocupação e busca do GHC. Acredito que, ao olhar de uma forma individual e humanizada para cada paciente portador de HPN, a escolha da terapia cirúrgica personalizada pode promover os melhores resultados funcionais e o menor custo operacional e com materiais.

A escolha do tema para redação deste texto sistematizado baseou-se no meu engajamento científico no atendimento e tratamento de pacientes portadores de HPN, mas também na importância que o problema representa para a sociedade que vem atingindo maior expectativa de vida e carece de ações que melhorem a qualidade de vida, além da longevidade.

5 Anexos

Anexo 1

Revisiting hydrocephalus as a model to study brain resilience

Matheus Fernandes de Oliveira*, Fernando Campos Gomes Pinto, Koshiro Nishikuni, Ricardo Vieira Botelho, Alessandra Moura Lima and José Marcus Rotta

Department of Neurosurgery, Hospital do Servidor Público Estadual de São Paulo, São Paulo, Brazil

Edited by:

João Ricardo Mendes Oliveira,
Federal University of Pernambuco,
Brazil

Reviewed by:

João Ricardo Mendes Oliveira,
Federal University of Pernambuco,
Brazil
Carlos Augusto Carvalho De
Mendonça, Federal University of
Pernambuco, Brazil

*Correspondence:

Matheus Fernandes de Oliveira,
Hospital do Servidor Público Estadual
de São Paulo, Avenida Pedro de
Abreu, 1900, Vila Clementino, São
Paulo, Brazil
e-mail: mfo@oliveira@yahoo.com.br

Hydrocephalus is an entity which embraces a variety of diseases whose final result is the enlarged size of cerebral ventricular system, partially or completely. The physiopathology of hydrocephalus lies in the dynamics of circulation of cerebrospinal fluid (CSF). The consequent CSF stasis in hydrocephalus interferes with cerebral and ventricular system development. Children and adults who sustain congenital or acquired brain injury typically experience a diffuse insult that impacts many areas of the brain. Development and recovery after such injuries reflects both restoration and reorganization of cognitive functions. Classic examples were already reported in literature. This suggests the presence of biological mechanisms associated with resilient adaptation of brain networks. We will settle a link between the notable modifications to neurophysiology secondary to hydrocephalus and the ability of neuronal tissue to reassume and reorganize its functions.

Keywords: hydrocephalus, resilience, brain, neural networks, plasticity

PRESENTATION

Hydrocephalus is an entity which embraces a variety of diseases whose final result is the enlarged size of cerebral ventricular system, partially or completely. Among usual classifications, the most important are those who differ the communicating from non-communicating and congenital from acquired. Its prevalence is near 1–1.5% among general population and is progressively rising with populational growth, thus representing an impressive healthy concern. Congenital hydrocephalus due to a myriad of causes has a rate of 1–2/1000 births, being a common finding among pediatric age (Rekate, 2009).

The physiopathology of hydrocephalus lies in the dynamics of circulation of cerebrospinal fluid (CSF). There should be a disturbance either in production, circulation, or in reabsorption, resulting in positive balances and dilation of ventricular system, producing abnormal high pressure on the ventricles walls. Elevated pressure reflects blocked blood flow out of the lateral ventricle. The consequent CSF stasis in hydrocephalus interferes with cerebral and ventricular system development (Penn and Linninger, 2009).

Responses to elevated CSF pressure can be marked oxidative changes in hydrocephalus that are reflected in the way that injured neurons metabolize neurotransmitters and myelin. Contrary to the previously held belief that gliosis in the hydrocephalic brain is restricted only to the periventricular white-matter, gliosis extends through all of the cortex and the peri-aqueductal area (Penn and Linninger, 2009).

The pathology of cerebral cortex in human hydrocephalus show nerve cells swelling. The neighboring neuropil exhibits notable enlargement of extracellular space, synaptic plasticity and degeneration, damage of myelinated axons, and myelination delay. The astrocytes reveal edematous changes and phagocytic activity.

Glycogen rich- and glycogen-depleted astrocytes are observed. Some oligodendroglial cells exhibit normal morphology, and other exhibit hydropic changes. The capillary wall shows signs of blood-brain barrier dysfunction. The role of ischemia, oxidative stress, increased calcium concentration, activation of NMDA receptors, and disturbance of ion homeostasis are discussed in relationship with the fine structural alterations of hydrocephalic brain parenchyma (Castejón, 2010).

Clinical manifestations depend especially on the time of appearance and form of onset, if acute/subacute or chronic. As a general rule, acute hydrocephalus produce pronounced symptoms as headache, vomiting, papilledema, and impaired consciousness, leading patient to coma and death (Drake, 2008). Chronic hydrocephalus, on other hand, produces skull enlargement, spasticity, progressive neurological deficits in children and dementia, urinary incontinence, and gait changes in elderly (Bergsneider et al., 2008; Ishikawa et al., 2008; Mizori et al., 2010).

The treatment, usually represented by some variation of a diversion procedure, consists in deviating CSF flux and acts by reducing intracranial pressure, restoring periventricular, and global perfusion (Bergsneider et al., 2008; Drake, 2008). In children, it is generally performed to restore CSF dynamics and prevent worsening of symptoms. In chronic cases, it controls symptoms of intracranial pressure and interfere in cognitive and motor functions (Ishikawa et al., 2008; McGirt et al., 2008; Ladika and Gurevitz, 2011).

Thus, the form of onset is also the great determinant of cerebral tissue response, leading to physical adaptations, changing elastance and complacency, determining chemical and biological changes, including neuronal plasticity (Penn and Linninger, 2009).

In this context, we will try to settle a link between the notable modifications to neurophysiology secondary to hydrocephalus

and the ability of neuronal tissue to reassume and reorganize its functions toward adaptation.

HYPOTHESIS

Computational models such as the “small-world” and “scale-free” network might explain clinical resilience in various situations (Friston and Price, 2003; Noppeney et al., 2004; Achard and Bullmore, 2007; Van den Heuvel et al., 2008). Small-world networks predicts that neuronal cells are engaged in clustered connectivity with fewer long-range connections (Friston and Price, 2003; Achard et al., 2006). Thus, there would be a shorter path length between any pair of neurons or brain regions, resulting in higher dynamical complexity, lower wiring costs, and resilience to tissue insults. A scale-free network is characterized by the existence of a small number of nodes having more connections than the other nodes. The nodes that have such a high connectivity degree are referred to as hub-nodes and are suggested to play an important role in the overall network organization (Friston and Price, 2003).

Brain resilience may be also the final result of processes such as redundancy, degeneracy, and pluripotentiality of neural systems (Friston and Price, 2003; Noppeney et al., 2004). Another possible mechanism would be the local neurogenesis already reported in structures such as the basal ganglia, with preferential distribution in sub-regions of the ventral striatum (Stoczyński et al., 2006).

SCIENTIFIC BACKGROUND

Neuronal plasticity is a continuous process where the central nervous system learn skills and remember information, structure neuronal networks in response to environment, and recover from brain and spinal cord injuries, being a fundamental tool in brain resilience to lesions (Johnston, 2009). Basic mechanisms that are involved in plasticity include neurogenesis, programmed cell death, and activity-dependent synaptic plasticity (Wojtowicz, 2011).

Clinical examples of adaptive neuronal plasticity include reorganization of cortical maps of the fingers in response to practice playing a stringed instrument and constraint-induced movement therapy to improve hemiparesis caused by stroke or cerebral palsy (Ewing-Cobbs et al., 2003; Johnston, 2009). Hydrocephalus, congenital or acquired, represents a model of brain resilience too, once transient or permanent perfusional deficits generate structural and/or functional injuries, being partially or completely compensated by remaining cortical areas (Ewing-Cobbs et al., 2003).

Much evidence shows that the brain has an astounding ability to modulate cognitive and motor skills after acute insults, during insidious neurodegenerative processes, psychological stress, or even along the aging course (Price and Friston, 2002; Menner et al., 2009; Oliveira et al., 2011). Permanent and transient lesions caused by strokes, tumors, head trauma, and hydrocephalus are good models to understand how the compensation process works, following focal or even broader damage (Price and Friston, 2002; Oliveira et al., 2011).

Classic examples were already reported in literature. John Lorber (1915–1996), a British pediatrician recognized by his work with spina bifida and ethnic issues in Sheffield University, had the opportunity of attending two young children with hydrocephalus presenting with normal mental development for their age. In both children, there was no evidence of a cerebral cortex, which was

filled by CSF. One of the children died at age 3 months, the second at 12 months. Later, a young man with macrocephaly was referred to Lorber (Lawin, 1980). Although the boy had an IQ of 126 and had a first class honors degree in mathematics, he had “virtually no brain.” Thus, he thought, there should be a tremendous amount of redundancy or spare capacity in the brain. These ideas were shared with scientific community in a pediatric conference in 1980. Later in the same year, his ideas were published by Roger Levin in *Science* magazine.

Additionally, Norman Geschwind (1926–1984), an American neurologist at Boston’s Beth Israel Hospital known for his works with behavioral neurology, also stated a certainty of capacity for reassigning functions following trauma and injuries in the brain, what should represent a high level of organization of cerebral tissue in order to promote adaptation (Berker et al., 1992).

Other reports even generate a scientific query in the past, where the main question was the seemingly normal brain function with remarkable images of hydrocephalus and congenital malformations (Lawin, 1980). For example, scans of a 44-year-old man’s brain, showed fluid-filled ventricles, leaving little more than a thin sheet of actual brain tissue. He was married and father of two children, and worked as a civil servant. The man went to a hospital after he had mild weakness in his left leg. He used to have a shunt inserted into his head to drain away hydrocephalus as an infant and was removed when he was 14. Intelligence tests showed the man had an IQ of 75, below the average score of 100 but not considered mentally retarded or disabled, either (Feuillet et al., 2007). In Figure 1, we try to illustrate this scene by presenting the brain parenchyma of a normal subject followed by the brain of a normal subject with impressive hydrocephalus (Oliveira et al., unpublished data) and then an equally impressive hydrocephalus of a patient with profound symptoms (Oliveira et al., unpublished data).

The surprising question is that patients with very similar neuro-radiological aspects may present with different and complex neurological impairments, from motor to cognitive.

DISCUSSION

Some important discussions about symptoms in hydrocephalic and non-hydrocephalic patients were already reported. Previous studies of 10 sets of twins discordant for hydrocephalus in early life displayed differences in quality and quantity of development of verbal versus non-verbal cognitive functions, birth order, and hand and eye preference (Berker et al., 1992). The differences between those discordant twins seems to indicate systematic changes in pre-, peri-, and/or early postnatal organization and development of hemispheric function (Berker et al., 1992).

Other study considering the development of five language domains (word finding, fluency and automaticity, immediate sentence memory, understanding of grammar, and metalinguistic awareness) was held in children and adolescents, 75 with hydrocephalus in the first year of life, and 50 normal controls (Dennis et al., 1987). The results revealed a limited resilience of language to the effects of early hydrocephalus (Dennis et al., 1987).

OUTCOME

In adult hydrocephalus, especially idiopathic normal pressure hydrocephalus (INPH), it is observed recover after shunting

FIGURE 1 | The contrast among a normal brain in a normal adult (left), the brain of a normal man with impressive hydrocephalus (Oliveira et al., unpublished data; middle), and an equally impressive hydrocephalus in a 54-year-old man with deep cognitive and motor impairment since childhood (right; Oliveira et al., unpublished data).

FIGURE 2 | Neuroimaging in normal pressure hydrocephalus.

procedures, which represents proof of brain resilience (Bergsneider et al., 2008; Ishikawa et al., 2008; Ladika and Gurevitz, 2011). A study displayed significant improvements at follow-up demonstrated on tests of verbal memory as well as in one test of psychomotor speed. Eight of 10 patients showed improvement by more than 1 SD on at least one memory test. Six of 10 patients improved significantly on more than 50% of the tests administered (McGirt et al., 2008; Simon et al., 2009). Our own experience with INPH shunting is also in accordance with literature results. Patients elected for surgery and with good response after execution of tap test in the pre-operative period, usually present a remarkable recovery in cognitive and especially motor functions gradually (Oliveira et al., unpublished data). In a report, there was a significant reversal in neuropsychological test scores with increased brain volume and increased regional cerebral glucose utilization in several brain regions after shunting of INPH (Simon et al., 2009; Figure 2).

Rat models of chronic hydrocephalus suggested that disturbance in the postsynaptic integration processes, rather than

axonal conduction or synaptic transmission, are more important for the production of the neurological deficits seen in chronic hydrocephalus (Kaye et al., 1990; Miller and McAllister, 2007; Kordziella et al., 2008). In the same models, it was found impaired hippocampal plasticity (Tsubokawa et al., 1988).

Recent evidences also hypothesize the role played by dopamine D2 receptors in normal pressure hydrocephalus. In NPH, D2 receptor down regulation was attenuated at 1 month after shunt surgery (Nakayama et al., 2007). A PET study showed significant increases of glucose metabolism in the cerebral cortical areas after surgery and a micro dialysis study showed a postoperative reduction in the glutamate content of the cerebral cortex, pointing that shunting and consecutively better regional perfusion reestablish the citoarchitecture and synthesis of dopamine D2 receptors, attenuating motor dysfunctions (Nakayama et al., 2007).

CONCLUSION

Therefore, several examples can be elicited to assign neural plasticity and resilience applied to hydrocephalic models, reassessing concepts of basic neurophysiology and discussing neural networks and integration, regeneration of neuronal tissue, and resilience to injuries. Degeneracy and resilience are probably continuous and simultaneous events taking part in this complex process.

We should not forget that, as long as there are large hydrocephalic, tumoral, traumatic, and ischemic samples of brain resilience and recovery, there are also cases of specific and punctiform lesions, sometimes only seen in high definition image studies, causing aggressive impairment of neurological function, even compatible with death.

Clinical experience and experimental models have already shown the resistance of the brain tissue to injuries, acute or chronic. Until now, what we have summarized are pieces of individual reports and atypical manifestations of neurological diseases. Doubtlessly, further multicenter investigations will be needed to clarify the infinite questions asked about neuronal tissue physiology.

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Anexo 2

FERNANDO CAMPOS GOMES PINTO

HIDROCEFALIA

de pressão normal (HPN)

Do reconhecimento da doença ao
tratamento multiprofissional

**HIDROCEFALIA DE PRESSÃO NORMAL (HPN)
DO RECONHECIMENTO DA DOENÇA AO TRATAMENTO MULTIPROFISSIONAL**

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Anexo 3

Neurosurgery

Endoscopic Third Ventriculostomy and Ventriculoperitoneal Shunt in Idiopathic Normal Pressure Hydrocephalus: A Preliminary Report of a Prospective Study

--Manuscript Draft--

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Corresponding Author:	Fernando Campos Gomes Pinto, Ph.D. Hospital das Clínicas, University of São Paulo, Brazil São Paulo, BRAZIL
Order of Authors:	Fernando Campos Gomes Pinto, Ph.D. Felipe Saad, MD Matheus Fernandes de Oliveira, MD Renan Muralho Pereira, student Fernanda Letkaske de Miranda, MD Juliana Benevenuto Tornai, MD Maria Izabel Romão Lopes, MD Eduardo Santamaria Carvalho Ribas, MD Emília Aparecida Valinetti, PhD Manoel Jacobsen Teixeira, PhD
Manuscript Region of Origin:	BRAZIL
Abstract:	<p>Background: Currently, the most often performed treatment for idiopathic normal pressure hydrocephalus (INPH) is the ventriculoperitoneal shunt (VPS), mainly with programmable valve implantation. The endoscopic third ventriculostomy (ETV) is a treatment option, with the advantage of not needing prosthesis implantation.</p> <p>Objective: To compare the functional neurological outcome after 12 months of treatment of patients with INPH through two different techniques: ETV or VPS.</p> <p>Methods: This was a prospective and randomized study of 42 patients with INPH and positive response to tap-test (TT), from January 2009 to January 2012. ETV was performed with rigid endoscope with 30° lens (Minop®, AËSCULAP) and VPS performed with fixed-pressure valve (PS Medical®, MEDTRONIC). The outcome occurs 12 months after surgery. The comparison of the neurological function outcome is carried out by the results of six clinical scales: mini-mental, Berg balance scale, dynamic gait index, functional independence measure, timed up and go and NPH scale.</p> <p>Results: There was no statistically significant difference between the percentage of patients who improved in both groups after 12 months of follow-up (ETV = 75%, VPS = 76.9%). However, when observing the degree of improvement through the mean score on each scale, VPS group showed the best results. Patients submitted to ETV that showed up and down movement of the third ventricle floor immediately after perforation ("flag signal"), showed clinical improvement.</p> <p>Conclusion: ETV and VPS promote clinical improvement in the same percentage of patients (75% and 76.9%, respectively), but the VPS shows the best functional neurological outcome 12 months after surgery.</p>
Suggested Reviewers:	<p>Michelangelo Gangemi Frederico II University, Naples, Italy mgangemi@unina.it Author - paper: "ENDOSCOPIC THIRD VENTRICULOSTOMY IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS: AN ITALIAN MULTICENTER STUDY",</p>

	<p>NORMAL PRESSURE HYDROCEPHALUS: AN ITALIAN MULTICENTER STUDY", Neurosurgery 63:62-69, 2008.</p> <p>Marvin Bergsneider Ronald Reagan UCLA Medical Center bergsnei@isurgery.medsch.ucla.edu Expert in Hydrocephalus</p>
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Cover Letter

18 MAY 2012

Nelson M. Oyesaku, MD, PhD, FACS, Editor-in-Chief, Neurosurgery®

The present manuscript is entitled: "ENDOSCOPIC THIRD VENTRICULOSTOMY AND VENTRICULO-PERITONEAL SHUNT IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS: A PRELIMINARY REPORT OF A PROSPECTIVE STUDY."

This article has not been submitted concurrently, accepted for publication, or published elsewhere. This study was performed at Hospital das Clínicas, University of São Paulo, São Paulo, Brazil. There is Ethical Adherence. There is no conflict of interest. There is no source of financial support.

The article has 10 authors, who contributed equally to the manuscript. Fernando Campos Gomes Pinto and Felipe Saad performed the surgeries and wrote the article. Renan Muralho Pereira, Matheus Fernandes de Oliveira, Fernanda Letkasko de Miranda, Juliana Benevenuto Tornai, Maria Izabel Romão Lopes, Eduardo Santamaria Carvalho Ribas, Emília Aparecida Valinetti and Manoel Jacobsen Teixeira also treated the patients, performed the literature review and participated in every clinical round to discuss the cases and write the article.

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Sincerely,

Fernando Campos Gomes Pinto
(on behalf of all the authors)

ENDOSCOPIC THIRD VENTRICULOSTOMY AND VENTRICULOPERITONEAL SHUNT IN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS: A PRELIMINARY REPORT OF A PROSPECTIVE STUDY

Fernando Campos Gomes Pinto PhD¹, Felipe Saad MD¹, Matheus Fernandes de Oliveira MD², Renan Muralho Pereira³, Fernanda Letkaski de Miranda MD¹, Juliana Benevenuto Tornai MD¹, Maria Izabel Romão Lopes MD³, Eduardo Santamaría Carvallal Ribas MD¹, Emília Aparecida Valinetti PhD¹, Manoel Jacobsen Teixeira PhD¹

- Department affiliations:

1. Division of Functional Neurosurgery of the Institute of Psychiatry, Hospital das Clínicas, Universidade de São Paulo, São Paulo, Brazil.
2. Neurosurgery Residency Program - Department of Neurosurgery - Hospital do Servidor Público Estadual de São Paulo, São Paulo, Brazil.
3. Neurosurgery League, Faculty of Medicine, University of São Paulo and medical student at Universidade Anhembis-Morumbi, São Paulo, Brazil

- This study was carried out at Hospital das Clínicas, University of São Paulo, São Paulo, Brazil. There is Ethical Adherence (CAPESQ 0348/09).

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- Corresponding author contact information:

Fernando Campos Gomes Pinto
Av. Angélica, 1968, cj.21
São Paulo, SP, Brazil
CEP 01228-200
FAX 55 11 3825-2444
neurofernando@gmail.com

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 2 IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS: PRELIMINARY REPORT OF A
 3 PROSPECTIVE STUDY

4
 5 ABSTRACT:

6 Background: Currently, the most often performed treatment for idiopathic normal pressure
 7 hydrocephalus (INPH) is the ventriculoperitoneal shunt (VPS), mainly with programmable valve
 8 implantation. The endoscopic third ventriculostomy (ETV) is a treatment option, with the advantage
 9 of not needing prosthesis implantation.

10 Objective: To compare the functional neurological outcome after 12 months of treatment of patients
 11 with INPH through two different techniques: ETV or VPS.

12
 13 Methods: This was a prospective and randomized study of 42 patients with INPH and positive
 14 response to tap-test (TT), from January 2009 to January 2012. ETV was performed with rigid
 15 endoscope with 30° lens (Minop®, AESCULAP) and VPS performed with fixed-pressure valve (PS
 16 Medical®, MEDTRONIC). The outcome occurs 12 months after surgery. The comparison of the
 17 neurological function outcome is carried out by the results of six clinical scales: mini-mental, Berg
 18 balance scale, dynamic gait index, functional independence measure, timed up and go and NPH
 19 scale.

20
 21 Results: There was no statistically significant difference between the percentage of patients who
 22 improved in both groups after 12 months of follow-up (ETV = 75%, VPS = 76.9%). However,
 23 when observing the degree of improvement through the mean score on each scale, VPS group
 24 showed the best results. Patients submitted to ETV that showed up and down movement of the third
 25 ventricle floor immediately after perforation ("flag signal"), showed clinical improvement.

26
 27 Conclusion: ETV and VPS promote clinical improvement in the same percentage of patients (75%
 28 and 76.9%, respectively), but the VPS shows the best functional neurological outcome 12 months
 29 after surgery.

30 KEY WORDS: Endoscopic third ventriculostomy, cerebrospinal fluid shunts, idiopathic normal
 31 pressure hydrocephalus.

32 RUNNING TITLE: Ventriculostomy or shunt for hydrocephalus

1 INTRODUCTION

2 Idiopathic Normal Pressure Hydrocephalus (INPH) is characterized by progressive gait
3 apraxia, cognitive dysfunction and urinary incontinence (Hakim-Adams syndrome) associated with
4 communicating hydrocephalus (as demonstrated by brain CT or MRI) and cerebrospinal fluid (CSF)
5 pressure within the normal range (7-24 cm H₂O). The clinical triad of Hakim-Adams syndrome is
6 present simultaneously in approximately 50% of cases; however, only one or a combination of two
7 symptoms should also be considered for diagnostic investigation.(1, 11, 12)

8 Currently, there are two main therapeutic options: ventriculoperitoneal shunt (VPS) and
9 endoscopic third ventriculostomy (ETV). The most widely accepted and performed option is the
10 VPS, especially with the programmable valve implantation. Nevertheless, the surgical treatment of
11 patients with INPH is a consensus, as it has a positive impact on the course of the disease natural
12 history.(7, 23)

13 In 2008, an Italian multicenter study showed benefits of ETV in the treatment of 110
14 patients with NPH, with at least a 24-month follow-up, showing that 69.1% of patients improved.
15 (10) This therapeutic success rate is consistent with the results obtained with the VPS, ranging from
16 69 to 90%. (3, 15, 17, 19, 24, 25, 28). However, that was a retrospective study and patients were not
17 submitted to predictive functional tests such as the tap test (TT), as suggested by literature
18 consensus.(14)

19 Thus, through a prospective randomized study, our objective is to compare the treatment
20 functional neurological outcome of patients with INPH through two different techniques: VPS or
21 ETV.

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1 METHOD

2 Prospective randomized study, carried out from January 2009 to January 2012, in patients with
3 INPH, at the Institute of Psychiatry, Hospital das Clínicas, Faculdade de Medicina da Universidade
4 de São Paulo, after approval by the ethics committee (CAPPESQ 0348/09).

5 The adopted diagnostic criteria for probable INPH were: (22)

- 6 a) Clinical: progressive clinical picture of gait apraxia, cognitive impairment (recent memory
7 and executive functions, mainly) and sphincter incontinence (urinary and/or fecal). The
8 presence of only one or a combination of two symptoms is also seen as suggestive criterion
9 of the diagnosis. No personal history of subarachnoid hemorrhage, head trauma, cranial
10 neurosurgery for any reason or prior history of central nervous system infection.
- 11 b) Radiological: ventricular dilation, confirmed by brain computed tomography (CT) and
12 magnetic resonance imaging (MRI), showing only the communicating hydrocephalus and
13 Evans index (EI) > 30%.
- 14 c) Manometric: cerebrospinal fluid pressure within the normal range, demonstrated by the
15 opening pressure on lumbar cerebrospinal fluid puncture between 7 and 24 cm H₂O.

16

17 - Inclusion criteria: diagnosis of probable INPH, age 55-75 years, duration of symptoms < 24
18 months, preserved ambulation even with two supports, absence of other dementia syndromes,
19 absence of malignant disease, compensated clinical comorbidities (hypertension, diabetes,
20 hormonal disorders), positive tap-test (TT) result and free and informed consent signed by patients
21 and family members.

22 - Exclusion criteria: diagnosis of secondary NPH, age < 55 or > 75 years, duration of symptoms >
23 24 months, other associated dementia syndromes, incapacity to walk, malignancy, uncontrolled
24 clinical comorbidities, negative TT test result, refusal to participate in the study by family and
25 patient.

26 The TT was performed in the preoperative period to determine the CSF pressure and
27 therapeutic prognosis by the withdrawal of 40 mL of cerebrospinal fluid. (26, 27) Clinical
28 evaluation was performed by a multidisciplinary team consist of a neurosurgeon, neurologist and
29 physiotherapist. Two pre-TT evaluations were performed with a one-week interval. After lumbar
30 puncture, two other evaluations were performed after 3 and 72 hours. Each evaluation consisted of
31 six clinical scales, and the TT was considered positive when the patient had a 10% higher score on
32 at least two of the six scales, always considering the best result of the two pre-TT evaluations and
33 the two post-TT assessments for comparison.

34

1 **SCALES USED:**

2 1. Mini Mental Status Examination – MM (5, 9)

3 Objective: to evaluate cognitive alterations.

4 Score: 0 – 30 (higher is better).

5

6 2. The Berg Balance Scale - BERG (2, 16)

7 Objective: to evaluate the functional balance capacity in different positions: sitting, standing
8 position and leg support.

9 Score: 0 – 56 (higher is better).

10

11 3. Functional Independence Measure – FIM (8)

12 Objective: to assess the degree of dependence for functional activities of daily living. Score: 18 -
13 126 (higher is better; 18-36 total dependence, 37-90 moderate dependence and 91-126
14 Independent).

15

16 4. Dynamic Gait Index – DGI (6)

17 Objective: to assess disorders of gait dynamics. The individual is submitted to a walking test,
18 consisting of walking 6 meters while making acceleration and deceleration movements and going
19 through obstacles.

20 Score: 0 – 24 (higher is better).

21

22 5. NPH Japanese Scale – NPH SCALE (17)

23 Objective: to score the patients according to undo clinical characteristics of the NPH triad.

24 Score: 0 – 12 (higher is worse).

25 GAIT DISORDER

26 0.....Absent

27 1.....Unstable gait, but independent

28 2.....Walks with 1 support

29 3.....Walks with 2 supports or walker

30 4.....Cannot walk

31 DEMENTIA

32 0.....Absent

33 1.....No apparent dementia, but apathetic

34 2.....Socially dependent, but independent at home

1 3.....Partially dependent at home

2 4.....Totally dependent

3 URINARY INCONTINENCE

4 0.....Absent

5 1.....Absent, but has polaciuria or urinary urgency

6 2.....Sometimes, only at night

7 3.....Sometimes, even during the day

8 4.....Frequently

9

10 6. Timed Up and Go – TUG (21)

11 Objective: to assess mobility and balance. The test quantifies functional mobility in seconds using
12 the time during which the individual performs the task. The time is measured from the moment
13 when the individual rises from the chair, walks for 3 meters up to a predetermined point, and returns
14 to the chair and sits down.

15 Normal performance for healthy adults: 10 – 12 seconds

16 Normal for impaired adults: 12.01 – 20 seconds

17 Functional impairment: > 20.01 seconds.

18

19 Electronic randomization was performed in the operating room after the patient had been
20 anesthetized. The patients were divided in two groups: Group 1 – ETV and Group 2 – VPS.

21 ETV was performed via a right precoronal bur hole (Kocher's point) with a rigid ventricular
22 neuroendoscope, 30° lens (Minop®, AESCULAP). The floor of the third ventricle was bluntly
23 perforated in the midline halfway between the mammillary bodies and the infundibular recess. The
24 fenestration was subsequently enlarged by inflating the balloon of a 4-Fr Fogarty catheter. The
25 ventriculostomy size was approximately 4–6 mm.

26 VPS was performed via a right precoronal bur hole (Kocher's point). The chosen valve
27 pressure (PS Medical®, MEDTRONIC) was based on the final manometry value at the TT. After
28 removal of 40 mL, final pressure of < 4 cm H₂O, the low-pressure valve was selected; final
29 pressure between 4 and 10 cm H₂O, the medium-pressure valve was selected and final pressure >
30 10 cm H₂O, high-pressure valve was selected.

31 All patients were followed for 12 months, with pre-scheduled consultations at 3, 6 and 12
32 months after surgery. At these visits, they were evaluated through the six scales at 3 and 12 months.
33 After one year, the late postoperative result was classified as positive when the patient had 10%
34 higher score on at least two of the six scales.

Complications such as cerebrospinal fluid leak, infection, shunt malfunction or hyperdrainage were strictly observed, treated and recorded for later comparison between groups.

In the immediate postoperative period and after 6 months, all patients underwent brain CT. In patients submitted to ETV and who did not show clinical improvement within 3 months, we performed a magnetic resonance with CSF flow study to determine the patency of the orifice on the third ventricle floor and the patient underwent VPS with fixed pressure valve. These patients were considered as ETV failure. The evolution after the second procedure (VPS) was not used for statistical calculations.

Statistics

In this study, numerical data are presented as mean with range. Categorical data are presented as percentages. Statistical analysis of clinical results 12 months after surgery (improvement or unchanged/worse) was performed by Fisher's exact test. Probability values < 0.05 were considered significant.

RESULTS

Of a total of 90 patients diagnosed with NPH treated in this period, 48 were excluded as they did not meet the inclusion criteria for this study. Forty-two patients were enrolled. Of these, 24 were men and 18 were women. The age ranged from 60 to 75 years (mean, 70 years). Twenty-one had the complete NPH clinical triad, 10 had gait apraxia and cognitive impairment, 4 had gait apraxia and urinary incontinence and 7 had gait apraxia, only. All had communicating hydrocephalus at CT and MRI, and the EI ranged from 30 to 50.6% (mean, 38.9%).

At TT, the initial pressure ranged from 20 to 12 cm H₂O (mean, 15) and the final pressure after the withdrawal of 40 mL ranged from 12 to 2 cm H₂O (mean, 6). Chemocytological analysis was normal in all samples and showed no reaction for syphilis, tuberculosis, cryptococcosis or neurocysticercosis.

Table 1 shows homogeneous values of the scores on six scales before and after TT and the postoperative follow-up period (3 to 12 months).

Group 1 – ETV

Of the 21 patients randomized to ETV, 5 had anatomical features that made the endoscopic procedure dangerous. One patient had a dolichobasilar artery that was in contact with the third

1 ventricle floor and 4 patients had short distance (<5 mm) between the brain stem and the clivus.
 2 These five patients were relocated to Group 2 for safety reasons, to avoid basilar artery injury. In
 3 the 16 patients that constituted Group 1, the initial pressure ranged from 18 to 10 cm H₂O (mean,
 4 15) at TT, and the final pressure after the withdrawal of 40 mL ranged from 12 to 3 cm H₂O (mean,
 5 6).

6 Of the patients submitted to ETV, four showed no clinical improvement after 3 months,
 7 underwent MRI and had a patent orifice in the third ventricle floor. They were then submitted to
 8 VPS, but only 2 (50%) showed improvement after 1 year of follow-up. The other 12 patients
 9 (12/16, 75%) improved at 3 months after ETV, but it was partially maintained after 12 months.

10 In the 12 patients that had some degree of clinical improvement, oscillatory up and down
 11 movements were observed on the third ventricle floor in the intraoperative period, immediately after
 12 ETV ("flag signal"). The four patients who did not improve showed no "flag signal".

13 There were no intraoperative or postoperative complications such as bleeding, fornix injury,
 14 infection, hematoma or cerebrospinal fluid leaks.

15 No patient submitted to ETV showed significant reduction in ventricular size on brain CT.
 16 The EI ranged from 31 to 50.6% (mean, 39.7%) preoperatively to 31 to 49.1% (mean, 39.1%) 6
 17 months after ETV.

18

19 Group 2 – VPS

20

21 In the 21 patients randomized to VPS and the 5 patients relocated from Group 1, 17 low-
 22 pressure valves were initially implanted and 9 medium-pressure ones (PS Medical®,
 23 MEDTRONIC).

24 At TT, the initial pressure ranged from 20 to 12 cm H₂O (mean, 16) and the final pressure
 25 after the withdrawal of 40 mL ranged from 10 to 2 cm H₂O (mean, 6).

26 In this group, 5 patients (5/26, 19%) who underwent implantation of a low-pressure valve
 27 had overdrainage with significant reduction in ventricular size and chronic subdural hematoma.
 28 They underwent reoperation with hematoma drainage and valve replacement for a medium-pressure
 29 one (PS Medical®, MEDTRONIC).

30 After 3 and 12 months of follow-up, 20 patients (20/26, 77%) showed improvement criteria.
 31 No patient showed signs of infection.

32 In the remaining patients, ventricular reduction on skull CT at 6 months was slight, but
 33 evident. In these patients, EI ranged from 30 to 48.1% (mean, 38.1%) preoperatively to 26.6 to
 34 41.4% (mean, 36.6%) 6 months after VPS.

Comparison between the groups

The ETV Group had slightly better scores on some scales (MM, BERG, NPH SCALE and TUG) after 3 months, but this improvement was partially maintained after 12 months and the scores regressed on some scales (BERG, DGI), whereas the TUG returned to pre-TT values (Table 1).

The VPS Group showed better scores in motor scales after 3 and 12 months (BERG, FIM, DGI, NPH SCALE and TUG). In addition to maintaining the improvement achieved at 3 months, it showed an increase in two additional scales (FIM and NPH SCALE). In the other scales, the variations were not significant and were considered stable. The TUG test score was considered better than the pre-TT value (Table 1).

The results were analyzed by Fisher's exact test, showing that there was no statistically significant difference between the percentage of patients who improved in both groups after 12 months of follow-up (Table 2). However, when observing the degree of improvement by the mean score on each scale for each group after 12 months, it is observed that the VPS group showed better results. The ETV group showed similar values to the initial pre-TT ones after 12 months (Table 1).

DISCUSSION

The identification of patients with INPH and implementation of effective treatment is the current challenge of Medicine and Neurosurgery. This is a disorder classified as a type of dementia, which affects the elderly, and can be reversed if promptly diagnosed and treated.

With the improvement in quality of life and consequent increase in life expectancy, it is expected that a greater number of elderly individuals will suffer from this disease. In 2008, the incidence and prevalence of INPH was identified in a stable community of 220,000 inhabitants in Norway, with values of 5.5/100,000 and 22/1,000,000 respectively. (4)

The currently recommended treatment is the implantation of VPS with programmable valve. However, this type of treatment has the inconvenience of prosthesis implant, and presents a medium to long-term risk of complications requiring reoperation, such as infection, mechanical malfunction and overdrainage. The UK registry shows VPS reoperation rates for the treatment of hydrocephalus in adults in general, of 22% in five years. (18) The siphoning effect, responsible for overdrainage, can be partially controlled with an anti-siphoning device associated with the valve system, a flow-regulated valve or by changing the programmable valve opening pressure so that overdrainage indications can be detected (subdural fluid collections). (13)

Thus, if the INPH patients could be treated by ETV with the same long-term results of VPS, this would be a great benefit to reduce the risk of complications in the medium and long term. This would be an advantage for elderly patients, who often have comorbidities.

The Italian multicenter retrospective study published in 2008 caused great debate in the neurosurgical community, by showing a treatment success rate of 69.1% of ETV in the treatment of 110 patients with INPH after a period of at least 2 years of follow-up. Much of the criticism toward this work originated from methodological reasons: lack of clear distinction between cases of idiopathic NPH and possible cases of secondary NPH, and because the predictive functional test was intracranial pressure monitoring and not the tests that are consensus in the literature, such as TT, lumbar infusion test and external lumbar drainage monitored for 72 hours. (10, 14)

Consequently, to answer these questions left unanswered in the literature, we improved the methodology and used in this study only patients with INPH with a positive response to the TT with preserved walking capacity. The design of the study is prospective and surgical treatment was randomized in the operating room, immediately after anesthesia induction. The initial objective was to compare the functional neurologic outcomes within 1 year after VPS with fixed pressure valve and ETV in the treatment of patients with INPH. In this study, we did not use the programmable valve prosthesis, as it is not available for use in the Brazilian public health system.

The TT showed to be a universal predictive test, with similar results for ETV and VPS. We observed that the percentage of patients who improved in the first year of follow-up was similar in both groups, with values similar to those found in the literature for VPS, ranging from 70 to 90%. (3, 15, 17, 19, 24, 25-28) However, patients treated with VPS showed a much more significant neurological functional gait improvement after 12 months than patients treated with ETV.

Five patients treated with VPS (5/26, 19%) showed overdrainage with significant reduction in ventricular size and chronic subdural hematoma. They underwent reoperation with hematoma drainage and valve replacement. We believe that it could be avoided using programmable valve.

The patients who did not initially improve with ETV had the VPS implanted and 50% improved after the second surgery, as already mentioned in literature. These patients had no pulse on the surgically opened third ventricle floor ("flag signal") immediately after the ETV. This finding was also described by Gangemi et al. and represents the most important information and predictive of therapeutic success of ETV. (10)

Our hypothesis to explain why ETV promotes functional improvement in these patients with INPH, when considering a communicating hydrocephalus, is that during systole, when there is peak intracranial pressure, the surgically opened third ventricle floor would function as a escape mechanism for this mechanical energy and, therefore, the frontal lobes, basal ganglia and thalami

1 receive a lower intensity of the pressure pulse. This would lead to improvement in blood perfusion
2 in these regions, enabling the functional recovery of neurons affected by the disease (INPH) in
3 progression. (20)

4 Considering the preliminary results of this first year of follow up, and taking into account
5 the common intraoperative characteristic (absence of the “flag signal”) in all cases of patients who
6 underwent ETV that did not improve, we suggest that if the therapeutic choice for patients with
7 INPH is the ETV and the “flag signal” is not observed intraoperatively the patient be immediately
8 submitted to VPS through the same burr, to avoid a new surgical anesthetic procedure in the future.

9 To assess the long-term evolution of ETV and VPS (five years), patients in this study
10 remain under surveillance and monitoring. Other patients who have recently been included in the
11 study, but not yet completed the follow-up period for observation, will increase our population for
12 future considerations.

13 Considering what has been observed so far, we cannot indicate the ETV as the best option
14 for initial treatment of INPH, as the VPS had better functional neurologic outcomes after 1 year.
15 However, the neurosurgeon should know that ETV can be considered a treatment option for INPH,
16 but with less significant clinical results than the VPS.

19 CONCLUSION

20 The ETV and VPS with fixed-pressure valve promote clinical improvement in the same
21 percentage of patients (75% and 76.9%, respectively), but VPS shows the best functional
22 neurological outcome 12 months after surgery. The positive predictive value of TT was similar for
23 both techniques. If the ETV is the adopted treatment option and “flag signal” is not observed
24 intraoperatively, we suggest that VPS implantation should be performed at the same surgery.

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Anexo 4

Performance of fixed-pressure valve with antisiphon device SPHERA® in hydrocephalus treatment and overdrainage prevention

Desempenho da válvula de pressão fixa com anti-sifão *SPHERA*® no tratamento da hidrocefalia e prevenção da ocorrência de hiperdrenagem

Título curto: Hydrocephalus: overdrainage prevention

Fernando Campos Gomes Pinto MD PhD¹, Renan Muralho Pereira², Felipe Saad MD¹, Manoel Jacobsen Teixeira MD PhD¹

1. Division of Functional Neurosurgery of the Institute of Psychiatry, Hospital das Clínicas, Faculty of Medicine, University of São Paulo, São Paulo, Brazil.
2. Liga de Neurocirurgia, Faculty of Medicine, University of Sao Paulo and medical student at the University Anhembi-Morumbi, São Paulo, Brazil

Correspondence:

Fernando Campos Gomes Pinto
 Av. Angélica, 1968 / cj.21
 CEP 01228-200 - São Paulo SP - Brasil
 E-mail : fernando.neuro@terra.com.br

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ABSTRACT

Patients with hydrocephalus and risk factors for overdrainage can be submitted to ventricular shunt (VS) implant with antisiphon device. The objective of this study is to prospectively evaluate for 2 years the clinical and tomographic results of the implant of fixed-pressure valves with antisiphon device *SPHERA*® in 35 adult patients with hydrocephalus and risk factors for overdrainage. Of these, three had congenital hydrocephalus in adult patients with very dilated ventricles (Evans index > 50%), three had symptomatic overdrainage after previous VS implant (subdural hematoma, hygroma or slit ventricle syndrome), 1 had previous chronic subdural hematoma, 15 had normal pressure hydrocephalus with final lumbar pressure < 5 cm H₂O after *tap test* (40 mL), 6 had pseudotumor cerebri and 7 had hydrocephalus due to other causes. Clinical improvement was observed and sustained in 94.3% of patients during the 2-year period with no CT evidence of hypo or overdrainage and no immediate early or late significant complications.

Key words: hydrocephalus, pseudotumor cerebri, cerebrospinal fluid shunts.

RESUMO

Pacientes com hidrocefalia e fatores de risco para hiperdrenagem podem ser submetidos ao implante de derivação ventricular (VS) com mecanismo anti-sifão.

O objetivo deste trabalho é avaliar prospectivamente os resultados clínicos e tomográficos do implante de válvulas de pressão fixa com anti-sifão *SPHERA*® em 35 pacientes adultos com hidrocefalia e risco de hiperdrenagem, acompanhados por 2 anos. Destes, três apresentavam hidrocefalia congênita em adulto, com ventrículos muito dilatados (Índice de EVANS > 50%); três tinham hiperdrenagem sintomática pós- derivação ventricular prévia (hematoma subdural, higroma ou slit ventricle syndrome); um apresentava hematoma subdural crônico pregresso; 15 apresentavam hidrocefalia de pressão normal com pressão lombar final < 5 cm H₂O após *tap test* (40mL); seis apresentavam pseudotumor cerebral; sete, outras causas.

A melhoria clínica foi detectada e sustentada em 94,3 % dos pacientes no período de 2 anos, sem indícios tomográficos de hipo ou hiperdrenagem e sem complicações significativas imediatas, precoces ou tardias.

Palavras-Chave: hidrocefalia, pseudotumor cerebral, derivações do líquido cefalorraquidiano.

Surgical treatment of hydrocephalus in adults is attained through the implantation of ventricular shunt (VS) systems, neuroendoscopy or through the association of both procedures, offering the possibility of significant neurological improvement¹.

The United Kingdom Shunt Registry showed in 13,206 adults with hydrocephalus submitted to VS implant, that 22% of patients required reoperation within 5 years².

Patients with hydrocephalus and risk factors for overdrainage can be submitted to VS implant with anti-siphon device. This valve-integrated device allows the patient, while in the orthostatic position, to increase the resistance to drainage of cerebrospinal fluid (CSF), reducing the siphoning effect that always occurs, thus avoiding overdrainage²⁻⁶.

The objective of this study is to prospectively evaluate for 2 years the clinical performance of fixed-pressure valve with *SPHERA*® antisiphon device in the treatment of 35 adult patients with hydrocephalus and high clinical susceptibility to overdrainage.

METHODS

After approval by the Ethics Committee, all patients admitted to the Cerebral Hydrodynamics Group (Division of Functional Neurosurgery of the Institute of Psychiatry; Hospital das Clínicas, Faculty of Medicine, University of São Paulo – HC FMUSP) from 01/01/2009 to 01/01/2010 with hydrocephalus and high risk for overdrainage, as the previously established inclusion criteria, were selected for implant of a fixed-pressure valve with antisiphon membrane mechanism (*SPHERA*®, HPBIO, São Paulo, Brazil) and clinical-radiological follow-up up to 01/01/2012.

The *SPHERA*® valve works through a coil spring mechanism, seat and ruby sphere. According to the characteristic of the spring, four strips of pressure difference ensure a flow of 21 ml/h, which corresponds to the physiological CSF production: extra-low (1-3 cm H₂O), low (3-7 cm H₂O), medium (7-11 cm H₂O) and high (11 to 14 cm H₂O).

The body of the prosthesis measures 42 x 14 x 6.5 mm. Its proximal portion contains the valve mechanism, the central part is a chamber for digital pumping or puncture, and its distal part contains the antisiphon membrane mechanism (Fig 1). When the pressure distal to the antisiphon mechanism becomes negative, the membrane temporarily occludes the system, avoiding overdrainage. This occurs when the patient is in the orthostatic position (up to -50 cm H₂O) or additionally during inspiration in patients with ventriculo-pleural shunt (up to -8 cm H₂O) (Fig 2).

The inclusion criteria were:

- Age > 16 years

- Clinical and radiological conditions considered to be high risk for overdrainage by VS: congenital hydrocephalus in adults with very dilated ventricles (Evans index > 50%); previous symptomatic overdrainage post-VS (subdural hematoma, hygroma or slit ventricle syndrome); previous chronic subdural hematoma (not related to VS); normal pressure hydrocephalus (NPH) with final lumbar pressure < 5 cm H₂O after *tap test* (40 mL); pseudotumor cerebri with VS indication.

Patients were evaluated for two years after surgery, through routine pre-established outpatient appointments with the Cerebral Hydrodynamics Group of HC-FMUSP: 10 days after surgery for stitch removal, 3 months [cranial computed tomography scan (CT) requested], 6 months, 1 year and 2 years after surgery. The evaluation criteria of patients were:

- Clinical: comparison of pre- and postoperative neurological assessment; postoperative infection; signs and symptoms of overdrainage or system malfunction (headache, postural headache, nausea, vomiting, visual alterations, altered level of consciousness);
- Radiological: pre- and postoperative CT, immediately after surgery and after 3 months (size of the ventricles, deviations of deep brain structures, patency and size of cisterns and cortical sulci, proximal catheter placement, subdural collections or hygroma).

RESULTS

The study included 35 patients, 21 men and 14 women. The age ranged from 16 to 86 years, with a mean of 51 years.

Table 1 shows the distribution of procedures by the hydrocephalus etiology and pressure valve used, indicating that two patients underwent ventriculo-pleural shunt and that 3 patients had symptomatic overdrainage after previous derivation.

Clinical Assessment

After 24 months of follow-up, thirty-three patients showed clinical improvement (33/35 = 94.3%). A patient with hydrocephalus after traumatic brain injury by gunshot wound showed no alteration at the neurological assessment and a patient with normal pressure hydrocephalus initially improved for one year, but showed a slight worsening in gait after 2 years of follow-up. In these two patients (2/35 = 5.7%), the valve worked

normally at digital compression of the pumping chamber and there was a decrease in ventricular dimensions with no evidence of overdrainage (subdural collections).

Patients with pseudotumor cerebri showed improvement in headache, sight and resolution of papilledema 3 months after surgery.

No patient had postural headache, nausea, vomiting or other signs of intracranial hypertension or hypotension during the 2 years of follow-up.

One patient with congenital hydrocephalus who had undergone five previous derivations, the latter being the implant of the low-pressure *SPHERA*® valve, showed postoperative ventriculitis; he was submitted to system removal, intravenous antibiotic therapy for 21 days and reimplantation of a new *SPHERA*® system and showed improvement at the neurological assessment.

The two patients submitted to ventriculo-pleural shunt showed improvement and had no complications.

Radiological assessment

The patients showed a reduction in ventricular size and no patient had subdural collections or hygroma.

The three patients who already had another valve and underwent surgery to treat the overdrainage condition showed an increase in ventricular dimensions and reduction of subdural collections associated with clinical improvement. Fig 3 shows the preoperative CT of one of these patients and the control CT 3 months after valve replacement. The resolution of bilateral subdural collection and ventricular increase was associated with improvement in postural headache with no signs or symptoms of intracranial hypertension.

In patients who underwent brain MRI for reasons other than hydrocephalus control, it was observed that the tested valve did not produce artifacts in image acquisition.

DISCUSSION

The main complications related to VS include: infection (meningitis, ventriculitis, abdominal cyst), mechanical malfunction (system obstruction or disconnection) and overdrainage (subdural collections, collapsed ventricle syndrome, subdural hematomas). All these complications are severe, will require reoperation and may cause death^{2,3,7-13}.

Currently there is a consensus that, whenever possible and indicated, one should avoid VS implantation when a high complication rate is identified in the long-term (mean of

60 months) of up to 51% of cases; in these cases, ventricular neuroendoscopic procedures are given preference^{12,14-16}.

To prevent infectious complications, the institutional adoption of protocols, such as first described by Choux, is what shows the most positive impact and control of these complications¹⁸. Catheters impregnated with antibiotics or silver also appear to reduce infectious complications^{17,18}.

The prevention of mechanical malfunction is related to good surgical technique and proper choice of the type of valve and the distal site of VS implant. The frontal trepanation seems to be related to better positioning of the proximal catheter, due to puncture suitability offered by this site, as it accepts a wider range of introduction angles, that through points in the occipital or parietal regions^{19,20}.

All implanted VS have a siphon effect when the patient is in the orthostatic position, as there is a pressure difference between the two extremities of the system that exceeds the valve opening pressure. The term "siphon effect" is more used to describe the physical phenomenon involved, ruled by well-known Law of Stevin ($p_f = p_0 + d \cdot g \cdot h$).

The term overdrainage is commonly used to describe the physiopathological mechanism by which an internal or external CSF shunt generates specific radiological or one of the related clinical syndromes: CSF hypotension, intracranial hypertension due to the expanding effect of a hematoma or by intermittent obstruction in the collapsed ventricle syndrome. The degree of overdrainage, and therefore the risk of clinical manifestations, is associated both with the intracranial pressure (negative) and the intracranial CSF volume. Patients with pseudotumor, for instance, may have a overdrainage image with normal or slightly negative intracranial pressure. Overdrainage is associated with compensatory intracranial and intraspinal hemodynamic alterations, mainly venous ones at first. Clinical manifestations do not always occur, which depend on factors such as pre-VS brain turgor, degree of cerebral atrophy, pain sensitivity and drainage speed.

To reduce overdrainage the choice of the fixed-pressure valve opening pressure should be appropriate for the patient to ensure the necessary CSF flow to treat the hydrodynamic disorder, but without causing excessive drainage and symptomatic intracranial hypotension²⁻⁶.

The programmable valves offer the possibility of adjustment after surgery without the need for reoperation. The flow-regulated shunt (Orbis-sigma valve) ensures a steady

flow and, in theory, would better adjust to each patient, but large samples have not shown a superior performance of this system¹³.

On the other hand, the antisiphon mechanism can be implemented in series with any type of valve and works by increasing the resistance to flow whenever the pressure differential ($p_0 = \text{ventricular} / \text{distal site} = p_f$) increases, preventing overdrainage and reducing the siphon effect. A number of siphon regulatory devices have been developed over the past two decades. Basically there are two types of antisiphon mechanisms: gravity (spheres or parts that move with the force of gravity, hindering and reducing flow) and membrane (thin, flexible membrane that occludes the system when the pressure difference increases due to a decrease in distal pressure)².

Many factors can influence the dynamics of cerebrospinal fluid drainage and these can be both hydrodynamic and related to individual physiological characteristics, which makes their knowledge essential when choosing the most appropriate drainage system for each patient and even to identify probable causes of hypo- or overdrainage. The main forces acting on the flow drained through the VS system are the intracranial pressure (ICP), intra-abdominal pressure (IAP) and hydrostatic pressure (HP), and the correlation between these forces results in the perfusion pressure (PP), which can be calculated using the following formula: $PP = HP + (ICP - IAP)$ ⁵.

Large increases occur, especially in hydrostatic pressure gradients, when the patient sits down or stands up, causing excessive CSF drainage. Kajimoto et al. evaluated the association between postural changes and CSF pressure in ventriculoperitoneal shunt systems implanted in thirteen patients with hydrocephalus, with no incidence of overdrainage. For that purpose, they simultaneously measured the pressures of the various compartments in the supine and sitting positions. With the patients in the supine position, ICP, IAP, and HP were 4.6 ± 3 mm Hg, 5.7 ± 3.3 mm Hg, and 3.3 ± 1 mm Hg, respectively. As a result, the PP was only 2.2 ± 4.9 mm Hg. However, when patients sat down, the IAP increased to 14.7 ± 4.8 mmHg, and ICP decreased to -14.2 ± 4.5 mmHg. The increase in IAP and decrease in ICP compensated the HP in 67% (42.9 ± 3.5 mmHg), and consequently the PP (14 ± 6.3 mmHg) corresponded to only 33% of HP. They demonstrated that the high IAP and low ICP have preventive effects and that high HP has promoting effects on overdrainage. In addition, they observed that only a small fraction of individuals with VS becomes symptomatic due to the effects of CSF overdrainage⁴.

The gravitational anti-siphon mechanism reinforces this protective physiological mechanism, so that the weight of the spheres would simulate an even greater increase in IAP. However, such mechanism should be implemented strictly in the vertical position to work properly. It has a rate of general complications identified in the long-term follow-up (mean of 60 months) of up to 21% of cases, of which 5% are related to hypodrainage¹².

The individual's physiological characteristics also make it difficult to determine not only the vertical level of CSF in the cranial-spinal compartment, but also of the fluid level in the cavity where it is absorbed. Thus, it is difficult to precisely calculate the vertical hydrostatic difference between the two compartments. Among the main physiological characteristics that influence the vertical hydrostatic gradient are the child's growth, increase in the compliance of the cranial-spinal compartment (such as spinal stenosis, Chiari malformation I, pseudotumor cerebri, and a large intracranial mass lesion). In addition, weight loss increases the compliance of the peritoneal cavity (favoring overdrainage) and extreme constipation can decrease intraperitoneal compliance (resulting in increased IAP). Therefore, two individuals of the same height may have differences in vertical hydrostatic gradient, either by a difference in the cranial-spinal compartment, or by a difference in the abdominal compartment. It is possible that overdrainage prevention can be more effective with a certain anti-siphon device than another. Moreover, even during sleep, and episodically, vasogenic brain alterations can cause an increase in intracranial pressure and thus, result in overdrainage (e.g., Lundberg's B waves).

These physiological characteristics may explain why many patients with healthy cranial-spinal compartment and peritoneal cavity appear to tolerate a ventriculoperitoneal shunt with or without the use of an antisiphon mechanism, supporting the conclusions of Kajimoto, whereas in other patients with altered compliances hydrocephalus can be extremely difficult to treat through ventriculoperitoneal shunt (with no incidence of overdrainage), despite the use of several concomitant anti-siphon mechanisms.

In this study, we purposely selected patients with overdrainage or patients with hydrocephalus and high susceptibility to overdrainage to test the performance of the *SPHERA*® valve. The membrane antisiphon mechanism ensured therapeutic success in 94.3% of patients and showed tomographic resolution of patients with overdrainage. The only complication detected in this sample was infectious, not related to the functional performance of the valve.

The choice of the medium-pressure valve for pseudotumor cases and low-pressure valve for NPH was adequate hydrodynamic to treat these hydrodynamic disorders. The healing process did not hinder the performance of the membrane antisiphon mechanism. The case of NPH who showed a slight worsening in gait after the first year of improvement, showed no radiological signs of hypo- or overdrainage; it seems the worsening was due to disease progression unrelated to hydrocephalus due to functional alteration of the VS.

The membrane antisiphon mechanism has two advantages. The technical advantage exists because the valve can be placed in any position in the skull to function properly, differently from the gravity mechanism, in which the vertical positioning of the spheres is critical to proper operation of the system. Another benefit is in the antisiphon protection, regardless of position (supine or standing position). The antisiphon membrane can be used in ventricular-pleural shunts, in which cases the inspiratory pressure gradients, even when patients are lying down, can cause overdrainage.

In conclusion, the fixed-pressure valve with anti-siphon device *SPHERA®* can be used to treat patients with hydrocephalus and prevent overdrainage. Clinical improvement was observed and sustained in 94.3% of patients for a two-year period, with no tomographic evidence of hypo- or overdrainage and no significant immediate complications, either early or late ones.

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ETIOLOGY	NUMBER OF PATIENTS	HIGH PRESSURE	MEDIUM PRESSURE	LOW PRESSURE
Pseudotumor cerebri	6 ^b	-	6	-
Normal pressure hydrocephalus	15 ^b	-	-	15
Thalamic arteriovenous malformation	2 ^b	-	2	-
Congenital hydrocephalus	3 ^{a,a}	1	2	1
Post-meningitis	4	-	3	-
Brain tumor	2	-	1	1
Subarachnoid hemorrhage	2	-	2	-
After traumatic brain injury	1	-	1	-
TOTAL	35	1	17	18

Table 1 – Etiology of the cerebral hydrodynamic disease, number of cases and valve pressure. All patients underwent VPS, except 2 patients (a) with congenital hydrocephalus. These patients underwent VS to pleura as it was not possible to use the peritoneum as the distal place (previously treated peritonitis) and the atrium was tried before, without success. Three patients had ventriculoperitoneal shunt (VPS) and hyperdrainage (b): one case with pseudotumor cerebri had slit ventricle syndrome, one Normal pressure hydrocephalus had

chronic subdural hematoma and one patient with thalamic arteriovenous malformation had bilateral hypertensive subdural collections and slit ventricle syndrome.

Fig 1 – Illustrative picture of the SPHERA® valve: spring coil mechanism, seat and ruby sphere; chamber for digital pumping or puncture and membrane-type antisiphon mechanism (when the pressure distal to the antisiphon mechanism becomes negative, the membrane temporarily occludes).

Fig 2 – Chart: Pressure x Flow [SPHERA® valve (extra-low, low, medium and high pressure) in the horizontal and vertical positions].

Fig 3 - Patient with thalamic arteriovenous malformation to the right and slit ventricle syndrome after prior VS for 3 months with PS Medical valve with medium pressure. (A) CT without contrast, axial view, showing preoperative status: collapsed ventricles, bilateral subdural collections and thalamic arteriovenous malformation to the right. (B) CT without contrast, axial view, three months after medium-pressure SPHERA® valve replacement: increased ventricular dimensions and resolution of bilateral collections.

Anexo 5

Original Article 103

Simulation of Endoscopic Third Ventriculostomy in fresh Cadaveric Specimens

Authors

A. D. C. Becerra Romero¹, C. A. Zicarelli¹, F. C. G. Pinto¹, C. A. Pasqualucci², P. H. P. Aguiar¹

Affiliations

¹ Department of Neurology of São Paulo Medical School, Division of Neurosurgery, Central Building, Hospital das Clínicas, São Paulo, Brazil² Department of Pathology, São Paulo Medical School, Brazil

Key words

- cerebral ventricles
- neuroendoscopy
- research methodology
- third ventricle
- endoscopic third ventriculostomy

Abstract

Objective: The purpose of this research is to describe and analyze the endoscopic anatomy of cerebral ventricles, especially of the lateral ventricle and third ventricle.

Methods: 47 brains of adult human cadavers were studied at the Death Check Unit (DCU) of São Paulo. Age, sex, day and approximate time of death, day and time of study, cause of death, outcome of puncture and number of attempts were recorded. A rigid neuroendoscope was utilized. The approach to the ventricular system was via the pre-coronal point on the right side.

Results: The number of individuals studied was 47, of which 22 (47%) were women and 25 (53%) were men. Age ranged from 20 to 95 years. The

minimum time lag between the death and the study was 8 h and the maximum time was 29 h. Of the cadavers studied, three presented alterations in the central nervous system as the cause of death. Successful puncture was obtained in 42 (89%) being 72% in the first attempt. In the analysis performed by Fisher's exact test with a 5% level of significance, an association between the number of attempts (2) and the cause of cerebral death was found ($p=0.018$).

Conclusions: The visualization of neural structures without bleeding, the possibility of training techniques such as third ventriculostomy, the development of new techniques and to help structure new concepts about anatomic landmarks have by far overcome the difficulties.

Introduction

Cerebral ventricles constitute the elected place where neuroendoscopy plays a well-defined role in procedures such as the third ventriculostomy. Several studies on ventricles with microsurgery dissection [1–6] have already been conducted and others focused on neuroendoscopy [7–12]. Difficulties carrying out neuroendoscopic studies on cadavers exist due to a number of reasons, namely specimens with normal ventricles and brains submitted to fixation. Which equipment was used in the study? What was the approach to the ventricular system of these specimens with normal ventricles? Is there any special age at which the ventricular puncture was more successful? The purpose of this research is to describe and analyze the endoscopic anatomy of cerebral ventricles, mainly of the lateral ventricle and third ventricle.

Methods

Forty seven brains of cadavers were studied in April 2008, on adult humans between 20–95 years of both sexes from the DCU of the University of São Paulo, Brazil, whose death had been natural. The cadavers were randomly selected from those submitted to the necropsy at the DCU in order to diagnose the cause of death. Cadavers with intracranial signs of fracture were excluded from the study. Age, sex, day and approximate time of death, day and time of study, cause of death, outcome of puncture and number of attempts were recorded. A successful puncture is understood to be up to 3 attempts: the identification of ventricular structures as the choroid plexus, the interventricular foramen and structures of the third ventricle floor. This study was approved by the Ethics Committee of the Clinical Board of Hospital das Clínicas and School of Medicine of the University of São Paulo in a session held on 05/30/2007, research protocol number 0363/07.

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Correspondence

A. D. C. Becerra Romero, MD
 Av Pirapó 150 apto 201
 Porto Alegre
 Brazil
 CEP 90470450
 Tel.: +55/51/33 34 87 94
 Fax: +55/51/33 34 87 94
 alicia21221@hotmail.com

Technical equipment: The Goob rigid neuroendoscope of Karl Storz was utilized, with 15-cm of length, 6.5-mm of diameter, equipped with a channel of instruments, 6° optics, xenon light source 175 W, with the following accessories: a micro-camera with 1 Charged-Coupled Device (CCD) as objective lens, a monitor LG LCD model M1721A and a DVD LG recorder D8205.

Approach to the ventricular system: The head was placed in supine position, midline with a support on the back of the patient (7 cm high), neck in extension. The approach to the ventricular system was via pre-coronal point on the right (0.5–1 cm anterior to the coronal suture and 1.5 cm lateral to the midline). Incision and burr hole were carried out. The dura mater was opened with a doctor's scalpel. After the burr hole and the opening of the dura mater, the frontal horn of the lateral ventricle was punctured perpendicularly, aiming at the intersection of a plane between the external auditory meatus and the medial corner of the ipsilateral eye and 6 cm deep. The endoscope was connected to the system and the recording system was switched on. From this moment on, continuous irrigation was utilized in all the cases. Once in the lateral ventricle, the orientation was established. If the subependymal vessels were seen to the left of the choroid plexus, the lateral left ventricle was punctured and if the vessels were seen to the right of the choroid plexus, the lateral right ventricle was then punctured. The following anatomic references were identified (Fig. 1): septum pellucidum (1), choroid plexus (2), anterior vein of septum pellucidum (3), thalamostriate vein (4) and interventricular foramen (5). When the ventriculoscope passed through the interventricular foramen, it entered the third ventricle, the following anatomic references were identified (Fig. 2): mammillary bodies (1), tuber cinereum (2) and infundibular recess (3). When the floor

of the third ventricle was fenestrated, simulating a third ventriculostomy (Fig. 3), the meniscus of Lissencephalus was identified (Fig. 4) and so was the basilar artery right after (Fig. 5, number 1). In some cases, it was possible to identify even the low cranial nerves (Fig. 6). Results were submitted to the statistical analysis of Fisher's exact test, with a significance level of 5%.

Results

The number of individuals studied was 47, of which 22 (47%) were women and 25 (53%) were men. Age ranged from 20 to 95 years, median 66 years, breaking down into four classes: 20–40 years $n=4$, 40–60 years $n=13$, 60–80 years $n=20$, 80–100 years $n=10$. The minimum time lag between the death and the study

Fig. 3 Third ventriculostomy was performed.

Fig. 1 Interventricular foramen.

Fig. 4 Lissencephalus meniscus.

Fig. 2 Floor of the third ventricle.

Fig. 5 Basilar artery.

was 8 hours and the maximum time was 29 h, mean 14.26 h. Of the cadavers studied 3 presented alterations in the central nervous system as the cause of death: two with cerebral edema and one with subarachnoid hemorrhage. Of the 47 cases, successful puncture was obtained in 42 (89%). In 72%, the first puncture was successful. In the first 5 attempts, there were 3 failures of the puncture observed. In the analysis through Fisher's exact test there is no evidence of an association among the variables age, sex, time between the death and the study, cause of death with successful puncture. However, an association between the number of attempts (2) and the cause of cerebral death ($p=0.018$) was found (Table 1).

Discussion

Upon choosing the method of studying ventricular neuroendoscopy, brains that had not been submitted to fixation were selected. The reason is that fixation may influence the size of ventricles leading to a cerebral edema [5] and consequently to a greater difficulty to puncture. Riegel et al. describe an endoscopic anatomic study of the third ventricle in the brain without fixation, with the idea of simulating the procedure and its physiological relations [13]. Something that might have influenced the negative outcome of the puncture is the fact that in the pathological examination, the ventricles usually look smaller in sections of the brain than *in vivo*, which may be due to the edema together with the reduction of the cerebrospinal fluid [5]. The first two days after death is the best time for the ventricular study, according to Resch et al. [14]. However, this study was conducted on specimens up to the first 29 hours after death and no statistically significant association with the success of the puncture was found. Despite reports by Resch et al. [14] that puncture in younger specimens may result in failure; this was not found in the present study. The death cause of cerebral origin was associated ($p=0.018$) with the degree of puncture difficulty (number of attempts >2), probably related to the cerebral edema, which had diminished the ventricular size. In the first

five attempts, three failures were observed, improving therefore the rate of success, since there were 2 modifications in the method: first, the alteration of the pre-coronal point from 1 to 0.5 cm anterior to the coronal suture and the placement of a support on the back of the cadaver, which made the ventricular puncture easier.

Why did we choose an approach other than the one known as the Kocher's point? The main reason is that, in the brains under study, the ventricles were from cadavers without hydrocephaly. Kocher's point locates the catheter on the frontal horn, this being the entrance place: two-thirds cm of the midline and 1 cm anterior to the coronal suture [15]. There are different reports as where the burr hole would be best for the third ventriculostomy: the position for the best burr hole for the third ventriculostomy is different in hydrocephalic patients, according to Duffner et al. [16]. For enlarged ventricles, Brockmeyer suggests: intersection of coronal suture with mid-pupilar line, with the trajectory of the endoscope medially directed and oriented aligned with the external acoustic meatus in antero-posterior direction [17]. As for small ventricles: the burr hole should be placed more medially to the mid-pupilar line [17]. Walker emphasizes that the patient's position is crucial; keeping the head in midline simplifies the surgeon's visualization of anatomic references [18]. Walker reports that planning the incision plays an important role in avoiding damage to the parenchyma, a third narrow ventricle requiring a more medial burr hole with a slightly more vertical trajectory [18]. Grant et al. defined through stereotaxis the burr hole point for ventriculostomy in 12 patients as being 15 to 30 mm lateral to the midline and between 10 mm to the front and 25 mm behind the coronal suture [19]. For Ernestus et al., in 30 patients with obstructive hydrocephaly submitted to the third ventriculostomy, the burr hole site was 1 cm anterior to the coronal and 2 cm lateral to the midline [20]. Navarro et al. place the burr hole for the third ventriculostomy in the coronal suture and slightly medial to the pupilar line [21]. Grotenhuis in his book [22] describes the distance of the dura mater to the interventricular foramen in 6 cm (in moderate hydrocephalic it is 4–4.5 cm) [22].

Advantages and disadvantages of the method utilized.

Advantages:

1. Procedure without bleeding facilitates visualization.
2. Possibility to study the anatomy.
3. Possibility to train the most utilized techniques and develop new ones.
4. Method very close to real procedure overrides any other model of artificially constructed ventricles.

Disadvantages:

1. Difficulty in puncturing normal ventricles in relation to hydrocephalic patients.

In the study by Duffner et al. [16] the measure of interventricular foramen through magnetic resonance on the coronal plane (width and height) in controls is 1.6×1.5 mm (average rates) and in hydrocephalic 7.3×7.4 mm (average rates), or 20 times

Fig. 6 Low frontal nerves.

Table 1 Correlation between the number of punctures and the cause of death.

cause of death			Number of punctures			
			0	1	2	3
cerebral	frequency		1	0	0	0
	%		20%	0.00%	28.57%	0.00%
other	frequency		4	34	5	1
	%		80%	100%	71.43%	100%

the size of the foramen of normal individuals. According to Duffner et al. [16] the average height of the 3rd ventricle is only 0.86 times greater compared to volunteers, but its width is 4.39 times greater in hydrocephalic (14.5 mm) than in the controls (3.3 mm).

2. The position with the back elevated causes air bubbles that may be removed by removing the cushion right after the puncture and also by using irrigation.

Despite all difficulties encountered, this method showed to be fully satisfactory in the intent to study the cerebral ventricles.

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Anexo 6

Article

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TREATMENT OF COLLOID CYSTS OF THE THIRD VENTRICLE THROUGH NEUROENDOSCOPIC Nd:YAG LASER STEREOTAXIS

Fernando Campos Gomes Pinto¹, Maria Cristina Chavantes²,
Erich Talamoni Fonoff¹, Manoel Jacobsen Teixeira¹

Abstract – **Objective:** Colloid cysts (IIVT CC) are benign neuroepithelial cysts located in the anterior third ventricle. The authors propose the use of Nd:YAG laser stereotactic neuroendoscopic for guided resection of the third ventricle colloid cysts. **Method:** Eleven patients presented third ventricle colloid cysts and were treated by Nd:YAG laser guided with stereotactic endoscopy (n=7), stereotactic endoscopy (n=3) or stereotactically guided puncture (n=1). The patients were followed prospectively (average 33 months, range 19–64 months). The clinical data, neuroimaging findings, hospitalization stay, outcomes and complications of the method were evaluated. **Results:** All patients presented headache; six had papilledema, one had gait disturbance and one had third-nerve palsy. Neuroimaging showed hydrocephalus and a IIVT CC with 14.4-mm mean diameter. After surgery all patients presented clinical and image improvement. Only two patients presented transient morbidities that were easily treated. One had diabetes insipidus that lasted for two days and was treated with a single dose of DDAVP, and another had chemical aseptic meningitis, probably due to the contact of the cyst content with the CSF. This patient was treated with antibiotics and corticosteroids with complete resolution of the problem without sequel. The other patients were discharged from the hospital 48 h after surgery. **Conclusion:** The stereotactic neuroendoscopy-guided procedure with Nd:YAG laser allowed the complete removal of the third ventricle colloid cysts, without definitive morbidities, sequelae or recurrence of the lesion.

KEY WORDS: laser, neuroendoscopy, third ventricle, colloid cysts.

Tratamento do cisto colóide do terceiro ventrículo por neuroendoscopia estereotática com laser Nd:YAG

Resumo – **Objetivo:** Os cistos colóides (CC IIVT) são lesões neuroepiteliais benignas localizadas anteriormente no terceiro ventrículo. Nós propomos a ressecção neuroendoscópica com o uso do Nd:YAG laser guiada por estereotaxia. **Método:** Onze pacientes portadores de cisto colóide do terceiro ventrículo foram tratados por neuroendoscopia estereotática com laser Nd:YAG (n=7), neuroendoscopia estereotática (n=3) ou punção estereotática (n=1) e foram seguidos prospectivamente (média 33 meses, variação 19–64 meses). Os dados clínicos, achados de neuroimagem, tempo de hospitalização, evolução e complicações referentes à técnica foram avaliados. **Resultados:** Todos pacientes apresentaram cefaleia; seis tiveram papiledeema, um apresentou distúrbio de marcha e um apresentou paresia do terceiro nervo. Os exames de neuroimagem evidenciaram hidrocefalia e CC IIVT com diâmetro médio de 14,4 mm. Depois da cirurgia todos os pacientes apresentaram melhora clínica e de imagem. Apenas dois pacientes apresentaram morbidades transitórias que foram facilmente tratadas: um apresentou diabetes insipidus que durou dois dias e foi tratada com uma única dose de DDAVP, o outro apresentou meningite química asséptica, provavelmente pelo contato do conteúdo do cisto com o líquido. Este paciente recebeu antibióticos e corticóide com resolução completa do problema. Os outros pacientes receberam alta hospitalar após 48 h. **Conclusão:** A ressecção neuroendoscópica com o uso do Nd:YAG laser guiada por estereotaxia possibilitou a remoção completa do cisto colóide sem morbidades definitivas, sequelas ou recorrência da lesão.

PALAVRAS-CHAVE: laser, neuroendoscopia, terceiro ventrículo, cisto colóide.

¹Division of Functional Neurosurgery of the Institute of Psychiatry, Hospital das Clínicas, University of São Paulo, São Paulo SP, Brazil; ²Laser Medical Center of the Institute of Heart of the Medical School, University of São Paulo, São Paulo SP, Brazil.

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Dr. Fernando Campos Gomes Pinto – Avenida Angélica 1968 / 21 - 01228-200 São Paulo SP - Brasil. E-mail: fernando.neuro@terra.com.br

Colloid cysts are benign unilocular cysts of neuroepithelial origin, consistently located in the anterior third ventricle¹¹. They represent 0.2 to 2.0% of all intracranial tumors¹⁵. Most of the cysts reported in the literature are symptomatic. The current consensus is that symptomatic colloid cysts should be treated; however, the treatment of asymptomatic colloid cysts without ventricular enlargement remains a controversial issue.

Several therapeutic options have been proposed for its treatment: non-surgical treatment with control of sequential images, shunting of cerebrospinal fluid, stereotactic aspiration of its content, microsurgical removal, stereotactically-guided endoscopy, neuroendoscopy, stereotactically-guided craniectomy and neuronavigation-assisted endoscopy²⁻⁹.

Since 1960, CO₂, Argon, Nd:YAG and Diode lasers have been used in neurosurgical procedures¹.

We propose the use of stereotactically-guided neuroendoscopy for the treatment of third ventricle colloid cysts and describe its use in eleven cases with Nd:YAG laser. This technique will be described herein.

METHOD

Eleven Caucasian patients, five males and six females, with ages ranging from 26 yrs to 61 yrs (mean 38 years old), with obstructive hydrocephalus due to third ventricle colloid cysts have been referred to the Hospital das Clínicas, University of São Paulo, Brazil, from 1992 to 2007 (period of fifteen years).

All patients presented obstructive hydrocephalus and third-ventricle colloid cyst at the CT and MRI images. The mean diameter of the lesion ranged from 7 mm to 22 mm (mean 14.4 mm). One patient with bilateral ventricular shunt presented slit ventricle and a 15-mm third ventricle colloid cyst.

Seven patients were treated with Nd:YAG laser neuroendoscopic, stereotactically guided, three patients were treated with

neuroendoscopic stereotactically guided, but without Nd:YAG laser and one patient was treated with stereotactically guided puncture for colloid cysts removal. The stereotactic frame (Micromart Diadema, São Paulo, Brazil) was fixed to the head of the patients under local anesthesia (2% lidocaine) and a stereotactic reconstruction of the brain and lesion was performed. The trajectory was constructed with CT and MRI aiming at the avoidance of the foramen, internal cerebral vein, septal veins and the center of the lesion was used as the target. A right frontal 18-mm trephination was used and a rigid neuroendoscope with a 30° lens (Chavantes-Zamorano Neuroendoscopy Storz® or Aesculap®) was attached to the stereotactic frame and its axis directed to the center of the lesion. We used in all surgeries, through the neuroendoscope working channel, a Nd:YAG Laser, CW (Surgilase®) with a 600-µm diameter silica fiber; contact mode was used in all cases.

Table 1 shows the treatment protocol. Table 2 shows the patients' age, gender, symptoms and CT/MRI findings at admission, operative procedures, date of surgery, morbidity, follow-up period, current clinical status and CT/MRI postoperative images.

RESULTS

All patients presented severe, constant or episodic headaches as the first symptom; six had papilledema, one had gait disturbance and another, diplopia.

A rigid neuroendoscope with a 30° lens and four channels (Aesculap®) was used and in the first case, the Chavantes-Zamorano neuroendoscope was used to monitor the intracranial pressure.

The neuroendoscopic approach was preferably carried out through the right lateral ventricle or through the more enlarged lateral ventricle (Fig 1). After the insertion of the neuroendoscope into the lateral ventricle, the anatomic landmarks such as septal vein, thalamostriate vein, choroid plexus and the Foramen of Monro were identified. The capsule of the cyst was then identified and coagulated.

Table 1. Treatment protocol.

1. Diagnosis based on clinical presentation and CT/ MRI with hydrocephalus and colloid cyst in third ventricle.
2. Neuropsychological examination.
3. Stereotomographic localization of the lesion.
4. Local or general anesthesia.
5. Neuroendoscopy guided by stereotaxis (frontal keyhole approach; right ventricle or the largest one) with 30° lens, identification of the lateral ventricle and the foramen of Monro.
6. Identification of the colloid cyst capsule.
7. Small hole in this capsule with Nd:YAG laser beam.
8. Aspiration of the content with a cannula.
9. Nd:YAG laser to vaporize the capsule with contact/non-contact shots.
10. First post-operative day CT.
11. Discharge after 48 hours.
12. CT first post-operative period, 3 months, 6 months, neuropsychological examination and afterward, annual MRI images of the brain.

Table 2. Patients' age, gender, symptoms and CT/MRI findings at admission, operative procedures, date of surgery, morbidity, follow-up period, current clinical status and CT/MRI postoperative images.

Patient	Age (yr) / gender	Symptoms at admission	CT/MRI findings at admission	Surgical procedure	Morbidity	Follow up (mo)	Current clinical status	CT/MRI control
1	32/F	Headache and vomiting	Hydrocephalus, 12 mm cyst	Endo-Laser+ Stereotaxis Local anesthesia	Fever 1 st day	54	Asymptomatic	No lesion, no hydrocephalus
2	35/F	Headache, vomiting, eye sight blurring	Hydrocephalus, 14 mm cyst	Endo-Laser+ Stereotaxis Local anesthesia	Headache and fever 1 st day	40	Asymptomatic	No lesion, no hydrocephalus
3	25/F	Headache, vomiting, eye sight blurring, bilateral ventricular shunt/slit ventricle	Slit ventricle, 15 mm cyst	Endo-Stereotaxis Local anesthesia	No	50	Asymptomatic	No lesion, slit ventricle
4	39/m	Headache, vomiting, eye sight blurring	Hydrocephalus, 16 mm cyst	Endo-Laser+ Stereotaxis General anesthesia	No	64	Asymptomatic	No lesion, Normal ventricles
5	52/m	Headache, vomiting, eye sight blurring	Hydrocephalus, 17 mm cyst	Local anesthesia+ Stereotaxis	No	28	Asymptomatic	No lesion, Normal ventricles
6	31/m	Headache, diplopia due to left III nerve syndrome	Hydrocephalus, 10 mm cyst	Endo-Laser+ Stereotaxis General anesthesia	Chemical meningitis	25	Asymptomatic	No lesion, Normal ventricles
7	35/F	Headache eye sight blurring	Hydrocephalus, 17 mm cyst	Endo-Laser+ Stereotaxis General anesthesia	No	23	Asymptomatic	No lesion, Normal ventricles
8	36/F	Headache, gait disturbance	Hydrocephalus, 17 mm cyst	Endo-Laser+ Stereotaxis General anesthesia	No	22	Asymptomatic	No lesion, Normal ventricles
9	61/m	Headache	Hydrocephalus, 7 mm cyst	Endo-Stereotaxis General anesthesia	No	20	Asymptomatic	No lesion, Normal ventricles
10	41/m	Headache	Hydrocephalus, 11 mm cyst	Endo-Laser+ Stereotaxis General anesthesia	Transient diabetes insipidus	20	Asymptomatic	No lesion, Normal ventricles
11	40/F	Headache, eye sight blurring	Hydrocephalus, 22 mm cyst	Endo-Laser+ Stereotaxis General anesthesia	No	19	Asymptomatic	No lesion, Normal ventricles

ed with contact Nd:YAG laser (20 Watts): a thin catheter was inserted through the working channel of the neuroendoscope and used for aspiration of the colloid content of the cyst. When the cyst became empty, the capsule was totally ablated by applying a Nd:YAG laser through a contact silica fiber inserted through the working channel of the neuroendoscope (Fig 2). Extra care was necessary with the laser application, in order to prevent damage to the hypothalamus and the fornix. Bleeding points were easily controlled with the application of contact laser.

All patients had CT scanning of the brain during the first 24 hours after surgery. No tumor and resolution of the preoperative hydrocephalus was observed in the acquired images.

One patient developed transient diabetes insipidus on the first postoperative day and was treated with a single dose of DDAVP. His discharge occurred five days later, without any symptoms or diabetes insipidus. One patient had chemical aseptic meningitis, probably due to the contact of the cyst content with the CSF. This pa-

Fig 1. Neuroendoscopic trajectory towards the upper aspect of the colloid cyst through one frontal burr hole. The stereotactic procedure defines the limits of boundaries of the cyst and its anatomical relationship with the floor of the third ventricle, foramen of Monro, veins, hypothalamus and fornix. The accuracy and safety of Nd:YAG laser resection was increased by the neuroendoscopic view and stereotaxis guidance.

Fig 2. The fiber of silica for Nd:YAG laser (diameter:600 µm).

of the hydrocephalus (Fig 3). The patients were followed prospectively (average 33 months, range 19–64 months).

DISCUSSION

Symptomatic colloid cysts are usually diagnosed in patients in their 2nd to 5th decades of life and equally affect both sexes. They can be asymptomatic, or present as paroxysmal headache with different severity degrees according to the position of the head, drop attacks, progressive or fluctuating dementia, clinical-like 'normal pressure hydrocephalus', or sudden death due to obstruction of the foramen of Monro followed by acute hydrocephalus⁴³. Non-contrast CT displays colloid cysts as a hypo-, iso-, or hyperdense, homogeneous and well-delineated round or ovoid masses. Contrast enhancement is absent or minimal. They are found incidentally at a rate of 1 in 1,000 CT. In MRI images, they present as homogeneously to heterogeneously hypointense or hyperintense masses in T1 and T2 weighted acquisitions. The outstanding characteristic is a sharply outlined round or ovoid mass in the anterior and superior third ventricle, near or at the foramen of Monro regions. Hydrocephalus is observed in most patients⁴.

The management of colloid cysts remains controversial. Several therapeutic options have been proposed for

tient was treated with antibiotics and corticosteroids with complete resolution of the problem without sequel.

Other patients were discharged from the hospital 48 h after the surgery; including two patients who had fever once time 24h after procedure.

Follow up

All patients had CT or MRI scanning of the head after the third, sixth and 12th month of the postoperative period. After the sixth month, all the patients underwent neuropsychological examination, without memory deficit. None of them presented recurrence of the lesion and

Fig 3. Patient #8: [A] Pre-operative CT of a 36 years old, female demonstrating hydrocephalus and a 17 mm colloid cyst of the third ventricle; [B] Pre-operative MRI, FLAIR, demonstrating hydrocephalus, transependymal edema and a 17 mm colloid cyst of the third ventricle; [C] First post-operative CT scan of the head showing complete removal of the colloid cyst, without evidence of blood in the surgical field, small pneumocephalus and reduction of the ventricles size; [D] Three month post-operative MRI, FLAIR, no tumor, no hydrocephalus and normal ventricles size.

asymptomatic and symptomatic patients. Non-surgical treatment and control image sequence can be the right attitude in asymptomatic cases, when the colloid cyst is small and the foramen of Monro is wide and no hydrocephalus is present⁵. Shunting of cerebrospinal fluid, stereotactic aspiration of its content, microsurgical removal, stereotactically-guided endoscopy, neuroendoscopy, stereotactically-guided craniectomy and neuronavigation-assisted endoscopy have been proposed for symptomatic patients^{3,4,9-11}.

Shunting is not recommended because the frequent problems related with the valves and the surgical procedures in the bilateral obstruction of the foramen of Monro requires bilateral ventricular shunting and it is not a curative treatment²⁷.

Open surgical excision of the colloid cyst was first successfully carried out by Walter Dandy in 1921. Microsurgical procedures are considered the gold standard for total removal by some authors¹². The transcortical approach, the transcallosal approach and the infratentorial-supracerebellar approach are the conventional techniques proposed for their removal⁶.

In 1975, Gutierrez-Lara et al first performed the free-hand puncturing of a colloid cyst and stereotactic aspiration was reported by Bosch in 1978. Stereotactically-guided aspiration should be performed in exceptional cases, because they often fail when the cyst content is hard^{27,28}. The success of aspiration is around 52%¹, and it is less effective than the open microsurgical or endoscopic procedures and the recurrence rate is high (62%)^{5,27,28}. This means that it can be indicated in patients with severe accompanying diseases⁵.

In 1983, Pawer et al.^{1,2} reported the first successful endoscopy aspiration of a third ventricle colloid cyst and after that, other authors replaced the open surgical procedures by endoscopy^{4,10,27}. The endoscopic removal is considered the therapy of choice, due to the satisfactory outcome^{2,3,10,27}, minimal rate of complications, short hospitalization time¹⁶, earlier return to the work and the reduced costs^{4,10,27-29}. Several endoscopic equipments have been described, but in general, the rigid endoscope is highly recommended and the most frequently used one^{3,5,26,30,31}. Neuronavigation-assisted endoscopy has shown to be an accurate and safe method^{3,23-25}.

The authors' intention is to reduce the invasiveness of intracranial procedures, while preventing brain tissue trauma in order to decrease the risk of neurological and mental deficits. The intracranial endoscopy proved to be a minimally-invasive technique that provides rapid access to the target via a small burr hole without the need for brain retraction, in contrast to craniotomy and microsurgical brain splitting and dissection that often causes injuries to the nervous tissues.

The endoscopic view may provide valuable additional information about the individual anatomy, which is not possible with the microscope; additionally, the aid of special instruments and bipolar diathermy, even highly vascularized lesions may be treated.

Laser is another interesting tool, useful for dissection or coagulation in many surgical procedures. It may also allow the resection of cyst capsule without causing bleeding or damage to the fornix, hypothalamus or the deep brain structures. The Nd:YAG laser has a 1064 nm wave length and it can penetrate 2.0 mm and 4.8 mm in the tissue when employed in the contact and non-contact modes, respectively. A 30° neuroendoscopy lens may provide a contralateral view of the capsule inside the third ventricle, enabling the use of the laser with direct visualization of all treated structures. The stereotactic method increases the safety of the laser application; considering the known limits of the lesion, the laser application to undesired structures can be prevented. In 1989, Abernathey et al. combined conventional and stereotactic techniques and achieved the total removal of the colloid cysts in twelve patients. They used bipolar cautery or defocused laser power to promote hemostasis. No mortality and minimal morbidity have been associated with the procedures and there was no evidence of recurrence in an average follow-up period of 19 months¹. In 1992, Merienne et al. reported on four intraventricular lesions (two colloid cysts of the third ventricle, one arachnoidal cyst and one intraventricular meningioma) surgically treated by endoscopic laser-therapy in stereotactic conditions. The laser beam (Nd:YAG) was used as a surgical knife on cystic lesions and also to vaporize the meningioma²⁸.

The stereotactically-guided neuroendoscopy and Nd:YAG techniques were used in seven of our eleven cases of colloid cysts and it ensured the safety of the use of laser inside the ventricles. The contact laser was very effective for hemostasis and the contact / non-contact laser were very useful to vaporize the empty cyst capsule. The total removal of the colloid cysts was possible without mortality or any evidence of recurrence in an average follow-up period of 33 months. The complications reported were such as intraoperative hemorrhage, memory deficit, mutism, third cranial nerve palsy, ventriculitis, seizures, venous infarction, fornix and thalamus contusion, transient or permanent hemiparesis and subdural fluid accumulation^{2,3,12,13,27,28}. In our series, only two patients presented transient morbidities that were easily treated: one had Diabetes insipidus that lasted for two days and was treated with a single dose of DDAVP, and another had chemical aseptic meningitis, probably due to the contact of the cyst content with the CSF. This patient was treated with antibiotics and corticosteroids with complete resolution of the problem without sequelae.

In conclusion, neuroendoscopic stereotactic-guided resection of the third ventricle colloid cysts is a very accurate, simple, safe and efficient treatment method. The Nd:YAG laser allowed total removal of the capsule without bleeding or neural damage.

Nd:YAG laser technology should be incorporated in the repertoire of the surgical instruments usually used in minimally-invasive surgery. It can be coupled to an endoscope that allows direct intraoperative visualization and monitoring the precise effects of the surgical maneuvers and its action is perfectly controllable, especially in areas where surgical traumatism must be avoided, such as the region of the fornices and the hypothalamus.

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Anexo 7

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SPECIAL ANNUAL ISSUE

Hydrocephalus in neurocysticercosis

Hamilton Matushita · Fernando Campos Gomes Pinto ·
Daniel Dante Cardeal · Manoel Jacobsen Teixeira

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Abstract

Introduction Cysticercosis (CC) is the most important of the parasitic diseases of the central nervous system due to its high incidence in the world. CC is the infection with the larval cysts of *Taenia solium*. It is the most common helminthic infection of the nervous system and is endemic in most underdeveloped countries as well as in industrialized nations. It is estimated that approximately 50,000 people die every year from neurocysticercosis (NCC) worldwide.

Discussion Humans with CC are incidental intermediate hosts, which replace the pig in the life cycle of the *T. solium*. Children are more frequently affected by parenchyma infestation of cysticercus, of which the main clinical manifestation is epilepsy. Hydrocephalus is more common in adults and is caused by cerebrospinal fluid blockage by ventricular cysts and inflammatory reactions (ependimitis/arachnoiditis). Treatment should be individualized based on clinical presentation, degree of infestation, location and viability of cysticercus, and host response. Hydrocephalus can be controlled only by removal of obstructive intraventricular cysts or associated with either ventriculoperitoneal shunt or endoscopic third ventriculostomy. The degree of infestation and complications related to the shunt represents the most important prognostic factors in the outcome of NCC.

Keywords Neurocysticercosis · Hydrocephalus · Infection · Arachnoiditis · Ependimitis · Ventriculostomy · Ventriculoperitoneal shunt

Introduction

Cysticercosis (CC) is the most important of the parasitic diseases of the central nervous system due to its high incidence, worldwide distribution, and variety of clinical presentations. Taeniasis and CC are old diseases, described since antiquity and are interlaced with the history of mankind. Humans are the only definitive host of *Taenia solium*; hence, its larval cysticercus needs to infect humans to reproduce. The recognition of swine CC was known since ancient Greece, the pig being considered as an impure animal. This was probably why the Koran forbade its consumption.

Neurocysticercosis (NCC) was first described in humans in the sixteenth century, although the nature of this disease remained unknown until the second half of the nineteenth century, when German researchers demonstrated that the larval form of *T. solium* was responsible for developing CC in animals and humans.

Epidemiology

CC is the infection with the larval cysts of the *T. solium*. It is the most common helminthic infection of the nervous system, endemic in most of Latin American countries, India, some places in Asia and sub-Saharan Africa, as well as in industrialized nations with a high immigrant influx of people coming from or traveling to endemic areas [90]. The mass immigration of people from endemic areas of disease, military incursions, and international business travel has caused outbreaks of CC in

H. Matushita (✉) · F. C. G. Pinto · D. D. Cardeal · M. J. Teixeira
Department of Neurosurgery/Pediatric Neurosurgery,
Clique Hospital, São Paulo University Medical School,
São Paulo, Brazil
e-mail: Matushita@uol.com.br

F. C. G. Pinto
e-mail: fernando.neuro@terra.com.br

D. D. Cardeal
e-mail: dcardeal@yahoo.com.br

M. J. Teixeira
e-mail: manoeljacobsen@gmail.com

areas where the disease was rare. In many of these areas after the outbreak, the area has become endemic for CC [74].

It is estimated that there are approximately 50 million people with CC [35], and about 50,000 people die every year from NCC worldwide [32]. Many prevalence rates of NCC tend to be underestimated because many infections are subclinical, there are few studies on population-based data, and there is lack of an inexpensive and highly-specific and sensitive diagnostic test. The major development and noninvasive tests for NCC was the computed axial tomography (CT) during the 1980s. This study provided a fourfold increase in the number of diagnosis of NCC in Los Angeles during 1977 and 1981 [72]. The development of a specific immunoblotting test for CC in 1989 by Tsang et al. [89] also showed an increase in incidence of CC in many Latin American countries [71].

A retrospective study in Brazilian literature, based on 136 published papers and covering the period of 1915–2002, identified the incidence of NCC in the clinical practice of neurology and neurosurgery ranging from 0.03% to 13.4%, and in autopsies ranging from 0.12% to 9%. Exclusively in general hospitals, the frequency of observed NCC was 1.13% [1]. Epidemiological studies based on compulsory notifications conducted in two different locations in Brazil showed the coefficient of prevalence of NCC ranging from 1.27/100,000 to 67/100,000 inhabitants [15, 58, 85]. Shenone et al. [73] estimated that the average prevalence of NCC in Latin America is 100/100,000 inhabitants.

The disease has socioeconomic importance because it decreases productivity of affected people; approximately 65% of cases of NCC are of working age [85]. NCC represents high cost of medical diagnosis and treatment. Estimated cost of US\$ 15 million per year for hospital admission of newly diagnosed cases of NCC in Mexico was reported by Flisser et al. in 1988 [28]. In children, it is considered infrequent compromising over the range between 6 and 9 years of age [55]. In an endemic area, it may affect 2.6% of children registered for neurological problems [43]. A large study conducted by Caselas [10] at our institution showed that 19.6% of patients with NCC were younger than 10 years old and the youngest patient was 14 months old. Gender does not seem to influence NCC occurrence; nevertheless, the gender of the individual may be a risk factor to the clinical course of disease, in which some forms of NCC are more severe and induce more intense inflammatory response in women, indicating a possible hormonal influence on development or in disease susceptibility [60, 84]. A study performed in the USA indicated gender disparity with significantly higher prevalence of CC in men, reflecting the greater immigration of young men in search for employment [75].

Some studies indicate a higher frequency of NCC in rural or periurban areas where the sanitary conditions are suboptimal [57, 73], although other studies describe the frequency of NCC as higher in people from urban areas [30, 52].

Outside endemic areas, in developed countries, the NCC has become an increasingly emerging infection. In the USA, a higher risk for acquiring NCC has been documented in patients who have traveled to endemic regions, are of Hispanic ethnicity, and have contact with *T. solium* tapeworm carriers [90]. The spread of NCC throughout the USA has largely followed the flow of immigration from Mexico and other Latin American countries. Prevalence rates are highest for Hispanics at 1.5 per 100,000 inhabitants and lowest among non-Hispanic whites at 0.02 per 100,000 inhabitants [90]. Shandera et al. [74] estimates that the incidence of NCC throughout the USA among Hispanics has been underreported due to the lack of health insurance, and probably it is at least eight to 10 per 100,000 per year with 1,000 new cases of NCC diagnosed each year. A prospective study on 11 American emergency departments showed that NCC now accounts for 10% of all seizures presented to the emergency room [59].

Etiologic agent

T. solium, a parasitic tapeworm, belongs to the class of Cestodea and presents three evolutionary forms: adult, embryonic or egg stage, and larvae. Adult *T. solium* worm is segmented 2 to 3 m long, which lives attached to the small intestine of humans. The worm has a head or scolex, neck, or strobilus, and segmented body made up of segments called proglottids. The organs are found in the scolex by which the parasite attaches to the intestine formed by suckers, rostellum or the rostrum, and the crown of hooks. The neck is the region of intense cell multiplication, responsible for formation of proglottids. The sum of proglottids is called a strobilus, which resembles a strip of tape. The proglottids, while retreating from the cephalic end, are undergoing a maturation process. *T. solium* worms are hermaphrodites and each strobilus has mature male and female sexual reproductive systems. The matured and gravid proglottids are at the far end of the strobilus and are released from the worm's body, being eliminated with the feces. Each proglottid segment contains 50,000 to 100,000 eggs. Eggs and mature proglottids are eliminated with human feces in the environment. They have high resistance to environmental variations and can survive for several weeks or months in mild temperature conditions. The larval phase or cysticercus cellulose of *T. solium* is formed from a vesicle with fluid of variable size, with an invaginated scolex inside. The vesicle membrane is translucent, thin, with microvilli which are responsible for the biological functions of the larva as food, excretion, and

protection. In certain locations such as at the intracranial cisterns or ventricles, the cyst may become multicystic and large with loss of scolex, called meconic form.

Life cycle of *T. solium*

The cycle of *T. solium* involves two hosts, one definitive and one intermediate stage and a free living environment. In the biological cycle of *T. solium*, the only definitive host is man, in his small intestine harboring the adult form of the parasite. There is no evidence that other mammals can be natural hosts of the adult form of the parasite. Humans become *T. solium* carriers, with taeniasis, by ingesting undercooked or raw flesh of infected pork containing cysticercus. The usual intermediate host is the pig in which the larval form of *T. solium*, the cysticercus, develops. Pigs acquire CC by ingestion of food or water contaminated with eggs or proglottids from the feces of a human *T. solium* carrier.

Humans can act as intermediate host and develop a larval phase in their tissues. Humans with CC are incidental intermediate hosts, which replace the pig in the life cycle of *T. solium*. The human CC can occur by three mechanisms of contamination:

- external hetero-infection when ingestion of food contaminated with *T. solium* eggs occurs;
- external auto-infection when people with taeniasis eat eggs eliminated in their own feces; and
- internal auto-infection when in patients with taeniasis reflux of intestinal contents into the stomach occurs, leading mature proglottids with eggs inside to come into contact with gastric juice.

Although transmission of CC may occur by ingestion of vegetables irrigated with water contaminated with human stools containing eggs of *T. solium*, some epidemiological data indicated that the most common source of infective eggs is asymptomatic household *T. solium* carrier [36]. Around 5–40% of patients with CC are *T. solium* carriers, and most of them do not develop symptomatic CC. However, human *T. solium* carriers are at risk for oral autoinoculation of eggs and subsequent development of CC. *T. solium* carriers may suffer a mechanism of self-infestation when the fertile eggs are released in the host's small intestine. It is admitted that the eggs must be exposed to the stomach acid and subsequent digestion in the duodenum of the high protective structure of the egg, the oncosphere, in the small intestine. Antiperistaltic movements and vomiting may expose the fertile eggs inside the proglottids to the stomach.

An important factor in the spread of taeniasis/CC is the deposition of human feces in places frequented by animals,

such as in rural areas. The soil and food may suffer contamination indirectly when inadequately treated human excreta are thrown in water supplies or water used to irrigate crops and pastures. The promiscuous relationship of the human carrier of taeniasis in their professional activities or in simple family life is another important factor in disease transmission.

Pathophysiology of neurocysticercosis

The development of human CC mainly occurs through the ingestion of mature eggs of *T. solium*. When the eggs reach the stomach, they suffer from the initial digestive action of gastric juice and are complete with the intervention of pancreatic pepsin. The hexacanth embryo, released from its capsule, insinuates itself by the intestinal mucosa, goes to the bloodstream, and are passively transported to different body tissues, especially for those with greater functional activity as the nervous system, skeletal and heart muscles, subcutaneous tissue, and eyeball. After the installation of the embryo in the capillaries of different tissues, the embryo undergoes formation of vesicles, giving rise to an invaginated scolex. The development of cysticercotic vesicles is observed in approximately 6 weeks after eating the eggs. It is possible to identify all pathological changes in the development of cysticercus in brain parenchyma, its infection until death [26]. This evolution can be described in four stages (Fig. 1):

- Vesicular stage** – this is the initial phase; the parasite presents as a thin membrane vesicle and transparent liquid, with scolex inside. This phase of infection is usually asymptomatic and cysticercus can remain in this stage for many years. The lifetime of a cysticercus in the CNS is controversial. It is assumed that the cysts

Fig. 1 a–b Coronal T1-weighted MRI with gadolinium of a 22-year-old patient demonstrating three lesions in different stages. **a** A parenchyma viable vesicle with scolex and a small nodular granuloma in the parietal sulcus. **b** A vesicle in colloidal stage in the sulcus in the right parietal lobe

survive 4–5 years on average and can live for up to 30 years. This long incubation period would explain the low prevalence of NCC in children [41]. *T. solium* has sophisticated means to evade its destruction, and several mechanisms have been observed in experimental models to explain its immunological tolerance. The cysticercus secretes the taeniestatin, a serine proteinase inhibitor, which inhibits complement activation, lymphocyte activation, and cytokine production. The parasite paramyosin may inhibit the complement activation pathway. The parasite's surface is covered with sulfated polysaccharides which maintain the complement away from the cyst wall. Production of prostaglandins and low molecular weight molecules may decrease inflammation and change the cytokine production. Another important virulence factor is the elaboration of proteinases by the parasite facilitating invasion and tissue damage, by degrading interleukin and immunoglobulin [92]. The viable cysticerci eliminate catabolites through a digestive pore, which can trigger an inflammation process limited to the vicinity of the cyst.

- (b) **Colloidal vesicular stage** – this represents the initial phase of natural degeneration or immunological phenomena triggered by the host. The liquid and the vesicle membrane become opaque. The vesicle becomes infiltrated and surrounded by inflammatory cells composed primarily of mononuclear cells, and variable influx of neutrophils and eosinophils occurs. The triggering of the inflammatory response leads to the development of perilesional brain edema, which is associated with onset of epileptic seizures.
- (c) **Granular nodular stage** – this represents the most advanced stage of degeneration, in which the cyst decreases in size, its membrane becomes thicker, and its liquid content becomes granular due to deposit of calcium salts.
- (d) **Calcified nodular stage** – this is the final stage of degeneration of the cyst with a very small size, and becomes fully calcified.

The infestation by cysticercus of the CNS can be single or multiple. It is not clearly understood as to why some cases have single and others have multiple cysts. Immunological differences may possibly account for this; defective functions of neutrophils and T lymphocytes have been reported in patients with multiple lesions only and not in those with single lesions [87]. In single and small infestations, degeneration and death of the parasites with spontaneous healing can occur. In multiple infestations, the immune allergic response is multiphase because of the different phases of vitality of the parasites. The immune allergic phenomenon triggered by a parasite follows another in an overlapping way. It is believed

that this cascade of events alters the immunological response to the heteroantigen of parasite and raises a self-antigen which along with the heteroantigen of parasite triggers immunological complex responses.

Massive infestation of cysticercus in brain parenchyma called military CC is described. The encounter of cysticercus in different stages in an individual may indicate multiple infestations or different capacities of resistance and maturation of the parasites [12]. Dependent on the degree of infestation by cysticercus of brain parenchyma, it may be triggered by intense inflammatory processes with diffuse cerebral edema and consequent severe intracranial hypertension. This form is known as cysticercotic encephalitis. According to Lopez-Hernandez [49], in children, intracranial hypertension is more frequently associated with secondary parenchymal edema to inflammatory process than to hydrocephalus. A study performed at our institution showed that the ventricular dilatation observed in children is most commonly associated with brain atrophy than ventricular block [53]. The parenchymal form of NCC is more frequent due to the preference of the parasite to places with higher vascularization.

The extraparenchymal installation of the cysticercus determines own pathogenic mechanisms. Extraparenchymal NCC is rare in children compared to adults. The cysticercus may be found in the ventricular cavities, basal cisterns, and cortical and spinal subarachnoid spaces (Fig. 2). The cysticerci reach the ventricular cavity through the choroid plexus. Recent series indicated the presence of cysticercus inside the cerebral ventricular systems in up to 30% in patients with NCC (Fig. 3) [20, 51, 70, 91]. Intraventricular cysts may be asymptomatic; however, it may become symptomatic due to obstructive phenomena or when the cystic beva dies and degenerates, triggering an inflammatory process.

They may circulate freely through the CSF pathways or become attached to the ependyma. The cysticerci tend to be displaced from the ventricular cavities to the subarachnoid space, and intraventricular obstruction and hydrocephalus may occur. Obstruction of CSF flow caused by the cysts may occur abruptly or gradually, and may be intermittent or permanent [48]. Not infrequently, too, it may clog the fourth ventricle and its foramina. Free cysts in the fourth ventricle can cause intermittent obstructions. The main locations of the ventricular obstructions include foramen of Monro, third ventricle, cerebral aqueduct, and fourth ventricle, although the sites most frequently encountered are the lateral ventricles and fourth ventricle. Acute CSF obstruction can cause acute hydrocephalus and intracranial hypertension symptoms. In intermittent acute obstruction, the head positional changes may improve or worsen symptoms [27, 88]. Permanent acute obstructions cause continuous and progressive increased intracranial pressure (ICP) symptoms with manifestations of symptoms in hours to days. Gradual obstructions of CSF flow occur more often in solitary large

Fig. 2 Neuroimaging studies of a 7-year-old boy with intense involvement by NCC. **a** Axial CT with contrast enhancement demonstrating periventricular cysts with encephalitis and basal meningitis. **b** Sagittal T1-weighted MRI with gadolinium showing

subarachnoid NCC affecting the Sylvian fissure. **c** Sagittal T1-weighted MRI with gadolinium showing severe spinal arachnoiditis and an intramedullary cysticercus

cyst in the fourth ventricle [19]. Increased ICP symptoms may be present several months before diagnosis.

The degeneration of ventricular cysts causes the release of cytokines and consequent activation of inflammatory process in the whole ventricular ependymal surface. The ependymite fix the parasites in the ventricular wall causing fibrotic scarring process and secondary stenosis to CSF flow.

Hydrocephalus progresses more slowly; however, the patient may become more symptomatic due to meningo-encephalic processes. Ventricular dilatation secondary to acute ependymite phase, although highly symptomatic, may temporarily improve with use of corticosteroids.

The cysticercus vesicles can be observed from the subarachnoid space, which is called the subarachnoid CC.

Fig. 3 Neuroimaging studies of four different adult patients displaying ventricular NCC

Some cysticerci in subarachnoid space, especially in the cisterns, may increase in number and size, accompanied by regression of the scolex forming racemose cysticerci. CC racemosa can expand to large sizes, exerting mass effect on brain tissue, and determine focal neurologic deficits. The cysticercus present in the cerebral convexity sulci may have overlapping pathogenic mechanisms to parenchymal forms, with onset of large cerebral inflammatory reactions. This location of cysticercus defines a form of CC called brain meningeal or pseudo-parenchymal. In this form, the cysts tend to be larger and more resistant to anti-parasitic drugs than true parenchymal forms [62]. Most patients with subarachnoid CC have large infestations that fill all cisterns of the base. Cysticercus in the basilar cisterns may induce arachnoiditis. Patients may present with meningeal signs or communicating hydrocephalus. Arachnoiditis may also be associated with vasculitis and may present with lacunar infarction or large-vessels stroke. CC-induced lacunar infarcts are usually located in the territory of the lenticulostriate branches of the anterior or middle cerebral artery and result from occlusive endarteritis secondary to intense inflammatory reaction within the subarachnoid space [11]. Meningitis and leptomeningeal thickening of cisterns at the base of the brain can cause dysfunction of cranial nerves by fibrous entrapment of these nerves.

Based on CT study of 710 cases of NCC, Rodríguez-Curbajal et al. [68] showed results according to the location of the cysticercus: parenchymal 65.2%, meningeal 18.3%, mixed 14%, and intraventricular 2.5%.

Spinal involvement occurs in 1% of cases. Most feature subarachnoid location and cause inflammatory and demyelinating changes of the roots of spinal nerves [4, 7]. Cysticercus can be intramedullary. These cysts often cause cord compression from mass effect or accompanying inflammation. Most patients with spinal CC also have an evidence of cerebral disease [92] (Fig. 2).

Clinical manifestation

The clinical spectrum of NCC is extremely broad ranging from asymptomatic to sudden death. This variation depends on the number, size, stage, and location of the cysticercus, and the immune status of the patient. In general, parenchymal infections manifest more frequently with epilepsy and extraparenchymal infections with symptoms of intracranial hypertension.

Epileptic seizures

Epileptic seizures are the most frequent symptom of NCC, occurring in 92% of parenchymal forms, and in 74% of those with the extra form and associated parenchymal [2].

A study performed at our institution showed high frequency in children up to 90.1% [54]. The epileptic seizures that occur in the NCC have different characteristics according to the evolutionary phase of the disease. Seizures can be classified as provoked or spontaneous [14]. Epileptic seizures are caused by cysticercus in the inflammatory phase and should be considered as caused because they occur in direct dependence on the inflammatory process, disappearing as the process is resolved. Yet in the early (vesicular stage) or late (nodular calcified stage) phases, crises should be considered as spontaneous, i.e., true forms of epilepsy. According to this view, the NCC would determine only epilepsy in patients with intact or calcified cysticercus, and those with cysticercus in stages of disintegration would present epileptic reaction limited to the inflammatory phase of the process and should not be regarded as epilepsy.

It is believed that in the inactive phase of calcified cysticercus, the peripheral gliosis to the same ones have epileptogenic activity. The most common type of seizures in children is partial crises especially simple partial ones [53]. The epileptic seizures are benign, as most no longer have a crisis or has low frequency. Apparently, the evolution of the crisis is independent of the treatment used in both provoked and spontaneous seizures [53]. The epileptic manifestation of NCC usually occurs singly or in combination with other events, especially headache [84].

Intracranial hypertension syndrome

Intracranial hypertension syndrome is the second most frequent form of presentation. The increased ICP can be secondary: (a) hydrocephalus from arachnoiditis, ependymitis, and blocks per ventricular cysts; (b) cerebral edema determining pseudotumor forms; (c) cysticercotic encephalitis; and (d) giant cysts.

Considering data from the neurosurgical clinics, intracranial hypertension is the main cause of presentation of NCC. In the series reported by Colli et al. [16], the cause of increased ICP was hydrocephalus in 91.6% and tumoral form in 12.9%.

Hydrocephalus is responsible for 15% to 30% of clinical manifestations. As the cysticercus moves freely with the flow of liquor, the fourth ventricle is most frequently affected [6].

Cysts in the fourth ventricle in children present distinct clinical characteristics of infratentorial tumors. Lefevre in 1966 [46] noted that the increased ICP associated with NCC was more often associated with epilepsy, mental disorders, and visual changes, while the increased ICP associated with tumors had more motor disorders. Disseminated miliary forms, with multiple cysts in different stages of development, are unusual but may have malignant

course with poor prognosis especially in children and women. In children, increased ICP is usually secondary to cerebral edema, which can have a severe course with fatality [86].

Other clinical manifestations

Mental disorders, motor manifestations, cranial nerve deficits, and meningoencephalitis signs are less common.

Diagnosis

The diagnosis of NCC can be difficult due to the variability of clinical presentation. The use of various auxiliary diagnostic procedures depends on the clinical presentation. Currently, the diagnosis of NCC follows criteria proposed by Del Brutto et al. [2] that permit to establish the definite and probable diagnosis. The diagnosis of NCC is based on clinical epidemiological data, cerebrospinal fluid (CSF) examination, neuroimaging, and histological examination of lesional biopsies.

Examination of CSF

CSF test has certain peculiarities that allow defining—cerebrospinal neurocysticercotic syndrome. This is characterized by pleocytosis with eosinophils and the presence of specific antibodies. A pleocytosis is mild to moderate with predominance of lymphocytes and monocytes and a lower proportion of neutrophils, plasma cells, and eosinophils. The eosinophil is not an element of certainty, as may occur in other situations. The immunological reactions are the immunobiological element of security. The Weinberg reaction (complement fixation reaction) is positive in 62–80% and cross-reaction with other situations can be easily recognized.

The reaction of immunofluorescence has a sensitivity and specificity similar to the reaction of Weinberg, being more significant. The immunoenzymatic test (ELISA) has sensitivity of 87% and specificity of 95%. The ELISA IGM has been quite reliable for active forms of NCC. The immunoblotting test (EIBT) initially showed a sensitivity of 98% and 100% specificity for CC [89]. Later studies confirmed the specificity of almost 100%, but sensitivity was shown to be limited in patients with single lesions [38]. The EIBT performed in serum may be used in epidemiological studies of the prevalence of CC [89].

CSF test can also help determine the developmental stage and diagnose disease exacerbation.

Although of all these variables have been studied, the CSF examination may show false negative results in 40% of cases, even in the active phase of the disease, especially

in patients with single lesion [61]. CSF test may be infeasible in the presence of intracranial hypertension.

Computerized tomography (CT)

CT is one of the most important complementary methods. It can identify numerous injuries, especially in brain parenchyma: (a) 2–7 mm nodular calcifications without contrast enhancement and no peripheral edema; (b) hypodense cystic lesions from 10 to 70 mm, regular, with small central or eccentric hyperdense point that corresponds to the scolex, and no peripheral edema (the identification of the scolex is the only pathognomonic radiographic finding); (c) cystic lesions with retaining ring of contrast and area of peripheral edema; (d) cystic lesions with homogeneous nodular retention of contrast with or without peripheral edema; (e) large hypodense area of the brain that can match the cysticercotic encephalitis signs or infarction secondary to vasculitis; and (f) meningeal thickening characterized by high contrast enhancement, especially the basal cisterns.

The occurrence of these lesions may be single or multiple, and preferred, in the junction between gray and white matter. In children, there is a prevalence of CC in the process of degeneration, with diffuse local encephalitic reactions, whereas intact vesicles are uncommon [53].

The ventricular system may be reduced by parenchymal edema or dilated by hydrocephalus. The identification of intraventricular cysticercosis may be difficult since it has the same attenuation coefficient of the CSF. The presence of intraventricular cysts may be suggested by the observation of deformity of the ventricular contours.

Magnetic resonance imaging (MRI)

MRI is more sensitive than CT in detecting the number of injuries, the stage of development, the degree of brain inflammation, basal arachnoiditis, and better bounds intraventricular, cisternal, and spinal CC (Fig. 3). The scolex can be identified on MRI as an eccentric mural nodule at the images on the FLAIR sequence and diffusion [50, 65]. MRI study shows that intraventricular cysticercosis occur in isolation in 15%, with predominance for the fourth ventricle, in approximately 60% [3]. Advanced techniques of image acquisition show that the use of 3D CISS sequence (constructive interference in steady state) has a high sensitivity for detecting intraventricular cystic lesions, with clear demonstration of the cyst wall and scolex [25]. In subarachnoid NCC, 3D CISS images also improve the determination of the number and extent of injuries. The FLAIR sequence associated with inhalation of oxygen for 5 min at 100% before the test is helpful in better delineation of the membrane of the cyst in the subarachnoid space [9].

Studies of proton spectroscopy on MRI showed that the cysts of NCC have a distinct pattern from other more frequent cysts such as congenital and tumor cysts [42].

Contrast-enhanced MRI is the examination of choice to rule out the existence of viable cysts inside the ventricles or subarachnoid space.

Treatment

The treatment of NCC should be individualized based on clinical presentation, degree of infestation, location, and viability of cysticercus, and the host response. Different treatment modalities are considered: (a) antiepileptic, (b) etiologic treatment, and (c) anti-inflammatory treatment.

Antiepileptic treatment

The use of antiepileptic drugs is recommended for patients with seizures and patients without seizures, but with high risk of presenting seizures. It is considered a high-risk condition, the stage of degeneration of the cysticercus with inflamed perilesional brain tissue, especially in multiple injuries. The choice of antiepileptic medication is inconsistent in the literature. In our institution, for economic reasons, we initially used phenobarbital, with good response [53]. After resolution of the inflammatory process in patients with solitary cysticercotic granuloma, 85% have no recurrence of seizures [66]. The duration of use of antiepileptic drugs is recommended until the disappearance of the inflammatory lesions, although patients with pre-treatment multiple seizures who maintain residual calcified and multiple lesions present greatest risk of seizure recurrence [21].

Etiologic treatment

The use of anti-parasitic drugs in the NCC is still very controversial. General rules of consensus were reported by Garcia et al. in 2002 [33]. The benefits in the use of anti-parasitic drugs are faster healing of viable cysticercus, better control of epilepsy, and a lower incidence of hydrocephalus. The risks highlighted in the use of anti-parasitic drugs were the worsening of perilesional inflammatory process, especially when multiple. The greatest benefits of these drugs are being observed in the parenchymal forms of NCC (Fig. 4). Currently, two drugs are used to destroy the cysticercus: praziquantel and albendazole. A recent study shows no difference in efficacy in the resolution of cysts and control of epilepsy in these two drugs, but because of lower costs, less administration time, and greater availability, albendazole is preferred [31].

Anti-inflammatory treatment

The use of corticoid is recommended in order to reduce the inflammation associated with the phase of degeneration of parasite, natural or induced by medication. Other investigated actions are the effects in the control of recurrent seizures and shortening the resolution of viable granulomas [37]. The use of corticoid, therefore, seems to be established for the parenchymal form with cysticercus in degeneration, especially in multiple infestations. For subarachnoid CC, corticoids have been recommended to decrease chronic meningitis with subsequent scarring retractions of basal meningitis and hydrocephalus. Prolonged use of association of corticoids and anti-parasitic drugs is recommended for the subarachnoid forms of NCC.

Surgical treatment

Neurosurgery is recommended for hydrocephalus, intraventricular cysts, and large cisternal or parenchymal cysts. Concomitant use of corticoid and anti-parasitic therapy are used to increase efficacy of surgery for active extraparenchymal disease. Studies indicate that intraventricular cysts respond less to anti-parasitic drugs than subarachnoid cysts, but improvement of ventricular NCC has been reported in patients without hydrocephalus [20, 63, 79].

Intraventricular cysts can cause increased intracranial pressure and obstructive hydrocephalus due to floating cysts and granular ependymitis promoted by excreted catabolites of the cysts or by its degeneration. Ependymitis can also obstruct the CSF at the foramina of Monroe or at the Sylvian aqueduct leading to hydrocephalus.

Initial studies recommended surgical removal of the ventricular cysticercus through microsurgical techniques in order to reestablish the CSF circulation. Relative contraindication to resection of extraparenchymal cysts is the presence of significant inflammation, typically demonstrated on MRI. Different surgical approaches were suggested according to location of the cysts: lateral and third ventricles via transcortical or transcallosal approach and for the fourth ventricle via suboccipital craniotomy [6, 76].

Currently, endoscopic surgery is the procedure of choice for intraventricular cysts because it is minimally invasive and very effective [56, 67]. In 2009, Proaño et al. [64] evaluated the efficacy of traditional treatment and minimal invasive flexible endoscopy surgery (MIFNES) in the treatment of ventricular and subarachnoid basal cisterns NCC, and the follow-up period was at least 6 months. They found that MIFNES is a good alternative for the management of ventricular and subarachnoid basal cisterns NCC because it allows removal of most of the parasites, rapid recovery of the patients, and removal and placement of shunt under direct vision when necessary [64]. For

Fig. 4 Illustrative case treated initially with anti-parasitic and anti-inflammatory medication followed by endoscopic third ventriculostomy and removal of the lateral ventricle cyst. Patient did not require further treatment for hydrocephalus. **a** Axial T1-weighted MRI at first hospitalization with a severe encephalitis, and multiple infections by cysticercus in August of 2006. **b** Axial CT scanning after medical treatment demonstrating regression of the inflammatory process and small

calcifications in the brain parenchyma—March 2004. **c** Coronal T1-weighted image with gadolinium showing three cysticercus cysts inside the left lateral ventricle—March 2005. **d**, **e**, **f** Intraoperative endoscopic images demonstrating small and stenotic foramen of Monro secondary to ependymitis, third ventriculostomy, and removal of the cyst. **asv** anterior septal vein, **lv** lateral ventricle, **Fch** Foramen of Monro, **lv** lateral ventricle, **cy** cyst. **g** Specimen of the cyst after removal

endoscopic removal of intraventricular, parenchymal, or cisternal cysts, it is essential to verify the absence of inflammatory processes surrounding the cysts since these fix the parasite in the ventricular walls and preclude their complete removal. MRI can demonstrate significant ependymal enhancement of gadolinium indicating the ependymitis. Because of the mobility of ventricular cysts, the patient should have repeated CT, close to the surgical procedure time, to evaluate the exact location of the cysts and degree of hydrocephalus.

Hydrocephalus can be controlled only by removal of the obstructive intraventricular cysts or associated with either ventriculoperitoneal (VP) shunt or endoscopic third ventriculostomy (Fig. 4). Associated with removal of ventricular cysts, the third ventriculostomy and choroid plexus coagulation can be performed for the optimum control of hydrocephalus. A review of 10 patients with cysticercus in the lateral and third ventricle, treated endoscopically, showed that seven patients did not require shunt [8].

Endoscopic transaqueductal removal of fourth ventricular NCC associated with third ventriculostomy may provide excellent control of hydrocephalus [40, 83, 94].

Suri et al. reported endoscopic excision of the ventricular cysticercus associated with third ventriculostomy, in pediatric series, with as good results as reported by general series [82].

Cisternal cysts can be removed combining minimally invasive keyhole procedure with endoscopy [39]. In some circumstances, removal of the ventricular cysts fails in controlling the hydrocephalus due to associated arachnoiditis of the basilar cistern or to ependymitis. For these situations, VP shunt is the only way to manage the hydrocephalus. VP shunt is an effective procedure for treatment of associated hydrocephalus with relief of 50–95% of the cases. However, shunts in these patients suffer from frequent obstructions and require multiple revisions. The VP shunt dysfunction rate is very high; Colli et al. [17] reported 82% of shunt dysfunction. The reasons for this occurrence are demonstrated in the literature and explained by shunt obstruction by proteinaceous debris [17, 44, 67, 77, 78]. A study by Kelley et al. [44] identified that the larger percentage of shunt obstruction in NCC is located at the distal segment, caused by inflammatory process in the peritoneal cavity, resulting in poor absorption on the CSF. The premature malfunctioning of the shunt within the first 6 months corroborates the involvement of the active inflammatory process. Additional

benefits in using medical therapy in ventricular NCC are related to decrease of rate of shunt failure and prolongation of shunt longevity [74, 81]. Kelley et al. demonstrated that the rate of shunt dysfunction is higher from shunt placed during the vesicular stage of infection (63%) than during the colloidal through the calcified stage of infection (29%). Use of antihelminthic medication helps to decrease significantly the rate of shunt failure from 90% to 33% [44].

The protocol for the treatment of hydrocephalus caused by NCC followed at our institution is shown in Fig. 5.

Surgical treatment for subarachnoid or even intraparenchymal CC seems justified when large cysts exert compressive effect on the brain or spinal cord [18, 78]. In very exceptional cases of acute encephalitic CC with severe increased intracranial pressure, internal or external decompression may be required, and for adhesive arachnoiditis of the basal cistern with progressive visual loss, decompression of the optoquiasmatic pathway may be effective [16, 69].

Outcome

The outcome depends upon the type of NCC, cyst location, and numbers. In general, parenchymal NCC has a better prognosis than extraparenchymal NC and single lesions have a better outcome as compared to multiple lesions. Patients harboring fewer than 20 parenchymal cysts are at very low risk for death associated with anti-parasitic therapy [22, 34]. In the absence of hydrocephalus, patients with low burden of parenchymal cysts rarely die after treatment but patients with intracranial hypertension, with no shunts, have higher risk for death [45].

Studies show that the NCC associated with intracranial hypertension has high mortality, ranging from 28.4% to 67% [17, 80]. In children, the hypertensive forms were usually secondary to cerebral edema, and extraparenchymal NCC is rare [3, 54].

The outcome for patients with intraventricular and parenchymal cysts is usually good, but for those with hydrocephalus associated with cisternal or racemose cysts and with cysticercotic meningitis, the mortality is high. Acute hydrocephalus may be fatal with a mortality rate of 13% [93]. The prognosis for patient with fourth ventricular cysts and hydrocephalus has been worse than other locations.

De Giorgio et al. 2001 reviewed the literature to delineate risk factor associated with CC-related death, and concluded that the risk of death is higher in patients with heavy cyst burdens and those with hydrocephalus primarily because of increased ICP and shunt-related infection. The long-term mortality rate reported by Colli et al. (1986) in patients in whom shunts were implanted was 30.8%.

Intracranial hypertension, shunt infection, and shunt malfunction are the major causes of death in patients with NCC.

Prophylaxis

The eradication of NCC is possible and a more effective approach is prevention of the disease which should be the primary goal of public health, particularly in countries in development, and that can be achieved through measures

Fig. 5 Diagram displaying management of patients with hydrocephalus and NCC

that interrupt the tape worm–host cycle such as public education, sanitation, and preventing access of pigs to human feces [13, 30]. Another possible solution is the vaccination of pigs against infection with the parasite, which indirectly reduces the appearance of new cases of the disease [29, 47]. But even with the development of vaccines, the most perspective for the eradication of the disease is education and public health measures.

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Anexo 8

Pediatric
Neurosurgery

Case Report

Pediatr Neurosurg 2011;47:303–306
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Case Report and Review of the LiteratureFernando Campos Gomes Pinto^b Malebranche Berardo Carneiro da Cunha Neto^a
Manuela Giuliani Marcondes Rocha^c Daniel Vicaria do Lago^c
Marcello Delano Bronstein^c Manoel Jacobsen Teixeira^b^aNeuroendocrine Unit, at ^bDivision of Functional Neurosurgery, Institute of Psychiatry, and ^cNeuroendocrine Unit, Division of Endocrinology and Metabolism, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil

Key Words

Amenorrhea · Endoscopic third ventriculostomy ·
Hypopituitarism · Hydrocephalus · Neuroendoscopy

Abstract

Introduction: Although rare, chronic hydrocephalus may cause amenorrhea and delayed puberty associated with obesity as the main endocrine manifestations. Since the first operation carried out in 1950 on a patient with amenorrhea and hydrocephalus, fewer than 30 patients with these features have been reported. **Case Report:** Our patient represents a teenage case of primary amenorrhea, partial adrenal insufficiency and adult growth hormone deficiency caused by hydrocephalus due to aqueductal stenosis. Our English-language literature search for similar well-documented cases yielded less than 30 cases. Our management consisted of endoscopic third ventriculostomy, which resulted in regular menstrual cycles and normalization of somato- and adrenocorticotrophic axes. **Discussion:** This is a rare case of a 20-year-old woman with primary amenorrhea caused by hydrocephalus due to aqueductal stenosis. Neurosurgical treatment produced relief in hypothalamic hydrodynamics tension, allowing recovery of hormonal function and restoring normal menstrual cycles.

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Introduction

Although rare, chronic hydrocephalus may cause amenorrhea and delayed puberty associated with obesity as the main endocrine manifestations. Since the first operation carried out in 1950 on a patient with amenorrhea and hydrocephalus [1], fewer than 30 patients with these features have been reported [2–12].

The hypothalamic gonadotropic function usually returns to normal within a few months after resolution of the hydrocephalus [6, 9, 10]. Other forms of hypopituitarism associated with normal-pressure hydrocephalus have been reported by Barber and Garvan [13] in 1978 and 1979, with no information on pituitary function after neurosurgical treatment.

Aqueductal stenosis is a major cause of hydrocephalus in infancy with latent manifestation in adulthood. Ventricular shunt diversion (VSD) or endoscopic third ventriculostomy (ETV) are the therapeutic options for these patients [11].

We report the case of a teenager with primary amenorrhea, partial adrenal insufficiency (PAI), and adult growth hormone deficiency (AGHD) caused by hydrocephalus due to aqueductal stenosis successfully treated by ETV. A review of the pertinent literature is presented.

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1616–2291/11/0474–0303\$38.00/0
Accessible online at:
www.karger.com/pswFernando Campos Gomes Pinto
Av. Angélica, 1908, c.123
São Paulo, SP 01228-200 (Brazil)
E-Mail: fernando.neto@terra.com.br

Table 1. Pituitary hormone levels after stimulation with insulin-induced hypoglycemia (0.1 IU/kg of insulin), 100 µg of GnRH, and 200 µg of TRH

	0 min	15 min	30 min	45 min	60 min	90 min
LH, IU/l	0.6	19.4	40.0	33.8	29.6	18.9
	4.3	15.5	25.0	27.3	28.0	32.9
FSH, IU/l	2.1	6.0	12.5	12.6	12.0	10.0
	3.9	5.5	7.7	8.8	9.1	10.7
Cortisol, µg/dl	6.5	11.5	10.5	12.3	14.6	10.3
	7.7	13.8	14.0	17.1	23.1	23.6
GH, ng/ml	0.3	0.5	0.7	1.6	1.4	0.4
	0.4	0.9	1.0	1.4	3.8	1.7
IGF-I, ng/ml	382	ref. value: 162–541				
	569	ref. value: 138–442				
TSH, µIU/ml	4.03	29.63	37.02	29.46	24.39	13.76
	2.19	16.77	20.21	18.21	13.39	8.97
Prolactin, ng/ml	4.0	25.0	20.5	13.2	11.6	6.4
	6.2	38.8	33.4	24.3	22.1	15.2
Estradiol, pg/ml	31					
	51					
Progesterone, ng/ml	<0.3					
	<0.3					

Data in each first line were obtained before ETV, and those in the second line 9 months after ETV.

Case Report

A 20-year-old single female college student suffering from congenital hydrocephalus due to aqueductal stenosis presented chronic headache and amenorrhea, without intellectual impairment. The patient was born at term, by cesarean delivery without complications and had normal growth and psychomotor development in childhood, always with good academic performance.

She presented with late appearance of secondary sexual characteristics and primary amenorrhea, and had been followed up in the Neuroendocrine Unit, Division of Endocrinology, Hospital das Clínicas, University of São Paulo, since 17 years of age. Physical examination revealed good general status, heart rate 84 bpm, blood pressure 100/70 mm Hg, weight 61.3 kg, height 164.5 cm (target height 163.5 cm), BMI 30.0, Tanner stages P4 (pubic hair), B3–4 (breast development), and normal female external genitalia. Pelvic ultrasonography showed pubertal but reduced for age uterus and ovaries, without malformations. The patient presented menses after medroxyprogesterone acetate stimulation.

An insulin tolerance test (ITT) combined with the secretagogues thyrotropin-releasing hormone (TRH) and luteinizing hormone-releasing hormone (LHRH) disclosed AGHD (even though the patient's clinical growth was adequate), PAI and normal thyroid-stimulating hormone (TSH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) responses (table 1).

Fig. 1. Preoperative MRI, T₂ sagittal: noncommunicating hydrocephalus with aqueductal stenosis.

The diagnosis of hypopituitarism prompted further investigations with CT scans and MRI, which showed a noncommunicating hydrocephalus with aqueductal stenosis (fig. 1).

The patient underwent neurosurgery to treat the hydrocephalus. A right frontal 18-mm burr hole was used as the approach for a rigid neuroendoscope with a 30° lens, and ETV was successfully performed. Sudden appearance of significant downward and upward movements of the third ventricular floor after ETV was observed intraoperatively.

One month after surgery, the patient initiated regular menstrual cycles and presented spontaneous weight loss of 18 kg (from 95 to 77 kg) in 6 months, with no reported changes in dietary or exercise habits. She had no further episodes of headache. ITT revealed restoration of both the somato- and adrenocorticotrophic axes. Basal and stimulated hormone levels before and after surgery are shown in table 1.

Discussion

Congenital aqueductal stenosis is the most common cause of aqueductal narrowing. Ten percent of hydrocephalus cases in adult patients result from aqueductal stenosis, leading to dilatation of the lateral and third ventricles [11]. Despite its congenital origin, the alteration of cerebrospinal fluid dynamics can remain compensated and undiagnosed for several years, and symptoms related to hydrocephalus due to congenital aque-

Fig. 2. Third month postoperative MRI. **a** T₁ sagittal: noncommunicating hydrocephalus with aqueductal stenosis and third ventriculostomy. The white arrow shows the neuroendoscopic pathway (frontal approach) and the ventriculostomy in the floor of the third ventricle. **b** MRI Cine flow study: third ventriculostomy is working (white arrow).

ductal stenosis may not occur until adult life [12]. Chronic hydrocephalus in adults is associated with visual disturbance, papilledema, dementia and ataxia. However, endocrine dysfunctions are uncommon and rarely revealing [2].

Villani et al. [12] reported that endocrine dysfunctions are evident in 28% of the cases with congenital aqueductal stenosis. The most common manifestations of endocrinological disturbances are hypothalamic-hypophyseal-gonadal axis impairments, such as precocious or delayed puberty, often associated with obesity and amenorrhea in girls and young women [12]. The precise mechanism of the association between amenorrhea and hydrocephalus is not well understood [3, 4, 6, 13–15]. Jawadi et al. [4] described secondary amenorrhea in a patient with hypothalamic astrocytoma. They suggested that the increased intracranial pressure due to hydrocephalus rather than the hypothalamic tumor exerted an inhibitory effect on the hypothalamus-pituitary-ovary axis at the level of the hypothalamus.

Amenorrhea is an unusual manifestation of endocrinological disturbances in patients with chronic hydrocephalus, but all of the patients who underwent surgical treatment reported to achieve normal menstruation. Hy-

pothalamohypophyseal impairment of the different neuroendocrine axes due to normal-pressure hydrocephalus has been reported by Kumar et al. [16] and Barber and Garvan [17].

Coenegracht et al. [3] postulated that the increased intraventricular pressure causes a functional disturbance only in the gonadotropin-releasing hormone (GnRH) secreting neurons in the ventral hypothalamus and not in the median eminence, leading to a relative GnRH deficiency. The relative GnRH deficiency theory has been supported by several authors using the GnRH infusion test or the 24-hour LH surge analysis [7, 8]. According to previous reports, it could be suggested that if the third ventricle is progressively dilated in chronic hydrocephalus, GnRH release is disturbed only in the ventral hypothalamus without disturbance in GnRH production elsewhere, subsequently causing a relative GnRH deficiency and resulting in amenorrhea. The persistence of responsiveness to GnRH together with progressive resumption of LH pulsatility after suppression of hypertension in the third ventricle suggests that the reproductive axis is blocked by mechanisms that impair the GnRH hypothalamic pulse generator. The fundamental change related to amenorrhea is dysfunctional hypothalamic generation of

GnRH pulses and therefore blocking of the LH and FSH cycles [10].

We postulate that the physiopathology of hypothalamic dysfunction caused by the hydrocephalus is due to pathological pressure pulses in the third ventricle, which presents abnormal dilatation secondary to aqueductal stenosis, resulting in the absence of a GnRH pulse generator. However, it is not observed in all patients with a hydrocephalus, probably because only some patients present with reduced functional complacency of the third ventricle as an individual and specific feature.

In this case report, ETV resulted in normalization of hypothalamic hydrodynamics, allowing the recovery of gonadal, adrenal and somatotrophic functions, clinically restoring normal menstrual cycles, even without ventricular size reduction (fig. 2).

Conclusion

In conclusion, hydrocephalus is a rare cause of primary and secondary amenorrhea, in the setting of hypothalamic-hypophyseal impairment. Chronic hydrocephalus can be cured by surgery, leading to normalization of the pituitary hormone axes, and restoration of reproductive function. A brain MRI should be performed in all patients with hypothalamic amenorrhea. The pathological problem is not limited to the enlarged third ventricle size, but also includes its association with abnormal hydrodynamic pulse pressure inside the arrested third ventricle, which can be restored if a cerebrospinal fluid exit is created (ETV or VSD).

Disclosure Statement

There is no conflict of interest.

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Anexo 9

A protocol for pressure adjustment of STRATA® programmable valve in the follow-up of idiopathic normal-pressure hydrocephalus patients: a prospective study.

Oliveira MF¹, Pinto FCG², Saad F³, Reis RC¹, Rotta JM².

- 1- Neurosurgery Residency Program - Department of Neurosurgery - Hospital do Servidor Público Estadual de São Paulo, São Paulo-Brazil
- 2- Department of Neurosurgery - Hospital do Servidor Público Estadual de São Paulo, São Paulo-Brazil
- 3- Post Graduation Progra9m - Hospital das Clínicas, Faculty of Medicine, University of São Paulo, São Paulo-Brazil

***Corresponding author:**

Matheus Fernandes de Oliveira

mafermoliv@yahoo.com.br

Av. Pedro de Toledo, 1800 – Vila Clementino, São Paulo – São Paulo - Brazil

Abstract

Background: The idiopathic normal pressure hydrocephalus (iNPH) is a condition characterized by gait disturbance, dementia and / or urinary incontinence, associated with dilation of the ventricular system with normal opening CSF pressure. Shunt surgery is the main operative procedure in the treatment of iNHP and valve systems can be used with fixed or variable pressures. Diversions with programmable valves are increasingly recommended, as the drainage pressure can be changed. Although the programmable valves are widely used, they still lack well-defined protocols to guide the steps to attain proper pressure for each patient. **Methods:** In our study, we report the experience of shunting 24 patients with iNPH using Strata® (Medtronic) valve, following a protocol based on a positive Tap Test. The initial valve setting was 2.5, and according to the monthly evaluations, the setting was altered towards clinical and radiological improvement. **Results:** We observed clinical improvement in 20 patients and stability/worsening in 4 patients. Complications were observed in 5 patients, including 1 death. The results show a high percentage of clinical improvement. Moreover, the complications occurred at a lower rate than those reported in other studies and were treated, in some cases, only by adjusting pressure settings. **Conclusions:** The Strata® valve used in the proposed protocol represents an efficient and safe tool in the treatment of iNPH.

Key words: normal pressure hydrocephalus; cerebrospinal fluid shunts; treatment.

Background

Idiopathic normal pressure hydrocephalus (iNPH) is a condition characterized by gait disturbance, dementia and/or urinary incontinence without causative

disorders, as well as dilation of ventricular system due to disturbance of cerebrospinal fluid (CSF) circulation with normal CSF pressure and no secondary cause^[1,2,3]. It is a differential diagnosis for most of the dementia syndromes and occurs mainly in elderly populations^[4].

The known incidence is approximately 6 per 100,000 and it has a prevalence of 22 per 100,000 for suspected iNPH. There are associations with hypertension, cerebrovascular disease and Alzheimer disease^[1,2,3].

The clinical evolution of iNPH is not clear^[5]. Without surgery, most iNPH patients present early clinical deterioration. A small number of patients might improve without shunting; however, the extent of improvement is not clear^[3].

Ventricular CSF shunting is the main treatment in the management of iNPH, and its results in reducing the caregiver's burden when caring for iNPH patients is well-established^[6]. Shunting with programmable valves is indicated, as the drainage pressure can be adjusted. Theoretically, after shunting there is less pressure in ventricle walls, determining better perfusion and potentially reestablishing functions. Hemodynamic evaluations have already shown a higher cerebral blood flow in patients with INPH^[7,8]. Another theoretical statement is the linkage between perfusion and function, but also depending in increasing complexity of the neural network after shunting^[9,10,11].

However, the surgical approach to iNPH may result in complications, especially mechanical malfunction, infections and overdrainage. When the valve pressure is too low, there is excessive drainage, creating negative pressure inside the skull, sometimes causing rupture of veins in the subdural space, creating nontraumatic subdural hematomas or hygromas^[12,13,14,15].

This study aims to describe the experience with patients with iNPH at the stages of admission, diagnosis, surgery [programmable valve Strata® (Medtronic)] and postoperative follow-up and to propose a routine of follow-up and a standard protocol for valve adjustment.

Methods

We prospectively selected patients with a diagnosis of iNPH from January 2010 to January 2012 in a Brazilian tertiary hospital. They were users of this medical facility screened in the Hospital wards and forwarded by neurologists, geriatricians and other physicians. These patients underwent elective ventriculoperitoneal shunt with STRATA® programmable valve system. It is an interventional, non-controlled study with prospective features. The project was approved by the Research and Ethics Committee.

The accepted diagnostic criteria were: clinical syndrome consistent with Adams-Hakim (gait apraxia, urinary incontinence and dementia) associated with ventricular dilatation documented by cranial CT and MRI scans. Inclusion criteria: diagnosis of iNPH, absence of malignant disease, well-controlled clinical comorbidities (hypertension, diabetes mellitus, hormonal disorders, etc.). Exclusion criteria: diagnosis of secondary NPH, inability to walk, malignancy, uncontrolled clinical comorbidities.

To select the patients, we considered typical clinical settings, such as urinary incontinence, gait disturbance and dementia and compatible image studies associated to clinical response to Tap Test (TT). All patients underwent clinical evaluation, which consists of the Mini-Mental State Examination (MM)^[16] and Time Up and Go (TUG)^[17] tests and the application of Japanese Scale for Idiopathic Normal Pressure

Hydrocephalus (JSINPH)^[2] in three stages: prior to the TT, 3 hours after the TT and 72 hours after the TT (Figure 1).

All patients were submitted to imaging studies (CT scan and MRI of the skull with CSF flow study), to screen for secondary causes of hydrocephalus. The standard measure used to determine the concept of hydrocephalus was the Evans Ratio (ER), which consists in dividing the distance between frontal horns of lateral ventricles to maximal biparietal diameter. An ER value > 0.3 is compatible with ventriculomegaly.

Once the diagnosis of hydrocephalus is established and secondary causes are excluded, the testing phase was carried out to verify whether the diversion procedure with programmable valves would be adequate.

Each patient was submitted to a protocol, which consists of two steps:

Step 1.

- a. Performance of the Mini Mental Exam.
- b. Time Up and Go
- c. Application of the Japanese Scale for Idiopathic Normal Pressure Hydrocephalus
- d. Lumbar puncture with drainage of 40-50 ml of CSF and manometry (TT).

Step 2. Three hours after the puncture, steps a, b and c were repeated.

According to the results, patients were taken back to the clinic or submitted to peritoneal shunt with Strata® adjustable valve (Medtronic).

The Mini Mental State Examination^[16] (MM) is a standard test introduced by Folstein in order to evaluate the general patterns of dementia disorders. The Time Up and Go^[17] is a test that consists of measuring the time it takes for an individual to rise from a chair, walk 3 meters, and sit back, assessing gait independence. The cutoff is

approximately 12 seconds, although some authors diverge. Thus, patients able to perform the route in less than 12 seconds are considered independent with respect to gait, while those who take longer conceptually have a gait dysfunction. It should be noted that patients with orthopedic and neurological sequelae automatically take longer to complete the route. The Japanese grading scale for iNPH^[2] is a tool to access the patients' clinical background. It measures the three main symptoms in different degrees of presentation, and can be easily performed in the preoperative period and as an evaluation questionnaire and in the follow-up of the patients.

The TT^[1,2,3,18] is a recognized test, which consists in the removal of varying amounts of CSF (40 to 50 ml) by lumbar puncture, after which the patient with suspected iNPH has hypothetically symptom improvement. It is believed that the removal of the excessive cerebrospinal fluid CSF by puncturing allows a transient improvement in clinical pattern. Usually, the element that responds better to the TT is gait, followed by urinary incontinence. As there is a learning bias in the application of MM, we considered an improvement after TT in patients with any better scores in TUG and/or JSINPH. The subjective opinion was also considered, added to TUG and/or JSINPH.

Ventricular peritoneal shunt surgery was indicated for patients with improvement in at least one of the classic triad of symptoms, in any degree. As there is a learning bias for the MM, we decided to associate their improved score to an improvement in some other parameter (urinary incontinence or gait). The subjective improvement reported by patients was also considered, but as it was difficult to measure it and due to the low degree of reliability of some reports, even because of dementia, we chose to always associate an objective parameter.

Thus, patients with indication for surgery underwent ventricular peritoneal shunt through strict technique, with the right frontal trepanation point of Kocher. The valve applied in the study was the Strata® (Medtronic), which is an externally adjustable magnetic radiopaque with anti-siphoning valve programmed to one of five performance level settings, from 0.5 to 2.5, with 0.5 increments, with each level setting being correspondent to a drainage pressure^[19] (Table 1). The Strata ® valve (Medtronic) was then adjusted to 2.5 (140 mmHg) and the patient was discharged with monthly follow-up in the first three months and then quartely follow-up. Our final follow-up time was 1 year.

In this protocol, we propose the adjustment of the valve according to symptoms, assessed with the JSINPH, Time Up and Go, Mini Mental and pattern of hydrocephalus. The valve level should start in 2.5 and adjusted on a quarterly basis, with reductions of 0.5 per occasion towards the best clinical outcome avoiding complications and symptoms of overdrainage. The objective was to achieve the lowest performance level in order to reduce the hydrocephalus and its symptoms and the limits were the lowest level (0.5) or a level which caused new symptomatology suggesting overdrainage (headache, dizziness, slit ventricle syndrome and signs of dural detachment).

The team involved in the execution of the pre operative tasks consists of two neurosurgeons guided by a senior neurosurgeon. The evaluations of each patient before and after TT was performed by the same professional. The operative and follow-up tasks were conducted by the same team with the help of two more neurosurgeons.

Statistics

In this study, numerical data are presented as mean $\pm$ standard deviation or median with range when appropriate. Categorical data are presented as percentages. When comparing groups, the level of significance is considered when $p < 0.05$. To determine the distribution of our data, the Kolmogorov-Smirnov Test was used. As all our numerical variables were parametric, Student's *t* test was used in the statistical evaluation for paired and unpaired groups, when appropriate. For categorical variables evaluation, the Chi-Square and Mc'Nemar tests were used, when respectively appropriate.

Results and discussion

Characterization of patients

A total of 32 patients were selected for the protocol. Even with the clinical and imaging screening performed, 8 patients showed to unsuitable for the protocol. In one, the MRI revealed aqueduct stenosis. In the 7 others, the Tap Tests were negative in two occasions, and so, they were excluded (Table 2).

Thus, 24 patients (11 females and 13 males) underwent ventriculoperitoneal shunt with programmable Strata® (Medtronic) valve. The mean age was 77.1 with standard deviation (SD) of 5.99. The mean age of the female group was 76.36 with SD of 7.22. The mean age in the male group was 72.57 with SD of 4.91. The two groups were statistically equal ($p > 0.05$). As our hospital is reference for a population of approximately 2 million inhabitants, the incidence found was 1.2 per 100,000.

All 24 patients presented with some sort of symptoms from the Hakim's triad. As expected, the dementia symptoms were present for more time, for an average of 35 months previously to surgery. Gait apraxia was present for a mean of 25 months and urinary incontinence for 22 months.

The diagnostic and pre-operative mean Evan's ratio was 0.37 with SD of 0.03, with no statistically difference between females and males. The preoperative Mini Mental mean was 19 before TT and 21 after TT, with statistical difference ($p=0.01$). The mean preoperative Japanese Scale was 6 before TT and 5 after TT, with statistical difference ($p=0.001$). Mean preoperative TUG was 41 seconds before and 36.41 seconds after TT, with statistical difference ($p=0.003$). The CSF mean pressure was 152 mmHg before and 29 mmHg after the TT.

The initial valve status performance was 2.5 until follow-up. The patients were routinely discharged in the second postoperative day and were followed up monthly in the first three months and then quartely. The parameters used for adjustment of the valve were radiological findings and clinical symptoms. Our time of follow-up was 1 year.

Outcome

After one year of follow-up, the average number of adjustments in valve pressure was 3.125, varying from a single adjustment in four patients to six adjustments in other 4 patients (Table 2). The final performance mean setting adjustment was 1.5. All the patients had their settings between 1 and 2.

The objective clinical and radiological results were astounding. The mean MM changed from 19 to 21, with statistical difference ($p=0.03$). JSINPH changed from 6 to 4.63, with statistical significance $p=0.016$. TUG, which before surgery was 41 seconds, became 35.77 seconds in the follow-up, with $p=0.01$. The Evans ratio in CT scans changed from 0.37 to 0.33($p=0.0001$).

Analyzing each patient individually, 4 (3 males e 1 female) did not show clinical improvement. One presented with worsening of gait and dementia instead of

radiological improvement (Evans changed from 0.45 to 0.38); another patient presented with stroke during the course of the follow-up, resulting in confusional state and hemiparesis; another patient developed subdural hematoma followed by subdural empyema, resulting in septic shock and death; the only female referred worsening of gait instead of surgery.

The radiological results revealed that in 23 patients the Evans ratio decreased after shunting. Only one male patient (subject 2) presented with increase in Evans ratio (from 0.36 to 0.40), instead of clinical improvement.

Complications

There were 8 complications in 5 patients (3 males and 2 females). We consider major complications those requiring surgical correction, including subdural hematomas and empyemas, permanent shunt obstruction and shunt infection. We consider minor complications those in which the adjustment of pressure and clinical measures were sufficient and effective for the control, including wound dehiscence, slit ventricle syndrome, transient shunt obstruction and resetting after MRI procedures^[20,21] (Table 2).

In the follow-up, malfunctioning of the valve forced the valve revision in 2 patients. One patient presented with wound dehiscence and valve exposure after six months of the surgery, and it was necessary to remove the valve. There was no significant difference in complications rate between males and females ($p < 0.01$).

Subdural collections occurred in 4 patients. One of them developed subdural collection after ongoing MRI examination and having the valve pressure reset. Initially all collections were subdural hematomas, 2 managed conservatively with valve adjustment and 2 with surgical treatment. The decision was made considering

the patient clinical presentation, location and volume of the hematoma. The asymptomatic/oligosymptomatic patients had their valves adjusted and were followed with resolution of the hematomas. The symptomatic patients or those with large collections were managed aggressively with surgical drainage^[22].

The management of subdural hematomas with valve adjustment consisted of resetting the level to 2.5 and weekly follow-up until recovery from symptoms and absorption of the hematoma. After that, the patient began again the quarterly adjustment towards the best level without new complications.

Fortunately, shunt infections did not occur in our sample. However, in one case, the subdural hematoma recurred after the first drainage, and after the second drainage there was progression to subdural empyema. This patient died from septic shock.

Subjective opinion

After one year of the surgery, we asked the families of the patients and the patients themselves about the subjective outcome, in other words, if the family was satisfied or not and if there was improvement in the caregiver's burden. Of the 24 families/patients, 20 referred some degree of subjective improvement. Four families/patients referred no improvement, with stability of the clinical profile in 3 cases (including the patient who died from subdural empyema) and worsening of profile in 1 patient. The parameter that showed the best improvement after shunting was the gait, followed by urinary incontinence.

Discussion

INPH is one of the few causes of dementia that is potentially reversible. Hakim and Adams described in 1965 the classic triad which can characterize the disease in different degrees of combination^[3].

Diversions with programmable valves are recommended for the treatment of iNPH, since the drainage pressure can be adjusted. Although the programmable valves are widely used, they still lack well-defined protocols to guide the steps to attain proper pressure for each patient^[20].

Other reports on the use of valves are known. The Codman Medos valve allows pressure adjustment in 18 steps between 30 and 200 mm H₂O. A series of 90 patients was reported with satisfying clinical results^[23]. Another retrospective study was published with 583 patients with hydrocephalus due to various causes who were shunted with Codman Hakim programmable valve^[24]. The proGAV (Aesculap) valve also has literature support^[25].

The Strata® valve has been described before, including in pediatric patients^[19,26]. It has already been stated that adjustments can be used to treat signs or symptoms of cerebrospinal fluid overdrainage or hypodrainage, which may obviate the need for additional surgery. The number of hospital admissions and operations for valve malfunction has decreased^[27,28]. Recently, the Strata® valve was the object of a study with 72 patients with iNPH, with adequate control of symptoms and long term durability^[29].

The main objective of this study was to reanalyze Strata® performance in a specific protocol for diagnosis and adjustment only in patients with iNPH. The group of patients evaluated in this study was screened for iNPH and 24 showed possibility of improvement with shunting. After shunting, 20 presented with objective clinical improvement, measured through tests. According to other reports, approximately 60% of patients refer improvement after shunting^[12,13,20,24,29]. We attribute the better

results to the screening design and to the easily adjustable valve to fit each patient's behavior.

Nevertheless, 20.8% of the patients had complications. Looking at some published statistics of complications, it is possible to see that this percentage varies from 13% to near 40%^[12,13,20,22,24,29], and we had 5 major complications resulting in surgical interventions. Considering the age group of the shunted patients and the addition of comorbidities attributed to the surgery, the surgical approach to treatment of subdural collections or simply the switching of the valve carries an important weight in the improvement of clinical conditions and caregivers' burdens.

Nevertheless, the encouraging data are related to the two patients submitted to valve substitution, who showed improvement after the surgery. Another confirmed noteworthy aspect was the resolution of the subdural hematomas with no need for surgery, as only valve pressure adjustment was necessary^[22]. It is clear, however, that the advantage of adjusting the valve should be analyzed together with patient clinical status, as large subdural collections can cause altered consciousness state or neurological deficits and must be promptly surgically drained. The absence of shunt infections in our sample can be explained due to the elective characteristic of the surgery, resulting in shorter hospital stay in the pre and post-operative period.

An important concern about Strata® valve use is the potential change in settings after a magnetic resonance examination. It is necessary to follow the patient in order to reset the pressure after such examinations.

Some other questions should be raised. First, when the patient is older, one should be cautious about the results of dementia improvement after shunting. The

association with Alzheimer disease and other types of dementia ^[30] is known, sometimes with no improvement after shunting.

Unfortunately, we did not apply in this opportunity a multidisciplinary team approach, with the participation of neurologists, geriatricians, physiotherapists, occupational therapists. In addition, we did not apply in this study some known functional scales to evaluate the patients, such as Rankin Scale and Barthel Index. We surely recognize the validity of these tools but we have proposed a protocol based in other objective measurements (MM, TUG and JSINPH) and subjective opinion. Moreover, the screening for shunt surgery was based on repeated TT. Neither the Continuous Lumbar Drainage Test nor the Katzman Infusion Test were applied to this sample, which are recognized tools used to improve the sensitivity when diagnosing iNPH^[1,2,3]. All such observations must be considered and aimed in future projects.

Finally, our results are bound to a 1-year follow-up. Although encouraging, they are not yet enough to evaluate a more definitive pattern of response to the Strata valve®. However, our own initial experiences with larger follow-ups seem to corroborate the previous results.

Conclusions

Our results are quite satisfactory, as clinical and radiological improvement were observed in 83% of patients and the complications, although still frequent (21%), were easier to be dealt with, because of the capacity of manipulating valve pressure settings.

Indeed, further similar studies are necessary, nevertheless we have applied a unique protocol for diagnosis and follow-up of iNPH patients and propose that the use of Strata® is safe and effective to the treatment of iNPH.

List of Abbreviations

iNPH – Idiopathic Normal Pressure Hydrocephalus

CSF – Cerebrospinal fluid

CT – Computed Tomography

MRI – Magnetic Resonance Imaging

NPH – Normal Pressure Hydrocephalus

TT- Tap Test

MM – Mini Mental

TUG – Time Up and Go

JSINPH – Japanese Scale for Idiopathic Normal Pressure Hydrocephalus

ER – Evans Ratio

SD – Standard Deviation

Competing interests:

The authors declare no competing interests.

Author's contributions:

MFO was the main author, in charge of the study design, and experimental phase, analyzed and edited the paper. FCGP was, together with MFO, in charge of the study design, experimental phase and analyses of results. FS and RCR were crucial in the experimental phase (follow-up) of the patients, in collecting data and analyzing results. JMR was, together with MFO and FCGP, responsible for

the study design, experimental phase and editing the paper, with remarkable contributions to the discussion. All authors read and approved the final manuscript.

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Figure legends

Figure 1. Protocol design. The scheme displays the protocol consisting in patients selection and undergoing the tests MM, TUG and JSINPH before and after TT, in order to determine the suitability of diversion surgery.

Figure 2. JSINPH. JSINPH is a recognized tool to evaluate and grade the three main symptoms in iNPH.

Figure 3. Pre and post operative skull computed tomography in a typical subject from the sample (patient number 7), with change in Evans ratio from 0.38 to 0.35 after 1 year of surgery, related to clinical improvement, especially in gait pattern.

Figure 4. Skull computed tomography of the subject before shunting (column A), in the admission with moderate headache due to bilateral chronic subdural hematomas (column B) and before discharge, with remarkable recovery of sulci and

gyri (column C). In this case, due to adjustment of valve pressure, the surgical procedure was not necessary.

Tables

Table 1. Correspondence between level setting and drainage pressure in Strata® valve.

Level Setting	Drainage Pressure
0.5	20mmHg
1.0	40mmHg
1.5	80mmHg
2.0	110mmHg
2.5	140mmHg

Table 2. Characterization of patients in pre and postoperative periods.

SUBJECTS		TIME OF SYMPTOMS (months)			PRE OPERATIVE				POST OPERATIVE (1 YEAR)							
Patient	Age(years)	Gait	Dementia	Incontinence	EVANS	MM	TUG	ISINPH	EVANS	MM	TUG	ISINPH	Adjustments	Final setting	complication	OPINION
1	62	6	6	6	0,36	29	9	5	0,32	29	8	4	3	1,5		SATISFIED
2	79	36	56	56	0,36	28	13	6	0,4	26	14	3	6	1		SATISFIED
3	82	48	48	48	0,3	25	17	6	0,28	25	14	5	2	1,5		SATISFIED
4	80	34	18	18	0,36	29	20	4	0,35	29	19	3	5	1		SATISFIED
5	88	6	72	6	0,38	18	22	8	0,3	22	16	7	2	1		SATISFIED
6	70	10	24	12	0,37	19	24	5	0,32	21	29	3	1	2		SATISFIED
7	77	6	6	6	0,38	15	25	3	0,35	17	23	2	1	2		SATISFIED
8	70	72	96	60	0,4	20	36	4	0,36	21	33	3	2	1,5		SATISFIED
9	83	12	12	12	0,47	24	26	6	0,34	18	56	5	0	2	malfunction and subdural hematoma	UNSATISFIED
10	89	12	12	12	0,41	23	27	4	0,38	26	20	3	2	1,5		SATISFIED
11	82	72	72	24	0,42	18	29	5	0,38	19	26	4	6	1,5	malfunction and subdural hematoma	SATISFIED
12	75	12	86	12	0,37	21	37	8	0,34	21	50	7	6	1		UNSATISFIED
13	73	12	12	12	0,4	21	38	8	0,35	20	49	7	5	1		UNSATISFIED
14	82	72	72	36	0,41	8	40	4	0,35	14	38	3	3	2,5	subdural hematoma and empyema	UNSATISFIED
15	84	12	12	18	0,4	15	41	6	0,35	20	20	2	4	1,5	subdural hematoma	SATISFIED
16	75	18	18	24	0,35	13	45	6	0,31	18	30	1	3	1		SATISFIED
17	84	12	24	18	0,37	18	50	3	0,32	21	40	2	1	2		SATISFIED
18	73	12	12	12	0,35	20	37	5	0,34	23	45	3	2	1,5		SATISFIED
19	77	12	12	36	0,37	24	60	9	0,34	26	48	5	2	1,5		SATISFIED
20	78	36	36	36	0,38	21	66	10	0,32	23	60	8	2	1,5		SATISFIED
21	82	30	50	30	0,32	13	70	8	0,3	16	55	7	3	1		SATISFIED
22	75	24	24	24	0,38	11	164	0	0,33	11	133	7	2	1,5		SATISFIED
23	74	60	72	36	0,41	16	67	4	0,37	22	52	2	3	2		SATISFIED
24	79	6	96	12	0,34	14	80	12	0,31	19	58	11	1	2	valve exposure	SATISFIED

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