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Departamento de Clínica Médica – Centro de Ciências das Imagens e Física Médica

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Contribuição dos métodos de imagem no estudo das  
glândulas suprarrenais em pacientes com hiperplasia  
congênita de suprarrenal, com ênfase nas técnicas  
quantitativas por ressonância magnética

Ribeirão Preto 2014

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**TEIXEIRA, S. R. Contribuição dos métodos de imagem no estudo das glândulas suprarrenais em pacientes com hiperplasia congênita de suprarrenal, com ênfase nas técnicas quantitativas por ressonância magnética.** Tese apresentada à Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo para obtenção do título de Doutor em Medicina, pelo departamento de Clínica Médica, Centro de Ciências das Imagens e Física Médica.

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Ao Caio com amor e admiração, poço de serenidade.  
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## RESUMO

Teixeira, S. R. **Contribuição dos métodos de imagem no estudo das glândulas suprarrenais em pacientes com hiperplasia congênita de suprarrenal, com ênfase nas técnicas quantitativas por ressonância magnética.** 2014. 89f. Tese (Doutorado) - Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, 2014.

Hiperplasia congênita de suprarrenal (CAH) compreende um grupo de transtornos hereditários decorrentes de erros inatos do metabolismo dos esteróides adrenais. O aumento das dimensões das glândulas suprarrenais é um marco morfológico na CAH que pode ser avaliado por métodos de imagem com significativa correlação com o controle hormonal dos pacientes. Porém, técnicas de imagem que forneçam informações qualitativas e quantitativas relativas à citoarquitetura das glândulas ainda não foram estabelecidas neste contexto. A difusão por ressonância magnética (DWI) é uma técnica que pode fornecer informações quantitativas dos tecidos através do valor do coeficiente de difusão aparente (ADC). O papel do ADC na avaliação de lesões tumorais adrenais já foi estudado, no entanto, o valor do ADC das glândulas suprarrenais normais ainda não foi descrito. O objetivo geral desta tese foi investigar a utilidade dos métodos de imagem na avaliação da CAH. Os objetivos específicos foram apresentar uma revisão dos métodos por imagem já estabelecidos para avaliação da CAH, validar o cálculo do ADC da glândula suprarrenal e avaliar se o ADC e as dimensões das glândulas suprarrenais poderiam auxiliar no manejo de pacientes com CAH, correlacionando-os com controle hormonal. Esta tese é baseada em artigos, nos quais estão mostrados a metodologia, resultados e discussões relativos a cada uma das etapas. O primeiro artigo, *The role of imaging in congenital adrenal hyperplasia*, trata de uma revisão sistemática de imagem em CAH, com ênfase em genitografia, ultrassonografia, tomografia computadorizada e ressonância magnética (MRI). O segundo artigo, *Apparent Diffusion Coefficient (ADC) of the normal adrenal glands: preliminary results*, teve como principal objetivo validar o método de medida do ADC das glândulas suprarrenais. No terceiro artigo, *Quantitative magnetic resonance imaging in the evaluation of adrenal glands in children and young adults with congenital adrenal hyperplasia due to 21-hydroxylase deficiency*, foram estudados os parâmetros quantitativos por MRI (ADC, volume e medidas lineares) das glândulas suprarrenais que poderiam estar relacionados ao controle hormonal dos pacientes com CAH. Medir o ADC das suprarrenais normais é factível e reproduzível. Em indivíduos saudáveis após a adrenarca o ADC é significativamente menor. Todavia, o ADC não foi capaz de diferenciar indivíduos controles de pacientes com CAH, assim como não apresentou correlação com o status hormonal dos pacientes. O volume e as medidas lineares das glândulas adrenais foram os melhores parâmetros quantitativos por MRI para diferenciar pacientes de indivíduos controles, com correlação positiva com o status hormonal recente dos pacientes com CAH. As dimensões das glândulas suprarrenais avaliadas por MRI podem ser utilizadas como ferramenta auxiliar no acompanhamento dos pacientes e mostrar rapidamente os efeitos da exposição a altos níveis de hormônio adrenocorticotrópico. Apesar de ocorrerem modificações celulares na CAH e de ter sido mostrado neste estudo que em pacientes sem doença hormonal conhecida o ADC é mais baixo após a adrenarca, estas alterações celulares que ocorrem na CAH não foram detectadas pelas medidas de ADC.

**Palavra-chave:** Imagem por ressonância magnética. Difusão por ressonância magnética. Coeficiente aparente de difusão. Glândulas suprarrenais. Hiperplasia congênita de suprarrenal. Diagnóstico por imagem.

## ABSTRACT

Teixeira, S. R. **The role of imaging in evaluation of the adrenal glands in congenital adrenal hyperplasia, with an emphasis on quantitative magnetic resonance imaging.** 2014. 89p. Thesis (Doctorate) – Ribeirao Preto Medical School, University of Sao Paulo, Ribeirao Preto, 2014.

Congenital adrenal hyperplasia (CAH) is an autossomic recessive disorder caused by impaired steroidogenesis. A morphological hallmark in CAH is enlarged adrenal glands. Imaging studies have addressed mainly morphological aspects and dimensions of the adrenal glands, which correlate to the patients' hormonal statuses. However, no imaging technique was used to evaluate changes in the adrenal glands at a cellular level in these patients. Diffusion-weighted magnetic resonance imaging (DWI) is a magnetic resonance imaging (MRI) technique with the ability to provide quantitative information about intracellular and extracellular space, given by the apparent diffusion coefficient (ADC) values. The role of ADC in evaluation of adrenal lesions has already been studied. However, ADC of the normal adrenals has not yet been described. The main purposes of this study were: to investigate the role of imaging in CAH, to validate the method of calculating ADC values of the normal adrenal glands and to assess hormonal status in patients with CAH and its correlation to quantitative MRI. This is an article-based thesis divided in three articles. The first article, *The role of imaging in congenital adrenal hyperplasia*, is a systematic review of imaging in congenital adrenal hyperplasia, with emphasis on genitography, ultrasonography, computed tomography and MRI. The article *Apparent diffusion coefficient (ADC) of the normal adrenal glands: preliminary results* aimed to validate the method of measuring ADC of the adrenal glands. The study of quantitative parameters (ADC, volume and linear measurements) of the adrenals evaluated by MRI that correlate with hormonal status in patients with CAH is described in the third article, *Quantitative magnetic resonance imaging in evaluation of the adrenal glands in children and young adults with congenital adrenal hyperplasia due to 21-hydroxylase deficiency*. Measuring ADC of the normal adrenal glands is feasible and reproducible. In healthy subjects, ADC values were significantly lower after adrenarche. However, neither a difference between ADC values of controls and patients, nor correlations with patients' hormonal statuses were found. Volume and linear measurements of the adrenal glands were the best parameter to differentiate patients from controls. Moreover, a positive correlation was found between short-term hormonal control status and adrenal size. Adrenal size assessed by MRI might be a useful tool in the follow-up of patients with CAH. Although adrenal cell structure modifications in patients with CAH have been described, they were not detectable by DWI.

Keywords: Magnetic resonance imaging. Diffusion magnetic resonance imaging. Apparent diffusion coefficient. Adrenal glands. Adrenal hyperplasia, congenital. Diagnostic imaging.

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## 1. INTRODUÇÃO

Hiperplasia congênita de suprarrenal (CAH) é um grupo de doenças autossômicas recessivas causadas por mutações em uma das enzimas que participam da esteroidogênese adrenal. A enzima mais comumente afetada é a 21-hidroxilase, pertencente à superfamília do citocromo P450.<sup>1</sup> Com isso, há diminuição da retroalimentação mediada pelo cortisol, hipersecreção compensatória de hormônio adrenocorticotrópico (ACTH) e consequente hiperplasia adrenal funcional e estrutural.

A apresentação clínica da CAH é variável e depende da gravidade da deficiência enzimática.<sup>2</sup> Os pacientes com CAH podem apresentar vários graus de insuficiência adrenal, podendo apresentar perda ou não perda de sal, virilização, alteração na função reprodutiva, aumento da incidência de nódulos adrenais e tumores, como adenomas e mielolipomas,<sup>3</sup> ou ainda serem assintomáticos. No sexo masculino, há uma alta incidência de tumor testicular de restos adrenais (TART).<sup>4,5</sup>

O objetivo do tratamento é repor glicocorticoides e mineralocorticoides, suprimir o aumento de ACTH e normalizar os androgênios adrenais. O monitoramento dos pacientes é feito através de parâmetros clínicos e laboratoriais. A avaliação da velocidade de crescimento e da idade óssea através de radiografia simples são os parâmetros clínicos mais usados para o monitoramento. Os marcadores séricos mais comumente utilizados são 17-hidroxiprogesterona, androstenediona e testosterona.<sup>6</sup>

Aumento bilateral das glândulas suprarrenais é um marco morfológico na CAH, principalmente em pacientes não tratados ou não controlados clínico-laboratorialmente.<sup>7</sup> Nas análises histopatológicas, o córtex das glândulas suprarrenais é hiperplásico e espessado. Microscopicamente, há uma perda de diferenciação das zonas corticais e entrelaçamento das células da medula e do córtex adrenal.<sup>8</sup>

Os métodos de imagem podem ser utilizados em várias situações clínicas relacionadas à CAH como diagnóstico, controle de tratamento, avaliação pré cirúrgica e seguimento.<sup>2,9-13</sup> Além da possibilidade de volumetria e medidas lineares das glândulas suprarrenais, os métodos de imagem hoje permitem a obtenção de outras variáveis quantitativas que poderiam ter alguma utilidade na avaliação da CAH. Sendo assim, este trabalho tem como justificativas a revisão da utilidade dos métodos de imagem já consolidados para avaliação das suprarrenais em CAH e de novas técnicas quantitativas por MRI nesse contexto.

## 1.1 Técnicas de imagem quantitativas na avaliação da glândula suprarrenal

Atualmente, os principais métodos de imagem empregados para avaliação das glândulas suprarrenais são: ultrassonografia (US), tomografia computadorizada (CT) e ressonância magnética (MRI). Estes substituíram os métodos invasivos (ex.: angiografia digital) e são preferíveis tanto em crianças como em adultos.<sup>14,15</sup> Em recém-nascidos e crianças menores, US é o método de escolha<sup>14</sup> inicial pois fornece imagens de alta resolução, além de ser um método de menor custo, versátil e isento de radiação ionizante. Com a evolução da MRI, esta vem sendo cada vez mais empregada para avaliação de lesões adrenais, inclusive em crianças. Apesar de menos disponível e, em alguns casos, existir a necessidade de sedação, as vantagens da MRI comparada à CT são principalmente a alta resolução de contraste tecidual e ausência de radiação ionizante.<sup>16</sup> Ainda, sequências derivadas de técnicas avançadas por MRI que fornecem informações relativas à caracterização tecidual e citoarquitetura, como difusão por ressonância magnética (DWI) ou espectroscopia de prótons, podem ser realizadas no intuito de aumentar a acurácia diagnóstica, bem como predizer prognóstico de diversas doenças e avaliar resposta a tratamento.

Alterações da morfologia e medidas lineares da glândula suprarrenal podem ser tomadas por quaisquer dos métodos acima mencionados. Na US, o achado do padrão cerebriforme da glândula suprarrenal foi descrito como específico para o diagnóstico de CAH, tanto no período pré<sup>17,18</sup> como pós-natal.<sup>19,20</sup> Tanto aumento difuso como nodular<sup>21</sup> das glândulas suprarrenais também podem ser observados em pacientes com CAH. O aumento da glândula suprarrenal é definido como espessura da perna da glândula maior que 4,0 mm e medida longitudinal maior que 20 mm<sup>12</sup> na US em recém-nascidos e lactentes ou espessura da perna maior que 5 mm, espessura do corpo maior que 10 mm e medida longitudinal maior que 25 mm medida por CT.<sup>22,23</sup> Porém, as medidas longitudinais da suprarrenal podem não ser acuradas pois as pernas podem não ser totalmente vistas na mesma imagem, já que é um órgão ondulado,<sup>20</sup> além dos efeitos de volume parcial.<sup>22</sup>

O volume das glândulas suprarrenais pode ser medido por US. No período pré-natal a US 3D pode estimar com melhor acurácia o volume das suprarrenais quando comparado à US 2D.<sup>24</sup> O volume do órgão está relacionado ao peso fetal estimado a partir da 21<sup>a</sup> semana de gestação,<sup>25</sup> ao risco de parto prematuro,<sup>24</sup> ao aumento do stress fetal e ao baixo peso fetal em mulheres com inflamação amniótica.<sup>26</sup> Na CT o volume da glândula suprarrenal pode ser medido por segmentação manual<sup>27</sup> ou semi-automática.<sup>28</sup> Hiperfunção do córtex adrenal e

consequente hipertrofia e aumento do volume da glândula podem ocorrer em pacientes com depressão<sup>29,30</sup> e estão relacionados a hiper cortisolismo subclínico em adultos.<sup>31</sup> A ausência de aumento do volume da glândula em pacientes com choque séptico está relacionada a alto risco de mortalidade e pode ser usada como fator prognóstico.<sup>28,32</sup>

A MRI também permite a medida do volume das glândulas suprarrenais, com técnicas semelhantes às empregadas na CT. Com a mesma espessura de corte, o volume de phantoms medido pela MRI é mais acurado comparado com CT, superestimando o volume real em 20% versus 42% pela CT.<sup>33</sup> A volumetria da glândula suprarrenal realizada por MRI é factível e reproduzível tanto em adultos<sup>34</sup> como em crianças.<sup>35</sup> Esta técnica já foi usada para o estudo de pacientes com depressão,<sup>36</sup> com resultados semelhantes aos encontrados previamente com uso da CT neste grupo de pacientes. Em adultos com CAH, o volume total da suprarrenal e o tamanho de nódulos estão diretamente relacionados ao controle hormonal avaliado por dosagens séricas de androstenediona e 17-hidroxiprogesterona.<sup>11</sup> Porém, até o momento da preparação desta tese, desconhecem-se estudos sobre o valor clínico da MRI para determinar o volume das suprarrenais na faixa etária pediátrica em pacientes com CAH e se existe correlação com o controle hormonal.

Além das dimensões e morfologia da lesão, a medida da densidade por CT ou intensidade de sinal por MRI fornecem informações importantes para aumentar a especificidade no diagnóstico por imagem de lesões adrenais. Uma técnica quantitativa já bem estabelecida para avaliação de lesões na suprarrenal é a quantificação de gordura intracitoplasmática. O objetivo é aumentar a especificidade no diagnóstico de lesões benignas, como adenomas, e diferenciá-las corretamente de lesões malignas ou que mereçam intervenção. Em pacientes de baixo risco sem doença maligna conhecida, uma lesão descoberta em exames de imagem – “incidentaloma” – é provavelmente benigna e pode ser caracterizada com alta acurácia por exames de imagem em até 87% dos casos.<sup>37</sup>

No exame de CT sem contraste, características morfológicas compatíveis e coeficiente de atenuação menor que 10 unidades Hounsfield (UH) em uma lesão de suprarrenal é diagnóstico de adenoma.<sup>38</sup> Porém, como 17 a 22% dos adenomas podem não ser detectados com esta técnica,<sup>37,39</sup> a CT combinada com fases pós contraste incluindo fase tardia aumenta a especificidade deste método. Calculando-se o percentual de clareamento do contraste da lesão a partir de fases tardias após 15 minutos da injeção venosa de contraste, foi descrita sensibilidade de 88 a 96% e especificidade de 61 a 96% para o diagnóstico de adenomas *versus* lesões não adenomatosas.<sup>40,41</sup> Porém, para diferenciar metástases hipervasculares de adenomas pobres em gordura, este cálculo pode não ser útil, pois até 95% destas metástases

podem ser falsamente diagnosticadas como adenomas pobres em gordura.<sup>42</sup>

O efeito de desvio químico na MRI é baseado na diferença de frequência de ressonância dos prótons de gordura e água, sendo que os prótons de gordura apresentam frequência de precessão menor que os de água.<sup>43</sup> Este efeito pode levar ao cancelamento da contribuição desses prótons para a formação da imagem, com redução de sinal em imagens adquiridas com a técnica gradiente eco fora-de-fase, sendo possível caracterizar lesões com gordura intracelular como adenomas.<sup>44</sup> O desvio químico pode ser quantificado tanto pela razão de sinal suprarrenal-baço (ASR)<sup>44</sup> quanto pelo razão de sinal da suprarrenal nas sequências em-fase e fora-de-fase (SII), este último mais eficaz.<sup>45</sup> ASR e SII são dados pelas fórmulas:<sup>45</sup>

$$\text{SII} = \left[ \frac{\text{Adrenals}_{\text{SI}} \text{IP} - \text{Adrenals}_{\text{SI}} \text{OP}}{\text{Adrenals}_{\text{SI}} \text{IP}} \right] \times 100 \% \quad \text{ASR} = \left[ \frac{\text{Adrenals}_{\text{SI}} \text{OP} / \text{Baços}_{\text{SI}} \text{OP}}{\text{Adrenals}_{\text{SI}} \text{IP} / \text{Baços}_{\text{SI}} \text{IP}} \right] - 1 \times 100 \%$$

em que Adrenals<sub>SI</sub> é a intensidade de sinal da lesão adrenal, Baços<sub>SI</sub> é a intensidade de sinal do baço, IP é imagem gradiente eco em-fase e OP é imagem gradiente eco fora-de-fase.

Usando-se o ponto de corte de -25 para detecção de adenoma por ASR, a sensibilidade e especificidade são 100% e 78%, respectivamente.<sup>46</sup> Uma razão SII maior que 16,5% apresenta 100% de acurácia para detecção de adenomas<sup>45</sup> podendo variar dependendo dos parâmetros de imagem utilizados.<sup>47</sup> No entanto, foi mostrado que a avaliação qualitativa do desvio químico realizada por avaliadores experientes é semelhante à quantitativa,<sup>46</sup> portanto, estas medidas são mais úteis nas mãos de avaliadores menos experientes.

A relação entre o sinal de lesões adrenais com figado e baço nas sequências ponderadas em T2 também já foi usada para diferenciar adenomas de lesões malignas, porém com acurácia moderada.<sup>48,49</sup> O uso da relaxometria pode aumentar a especificidade destes achados, com tendência ao prolongamento do tempo T1 em metástase e carcinoma adrenocortical comparado ao do adenoma.<sup>48</sup> Porém as técnicas por desvio químico são mais específicas.<sup>50</sup>

Quanto ao uso de contraste venoso na MRI, alguns estudos mostraram resultados contraditórios em relação à intensidade de sinal pré e pós-contraste e percentagem de clareamento do contraste de lesões adrenais. Adenomas tipicamente apresentam discreto reforço pelo meio de contraste e rápido clareamento do contraste comparado às lesões não adenomatosas como metástases e feocromocitomas,<sup>51</sup> porém não foi encontrada diferença significativa entre o pico de reforço pós contraste dos adenomas comparado ao de lesões malignas.<sup>52</sup> Em outro estudo, apesar de ter sido mostrado um maior reforço pós-contraste de

lesões malignas comparadas aos adenomas, esta diferença não foi significativa; mas o “washout” máximo foi significativamente maior nos adenomas.<sup>53</sup>

Imagen de difusão por ressonância magnética (DWI) é uma técnica estabelecida e gradativamente incluída na maioria dos protocolos clínicos de MRI do abdome. DWI fornece informações qualitativas e quantitativas no nível celular, baseada em difusão molecular das moléculas de água.<sup>54</sup> Informações quantitativas dadas pelas medidas do coeficiente de difusão aparente (ADC) derivado da DWI são reconhecidas como potenciais biomarcadores,<sup>55,56</sup> com significativa correlação com celularidade tecidual, tortuosidade do espaço extra-cellular e integridade das membranas celulares.<sup>57-60</sup>

A DWI tem sido estudada para avaliar lesões em órgãos abdominais, tanto focais como difusas,<sup>61-66</sup> e para avaliar o aspecto habitual de diversos órgãos em indivíduos saudáveis.<sup>65-67</sup> Na glândula suprarrenal, esta técnica foi usada principalmente para diferenciar lesões malignas de benignas,<sup>68-70</sup> com resultados discordantes. Em dois estudos, comparando-se diferentes tipos de lesões malignas de benignas, valores de ADC não foram suficientes para diferenciá-las, apesar de que feocromocitomas apresentaram valores significativamente mais altos de ADC comparados às demais (ADC variando de  $1,59$  a  $1,84 \times 10^{-3} \text{ mm}^2/\text{s}$ ), com exceção dos cistos.<sup>70,71</sup> O ADC também não foi suficiente para diferenciar adenomas pobres em gordura de outras lesões não gordurosas.<sup>71</sup> Resultados semelhantes também foram encontrados por outros pesquisadores que mostraram que o ADC não pode ser usado para diferenciar lesões benignas, principalmente adenomas, de malignas, na sua maioria, metástases.<sup>72,73</sup>

Por outro lado, outros estudos mostraram a importância da DWI e da medida do ADC como uma das técnicas quantitativas que pode auxiliar no diagnóstico de lesões adrenais. Sandrasegaran e colaboradores<sup>68</sup> mostraram que o ADC de lesões benignas era significativamente mais alto que o de lesões malignas. Usando-se um ponto de corte de  $0,96 \times 10^{-3} \text{ mm}^2/\text{s}$  para o diagnóstico de lesões benignas, a sensibilidade foi 79,2% e a especificidade, 81%. Além disso, lesões benignas apresentaram valor de  $\text{ADC} < 1,0 \times 10^{-3} \text{ mm}^2/\text{s}$  e as malignas  $> 1,5 \times 10^{-3} \text{ mm}^2/\text{s}$ . Em um outro estudo que incluiu lesões com coeficientes de atenuação maior que 10 UH na CT sem contraste, ou seja, não lesões características para adenoma por este método, o ponto de corte de 1,04 mostrou sensibilidade de 61,4% e especificidade de 85,7%.<sup>69</sup> Ainda, o ADC mostrou-se útil para diferenciar adenomas de metástases<sup>74</sup> e feocromocitomas benignos de malignos, com um valor de corte de  $1,016 \times 10^{-3} \text{ mm}^2/\text{s}$ , sensibilidade de 93,3% e especificidade de 77,8%.<sup>75</sup>

Estudos por imagem das glândulas suprarrenais em pacientes com CAH foram

desenhados principalmente para mostrar as alterações morfológicas e dimensões das glândulas.<sup>7,11,21,76</sup> Porém, faltam trabalhos que investigassem a DWI em sujeitos saudáveis ou o papel da DWI em doenças que possam afetar difusamente a glândula, como a CAH.

Espectroscopia de prótons por MRI é uma técnica funcional de análise de metabólitos celulares que vem emergindo da pesquisa para o uso clínico.<sup>77</sup> Esta técnica consiste na obtenção de um espectro de picos que representam as intensidades de sinal em função da frequência de precessão dos metabólitos, expressos na unidade partes por milhão (ppm). O número de metabólitos que podem ser medidos depende dos parâmetros e do pulso das sequências, sempre levando-se em consideração o sinal do espectro e a relação sinal-ruído.<sup>77</sup> Creatina é um metabólito padrão usado para avaliar o metabolismo energético celular, já a colina participa de vários componentes que formam a membrana celular. Na avaliação de lesões adrenais, a espectroscopia por MRI parece ser uma técnica promissora. A percentagem de lipídios é significativamente maior em adenomas e hiperplasia secundária à doença de Cushing comparados com carcinomas adrenocorticiais.<sup>78,79</sup> Em outro estudo, a razão colina-creatina foi o melhor parâmetro para diferenciar lesões benignas de malignas, com ponto de corte de 1,20 (92% sensibilidade e 96% especificidade) comparando-se a outras como a razão colina-lipídio 0,38 (92% sensibilidade e 96% especificidade) e a razão lipídio-creatina 2,10 (45% sensibilidade e 100% especificidade).<sup>80</sup> Um pico em 6,8 ppm pode representar a presença de produtos da catecolamina intralesional e parece ser específico para o diagnóstico de feocromocitoma.<sup>81</sup>

## 1. OBJETIVO

O objetivo geral desta tese foi investigar a utilidade dos métodos de imagem na avaliação da CAH.

Os objetivos específicos foram:

- apresentar uma revisão dos métodos por imagem já estabelecidos para avaliação da CAH;
- validar o cálculo do ADC derivado da DWI da glândula suprarrenal;
- avaliar se o ADC e as dimensões (volume e medidas lineares) das glândulas suprarrenais poderiam auxiliar no manejo de pacientes com CAH, correlacionando-os com controle hormonal.

## 2. MÉTODOS

O projeto de pesquisa foi aprovado pelo Comitê de Ética Institucional (Anexo A) e consentimento informado assinado foi obtido dos participantes ou de seu responsável legal (Anexos B e C).

Para atingir o objetivo primário foi inicialmente feita uma revisão sistemática da literatura sobre o tema imagem em CAH. Em seguida, foram definidos quais parâmetros quantitativos por MRI seriam investigados. A validação do método de cálculo de ADC das glândulas suprarrenais foi feita paralelamente.

Cada uma destas etapas resultou em um artigo reproduzido nesta tese, organizada como descrito no tópico a seguir. Todos os artigos foram submetidos para jornais científicos e estão em fase de revisão.<sup>82-84</sup>

## 4. ORGANIZAÇÃO DA TESE

Esta tese integra três artigos.

O **tópico cinco** desta tese contém o primeiro artigo: “*The role of imaging in congenital adrenal hyperplasia*”. Neste artigo, foi feita uma revisão sistemática sobre o papel dos métodos de imagem em CAH, com ênfase em genitografia (RXC), US, CT e MRI.

A medida de ADC em estruturas pequenas pode muitas vezes ser difícil. No **tópico seis** está reproduzido o artigo “*Apparent Diffusion Coefficient (ADC) of the normal adrenal glands: preliminary results*”, que teve como objetivo validar o método de medida de ADC nas glândulas suprarrenais e definir o valor normal de ADC em sujeitos saudáveis.

O estudo sobre os parâmetros quantitativos (ADC, volume e medidas lineares) das glândulas suprarrenais avaliados por MRI e sua correlação com o status hormonal dos pacientes com CAH está descrito no artigo “*Quantitative magnetic resonance imaging in evaluation of adrenal glands in children and young adults with congenital adrenal hyperplasia due to 21-hydroxylase deficiency*” do **tópico sete**.

A discussão geral da tese é apresentada no **oitavo tópico** e conclusões finais no **nono tópico**. As referências bibliográficas estão inseridas após as conclusões finais. Embora dupliquem algumas das citações específicas de cada artigo, facilitam a localização das referências citadas ao longo dos demais tópicos deste documento. Os anexos aparecem no final deste documento.

## 5. O PAPEL DA IMAGEM EM HIPERPLASIA CONGÊNITA DE SUPRARRENAL

O artigo reproduzido abaixo “*The role of imaging in Congenital Adrenal Hyperplasia*” é uma revisão sistemática sobre o papel da imagem em pacientes com CAH. A partir deste estudo foram definidos os parâmetros quantitativos por MRI que poderiam correlacionar com o controle hormonal dos pacientes com CAH e auxiliar no seu manejo.

## The role of imaging in congenital adrenal hyperplasia

**5.1 Abstract:** Congenital adrenal hyperplasia is an autossomic recessive disorder caused by impaired steroidogenesis. Patients with CAH may present adrenal insufficiency with or without salt-wasting, as well as various degrees of virilization and fertility impairment, carrying a high incidence of testicular adrenal rest tumors and increased incidence of adrenal tumors. The diagnosis of CAH is made based on the adrenocortical profile hormonal evaluation and genotyping, in selected cases. Follow-up is mainly based on hormonal and clinical evaluation. Utility of imaging in this clinical setting may be helpful for the diagnosis, management, and follow-up of the patients, although recommendations according to most guidelines are weak when present. Thus, the authors aimed to conduct a narrative synthesis of how imaging can help in the management of patients with CAH, especially focused on genitography, ultrasonography, computed tomography, and magnetic resonance imaging.

**Key-words:** Adrenal hyperplasia, congenital; Magnetic resonance imaging; Computed tomography; Ultrasonography; Diagnostic imaging.

**Resumo:** Hiperplasia congênita adrenal (CAH) é uma doença autossômica recessiva causada por deficiências enzimáticas na esteroidogênese. Clinicamente, os pacientes com CAH podem apresentar insuficiência adrenal com ou sem perda de sal, vários graus de virilização e diminuição na fertilidade, alta incidência de tumores adrenais de restos testiculares e de tumores adrenais. O diagnóstico de CAH é feito baseado nos resultados da avaliação hormonal e genotípica, em casos selecionados. O seguimento dos pacientes é principalmente feito com avaliação clínica e hormonal. Métodos de diagnóstico por imagem podem ser muito úteis não só no diagnóstico como no manejo e seguimento dos pacientes com CAH. Porém as recomendações de acordo com a maioria dos consensos, quando existem, são escassas. Neste contexto, baseado em uma revisão sistemática, o objetivo deste artigo foi sintetizar a literatura em relação a como os métodos de diagnóstico por imagem podem ser úteis no manejo dos pacientes com CAH, com foco em genitografia, ultrassonografia, tomografia computadorizada e ressonância magnética.

**Palavras-chave:** Hiperplasia suprarrenal congênita; Imagem por ressonância magnética; Tomografia computadorizada; Ultrassonografia; Diagnóstico por imagem.

## 5.2 Introduction

Congenital adrenal hyperplasia (CAH) is an autossomic recessive disorder caused by impaired steroidogenesis, in approximately 95% of the cases, secondary to 21-hydroxylase deficiency. Patients may present adrenal insufficiency with or without salt-wasting, as well as various degrees of virilization and fertility impairment, carrying a high incidence of testicular adrenal rest tumors (TART) and increased incidence of adrenal tumors.<sup>1</sup> Neonatal screening is recommended because it reduces and prevents morbidity and mortality from salt-losing crisis.<sup>2</sup> The diagnosis is made with adrenocortical profile hormonal evaluation and genotyping in selected cases.<sup>2</sup>

Utility of imaging in this clinical setting may be helpful for the diagnosis, management, and follow-up of the patients, although recommendations according to most guidelines are weak when present.<sup>2</sup> Bone mineral density evaluation in children is not recommended and adrenal imaging is suggested only for patients with an atypical course.<sup>2</sup> Conversely, CAH must be excluded in cases of adrenal incidentaloma supposedly asymptomatic or oligosymptomatic. To evaluate gonads, ultrasonography (US) is recommended for screening males from adolescence, but there is no recommendation to screen females.<sup>2</sup>

Thus, the authors aim to conduct a narrative synthesis of how imaging can help in the management of patients with CAH, especially focused on genitography (GX), US, computed tomography (CT), and magnetic resonance imaging (MRI).

### *Search strategy and selection of articles*

A systematic search was conducted in MEDLINE<sup>®</sup> (from 1950 to July 2013) and in Web of Science<sup>®</sup> (from 1965 to July 2013) databases for articles published in English, Spanish, Portuguese, and French. On MEDLINE<sup>®</sup>, the MeSH term “Adrenal Hyperplasia, Congenital” was searched with the other imaging related MeSH terms with AND at a time using “Ultrasonography”, or “Magnetic Resonance Imaging”, or “Diffusion Magnetic Resonance Imaging”, or “Tomography, X-Ray Computed”, or “Multidetector Computed Tomography”, or “Positron-Emission Tomography and Computed Tomography”, or “Tomography Scanners, X-Ray Computed Radiography”, or “Diagnostic Imaging”. Web of Science<sup>®</sup> was searched for articles with the search terms “congenit\*and adren\* and hyperpl\*”

“AND imag\*”. Books and other selected references cited in the most relevant retrieved articles were also reviewed.

Studies that were conducted in animals and in which only scintigraphy or nuclear imaging modalities were used as imaging modalities were not within the scope of this review. Also, studies that only used X-Ray to evaluate bone age or any imaging modalities to assess bone mineral density were not extensively reviewed, as it is well established by the guidelines that bone age should be assessed annually after 2 years of age and regular evaluation of bone mineral density is not recommended.<sup>2</sup>

### **5.3 Imaging**

#### *Genitography*

The urogenital sinus is the embryologic precursor of the bladder, urethra, and distal third of the vagina in females. Excessive androgen exposure in utero leads to virilization of the external genitalia and urogenital malformations in females with CAH.<sup>1</sup> Signs of urogenital sinus malformation secondary to virilization are hydrocolpos or hydrometrocolpos and only two apertures (one of them is the anus) in the perineal region associated with ambiguous genitalia.<sup>3</sup> Typically, female patients with classic CAH have ambiguous genitalia at birth. Thus an anatomic detailed image plays an important role in planning strategy for feminizing surgery. Genitography shows the urethra, the level of external sphincter, the presence or absence of the vagina, the urethrovaginal confluence, and the cervical impression of the uterus.<sup>3</sup> (Figure 5.1)

Genitography associated with voiding cistography has also the ability to show upper genitourinary abnormalities, present in 21% – 80%<sup>4</sup> of the patients with CAH, mostly seen in girls.

Although some authors concluded that genitography did not add information to endoscopic<sup>5</sup> or surgical findings, many advocate its use as part of routine investigation in female patients with CAH,<sup>4</sup> particularly in those infants with ambiguous genitalia.

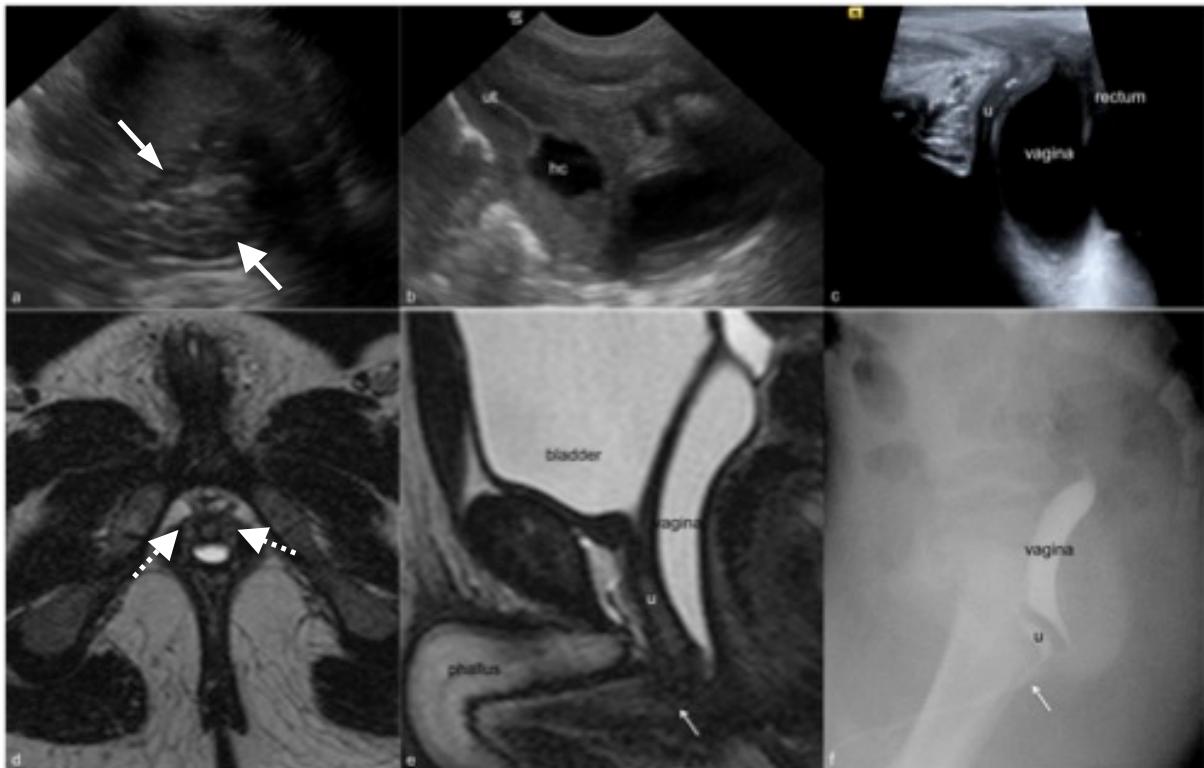


Figure 5.1 – Newborn with “non palpable testicles”. Ultrasonography (a-c) showed enlarged and cerebriform pattern of the adrenal glands (arrows in a). Sagittal view of the pelvis through the abdominal wall (b): the uterus (“ut”) and the presence of hydrocolpus (“hc”) are well depicted. The ovaries (not shown) were also present. Sagittal ultrasonography view of the pelvis through the perineum (c) was not sufficient to show with high confidence the confluence of the urethra and the vagina, which was better viewed on magnetic resonance imaging (MRI) (e, sagittal T2-weighted MRI of the pelvis) and genitography (f). The arrows in (e) and (f) are pointing the confluence of the vagina and the urethra (“u”). Axial T2-weighted MRI of the pelvis showing prostate tissue (dashed arrows in d) in this patient. The pattern of the adrenal glands and presence of mullerian derivatives allowed institution of therapy while laboratory tests were done to confirm congenital adrenal hyperplasia in this 46,XX neonate. MRI and genitography were requested for planning feminizing surgery.

### *Ultrasonography*

US is the modality of choice to image abdominal and pelvic organs in children and fetuses. It is widely available, versatile, and portable, with lack of ionizing radiation, there is no need for sedation, and provides high-resolution images in any required plane.

The adrenal glands in young children and fetuses are well depicted with US, especially in the neonate period. Sonographic abnormalities of the adrenal glands in CAH are

similar in pre- and postnatal periods. The most prevalent sign is bilateral enlarged glands with width measurements of one limb  $\geq 4$  mm.<sup>6</sup> In addition, adrenal size was positively correlated with plasma concentration of dehydroepiandrosterone sulphate.<sup>7</sup> Also, a coiled or cerebriform pattern<sup>8,9</sup> is specific for this condition. This finding should prompt a thorough investigation in male fetus and whenever a corticoid therapy is initiated serial US will show decrease in size of the adrenal glands.<sup>10</sup> In infants, the morphology was shown to be of valuable importance while waiting for laboratory results in patients investigated for suspicious of the disease, enabling earlier diagnosis and treatment.<sup>9</sup> However, it is very important to notice that normal adrenal glands do not exclude the possibility of CAH.<sup>6</sup>

Although the clinical features of CAH are usually present, testicular adrenal rest tumors (TART) may be the only clinical finding at presentation.<sup>11</sup> Based on microscopic studies, TARTs are reported to be present in all males with CAH.<sup>12</sup> On US, it has been documented with a prevalence of up to 94%.<sup>13</sup> The most common sonographic features are bilateral spokelike appearance intratesticular hypoechoic masses with no sound attenuation, surrounding the mediastinal testis.<sup>11</sup> On color Doppler they are hypo or avascular<sup>14</sup> and there is no deviation or changes in caliber of the vessels that course the lesions.<sup>11,14</sup> However, TART may also appear as heterogeneous or hyperechoic nodules,<sup>11,14,15</sup> and even as an epididymal nodule.<sup>11</sup> TART echogenicity is related to the size of the lesions, being hypoechoic in lesions smaller than 2 cm and heterogeneous or hyperechoic in lesions larger than 2 cm.<sup>14</sup> These hyperechoic areas may represent fibrosis or calcifications.<sup>14</sup> In addition, larger lesions may not be confined to the mediastinal testis and smaller lesions are more often seen unilaterally.<sup>14</sup> On follow-up, TART can vary in size,<sup>15</sup> but there is no correlation between hormonal control or hormonal markers and TART.<sup>15-17</sup> TARTs are thought to be responsible for testicular parenchymal damage that contributes to reduced fertility.<sup>17,18</sup> It can be found even in young children with a prevalence of 21%<sup>19</sup> and it is suggested that gonadal dysfunction is already present before puberty.<sup>19</sup> Therefore, early detection of testicular lesions is advised<sup>20</sup> to improve treatment and prevent longstanding gonadal impairment function. Thus, some authors advocate that not only adolescents should undergo US.<sup>21</sup> (Figure 5.2)

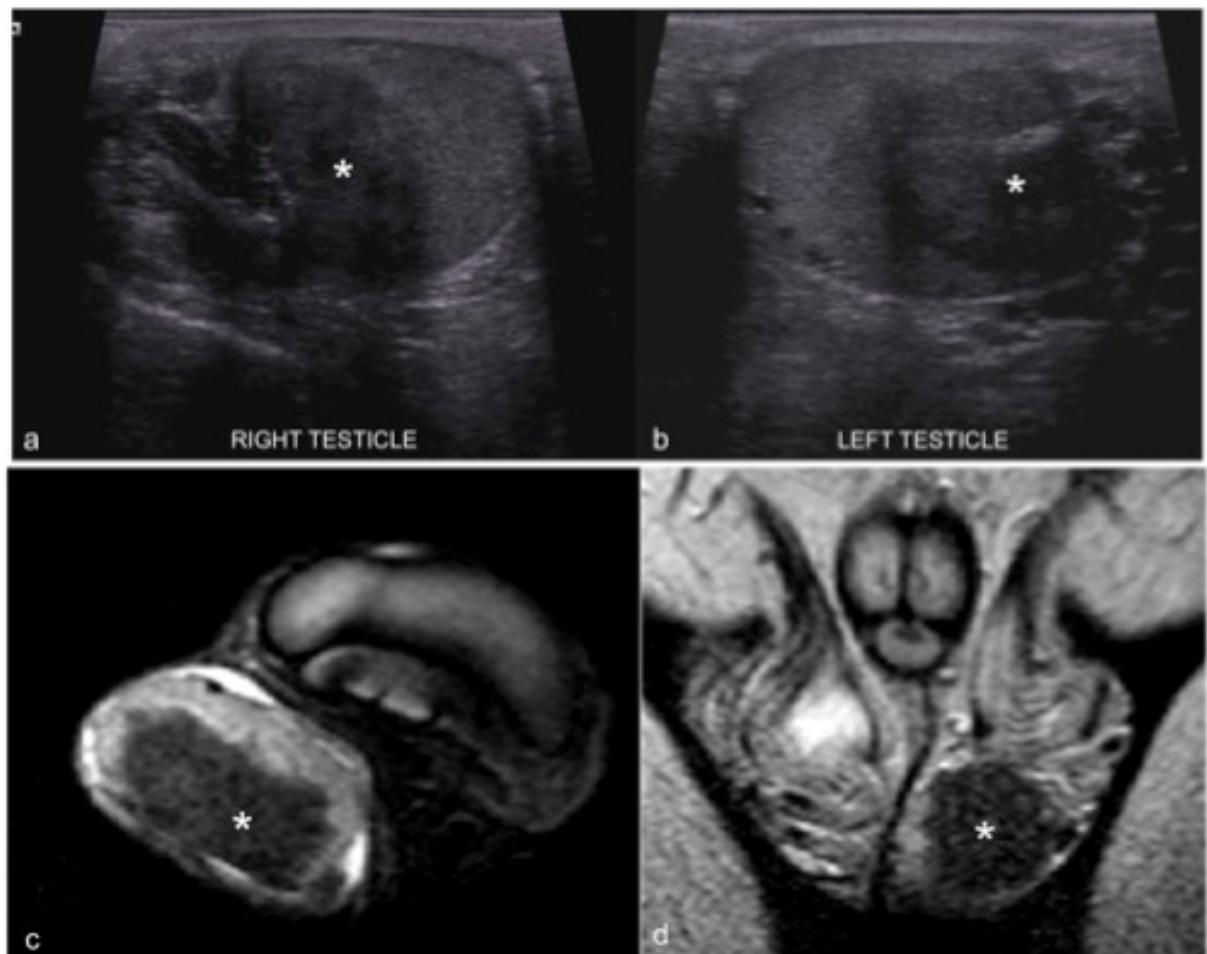


Figure 5.2 – Testicular adrenal rest tumor (TART) in a 14 year-old male, with simple virilizing congenital adrenal hyperplasia. On ultrasonography (a – b), there is a round heterogeneous, predominantly hypoechoic nodule (\*) within both testicles, in the region of the mediastinal testis. On magnetic resonance imaging (c, axial; d, coronal) the TARTs are hypointense on T2-weighted images.

High prevalence of impaired fertility is not restricted to men as it was reported also in women with CAH.<sup>13,17</sup> The prevalence of polycystic ovaries is increased in women with classical and nonclassical CAH.<sup>22</sup> Bilateral enlarged ovaries,<sup>23</sup> bilateral ovarian cysts, and ovarian adrenal rest tumors (OART)<sup>24</sup> may occur and can also be depicted by US. OART may present as hypoechoic nodules on US,<sup>24,25</sup> similar to TART.

The most common cause of disorders of sex differentiation in the perinatal period is CAH. A clue to the prenatal diagnosis of CAH is usually the presence of ambiguous genitalia that may be present by the second trimester. The most often presentation is of an enlarged clitoris, but more complex abnormalities can be seen.<sup>26</sup>

In postnatal period, to assess internal anatomy of the pelvis, US is the first choice. It is easily performed and must include images of the pelvis, scrotum, inguinal, perineal, renal, and adrenal regions.<sup>27</sup> The main purpose of the pelvic sonography is to depict accurately the size and morphology of the Mullerian structures, the uterus, the vagina, and the gonads.<sup>3</sup> In addition to the adrenal glands findings described above, the presence of a uterus in a patient with ambiguous genitalia indicates that the diagnosis is mostly likely CAH.<sup>9</sup> Ultrasound evaluation of the pelvic structures is not only performed for diagnosis but also as part of the preoperative approach for surgery, often in conjunction with other exams, such as genitography and MRI.<sup>3</sup> US provides adequate information about the vagina and urogenital sinus for preoperative decision-making.<sup>28</sup>

Many other abnormalities in patients with CAH can also be demonstrated by US: cardiac dysfunction that reverses with therapy,<sup>29</sup> vascular dysfunction and increased carotid intima media thickness,<sup>30</sup> skeletal and midface malformations in prenatal diagnosed fetuses,<sup>31</sup> hydrops of placental stem villi in a 46,XX fetus,<sup>32</sup> association with increased nuchal translucency detected in the prenatal period,<sup>33</sup> bilateral ovarian steroid cell tumor in a girl with CAH 11 beta-hydroxylase deficiency,<sup>34</sup> and adrenal rest tissue extending from the lower pole of the kidney.<sup>35</sup>

### *Computed Tomography*

Adrenocortical tumors in patients with CAH are not rare. A prevalence of up to 83% of adrenocortical masses in homozygote patients is reported.<sup>36</sup> Despite this high frequency, adrenocortical tumors in this setting are most likely to be benign, as malignant lesions are rare.<sup>36</sup> In many reports CT scans showed nodules<sup>36-38</sup> that may regress with adequate therapy,<sup>37</sup> adenomas,<sup>23</sup> myelolipomas<sup>39</sup> and the typical pattern of diffuse enlargement<sup>38</sup> with a heterogeneous enhancement (Figure 5.3).

Positron emission tomography with CT scan (PET-CT) was used in 3 case reports. In one, PET-CT was used to evaluate an adrenal mass in an untreated patient and showed a mass proved to be an adrenocortical tumor of uncertain prognosis.<sup>40</sup> In the other two, PET-CT depicted OARTs,<sup>25,41</sup> interestingly, in one of these reports both MRI and CT could not show this finding. On the other hand, adrenal rest tumors have already been described on conventional CT as a soft tissue mass in the ovary, OART,<sup>42</sup> and in the perirenal region.<sup>43</sup>

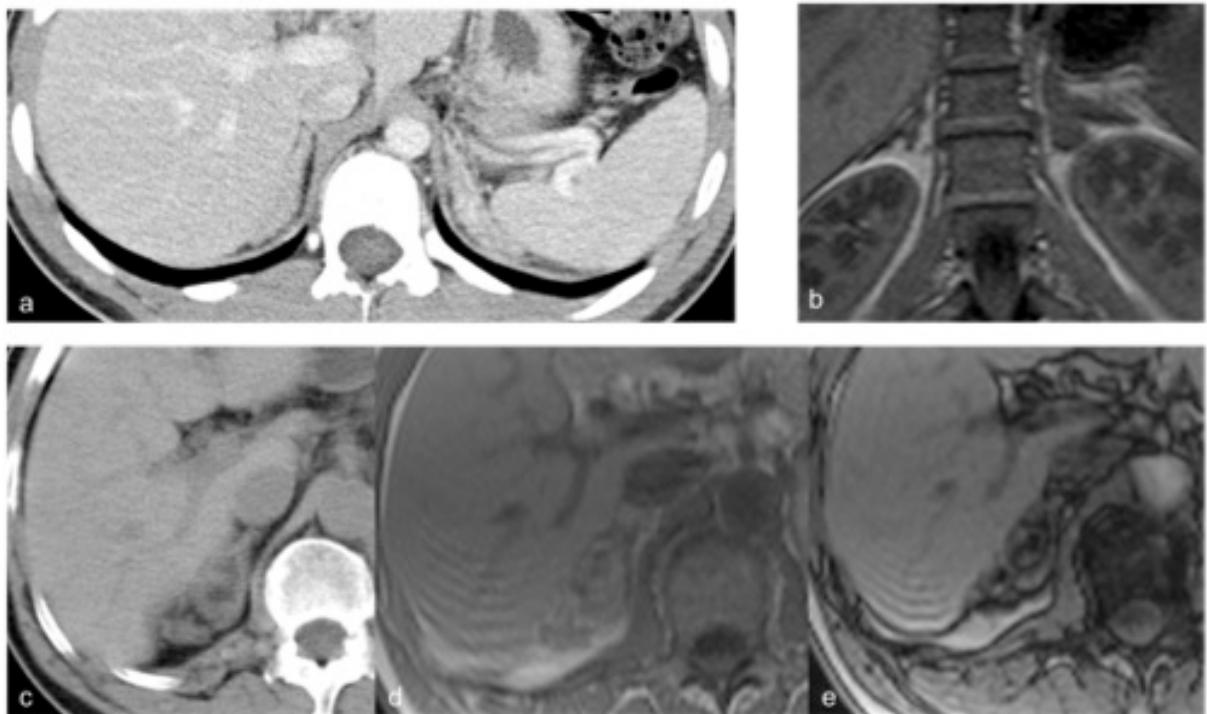


Figure 5.3 – Adrenal glands in three different patients with congenital adrenal hyperplasia (CAH). Enlarged adrenal glands (arrows) can be seen on computed tomography (a) and magnetic resonance imaging (b), in different patients. On “a”, the left adrenal gland had nodular margins (dashed arrow). On “b” the left adrenal gland (dashed arrow) is larger than the right adrenal gland, which was within normal limits. Another adult patient with abdominal pain in which ultrasonography (not shown) depicted an adrenal mass. Computed tomography (c) and magnetic resonance imaging (d – e) showed a right adrenal myelolipoma (circles). CAH was confirmed posteriorly.  
Axial contrast-enhanced computed tomography (a); Coronal T1-weighted magnetic resonance imaging (b); axial computed tomography (c) and T1-in-phase (d) and out-of-phase (e) magnetic resonance imaging.

### *Magnetic Resonance Imaging*

Studies based on MRI are in accordance with others performed with CT<sup>36</sup> demonstrating a high prevalence of adrenal nodules (73%) in adults with CAH.<sup>16</sup> Moreover, adrenal MRI imaging in CAH patients showed findings such as normal or diffuse enlarged adrenal glands,<sup>44</sup> adrenal nodules,<sup>16,37,45</sup> and myelolipomas,<sup>46,47</sup> which is consistent with US and CT findings. The size of the adrenal glands and presence of nodules may relate to hormonal control status; a significant correlation between adrenal and nodule sizes and hormonal parameters has been described.<sup>16</sup> Moreover, these morphological adrenal features are more prevalent in patients with a poor hormonal control status,<sup>48</sup> as well as the prevalence

of adrenal masses increases with adrenal volume,<sup>16</sup> which may regress with adequate treatment.<sup>49</sup>

Excellent soft-tissue contrast, spatial resolution, and capability of multiplanar imaging make MRI more sensitive than other imaging modalities to evaluate the pelvis. MRI is indicated when US fails to adequately demonstrate the morphology, size, and relationship between Mullerian duct derivatives in virilized female infants.<sup>3,27</sup> It is the primary imaging modality when evaluation of pelvic organs and morphology in older children, adolescents, and adults are needed. In addition, although rare, prostatic tissue has been shown in females with CAH with a prevalence of up to 15%.<sup>50</sup>

The prevalence of ectopic adrenal rest tumors in the testicles showed by MRI is high, ranging from around 29% (32) to 94%.<sup>14</sup> Despite this high incidence, presence of TART did not show any correlation with short hormonal parameters in adults.<sup>16</sup> On MRI, TARTs are typically isointense relatively to parenchyma on T1-weighted images, hypointense on T2-weighted images,<sup>14,51</sup> and present well-defined margins.<sup>14</sup> After intravenous injection of gadolinium they have a significant enhancement.<sup>51</sup> Although MRI has the same sensitivity as US in detecting TART,<sup>51</sup> when testis sparing surgery is considered MRI is recommended due to its better depiction of the tumor margins.<sup>14</sup> (Figure 5.4) Adrenal rest tissue was also documented in the retroperitoneum encasing the aorta with regression of the size after glucocorticoid treatment.<sup>52</sup>

Concerning brain changes in patients with CAH, MRI showed white matter abnormalities,<sup>53</sup> smaller amygdalas,<sup>54</sup> and temporal lobe atrophy in young population.<sup>55</sup> White matter abnormalities may also be secondary to electrolytic complications of the disease.<sup>56</sup> Pituitary abnormalities<sup>57</sup> and hypothalamic hamartoma<sup>58</sup> were described in CAH patients in anecdotal case reports. Functional MRI demonstrated different patterns of activation in emotional memory comparing CAH patients with controls,<sup>59</sup> and a virilized amygdala function in females affected.<sup>60</sup>

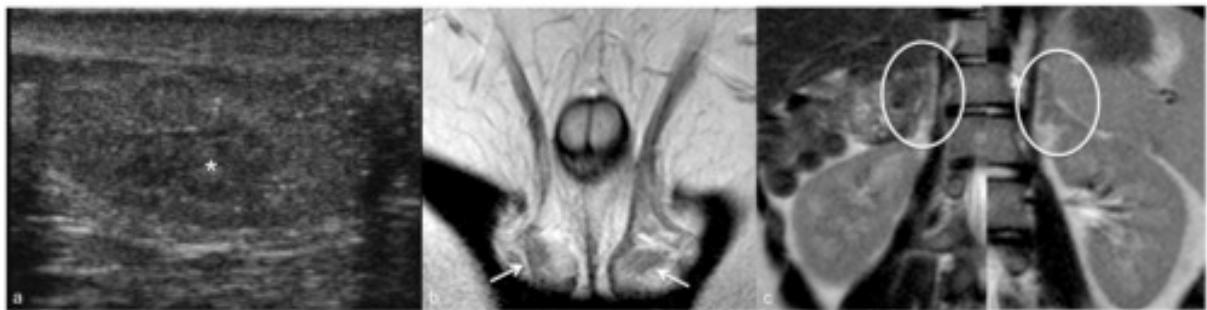


Figure 5.4 – Bilateral testicular adrenal rest tumor (TART) in a 9 year-old boy. This patient had a good clinical control since two years before the exam. Ultrasonography (a) showed a hypoechoic nodule, with ill defined margins, in the mediastinal testis (\*). TARTs (arrows) had a hypointense signal on coronal T2-weighted magnetic resonance imaging (b). Coronal T2-weighted magnetic resonance imaging of the normal sized adrenal glands (circles in c), without nodules.

#### 5.4 Summary

Although the diagnosis of CAH is based on hormonal dosages and genetic analysis, imaging still have an important role in the management of these patients regarding a proper clinical setting. In addition to radiographs evaluating bone age included as a tool in the clinical follow-up, genitography, US, MRI, CT, and other imaging modalities add important information for diagnosis, follow-up, and surgical planning.

The detection of TART is essential to be done as early as possible, as the patients can be monitored and treated more intensively, in order to prevent fertility impairment and testicles damage.<sup>20</sup> US figures as the modality of choice for this purpose.<sup>20,51</sup> Therefore, it should be used routinely and not only from adolescence. While laboratorial results are pending, US may show a specific coiled pattern and/or enlargement of the adrenal glands,<sup>6</sup> enabling early treatment of neonates with suspicious of CAH. Furthermore, US is the first modality to evaluate neonates and young infants with ambiguous genitalia,<sup>27</sup> a feature frequently present in virilized females. As a tool to help early detection of risk for cardiovascular diseases, US may be used to evaluate carotid vessels.<sup>30</sup>

MRI is a problem solving for detailed depiction of pelvic structures when US is not sufficient, mainly in cases of ambiguous genitalia.<sup>3,27</sup> It is recommended to evaluate TART before testes sparing surgery.<sup>14</sup> Also, MRI can evaluate in detail adrenal nodules. Due to its lack of radiation and better soft tissue contrast, MRI may be considered as the method of choice to follow-up patients, as adrenal changes on MRI correlate to hormonal parameters.<sup>16</sup>

CT is mainly used to evaluate the adrenal glands but with the drawback of ionizing radiation. To assess pelvic anatomy, genitography is used for planning feminizing surgery.<sup>3</sup>

For radiologists and sonographers, the detection of enlarged adrenal glands, adrenal gland nodules, and coiled adrenal glands in any imaging study should prompt raise the possibility of CAH. Also, they must keep in mind the possibility of CAH in cases of ambiguous genitalia, testis lesions, ovarian solid nodules, abnormal retroperitoneum solid tissues, and even white matter abnormalities seen in brain MRI.

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## 6. MEDIDA DO COEFICIENTE APARENTE DE DIFUSÃO DAS GLÂNDULAS SUPRARRENAIS

No artigo “*Apparent Diffusion Coefficient (ADC) of the normal adrenal glands: preliminary results*” estão descritos os passos de validação do método para medir o ADC das glândulas suprarrenais, que foi realizado em pacientes saudáveis. Este método foi posteriormente utilizado para medir o ADC dos pacientes com CAH e do grupo controle para comparação. O valor de ADC de glândulas suprarrenais em pacientes saudáveis ainda não tinha sido descrito e publicado na literatura científica até a produção desta tese.

## Apparent diffusion coefficient (ADC) of the normal adrenal glands: preliminary results

### **6.1 Abstract**

**Purpose:** To assess feasibility and reproducibility of apparent diffusion coefficient (ADC) measurements of normal adrenal glands. **Material and Methods:** Local ethics committee approved the study design. Written informed consent was waived. Between November 2011 and December 2012, 32 healthy subjects were retrospectively included. Subjects were divided in pre-pubertal group (PreP) ( $n=12$ ) aged from 2 months to 12.5 years-old (4 males; 8 females); and post-pubertal group (PostP) [ $n=20$ ] composed of adolescents (stages II–V of Tanner scale) and adults aged from 11.9 to 61 years-old (5 males; 15 females). Diffusion-weighted magnetic resonance images were acquired in a 1.5T scanner using  $b$  values of 0, 20, 500 and  $1000\text{ s/mm}^2$ . Two radiologists evaluated the images. ADC values were measured pixel-by-pixel by manual segmentation on DWI and automatic co-registration with ADC map was obtained. Data were evaluated using Student-t or Mann-Whitney tests according to presence or not of normal distribution. For assessment of interobserver agreement intraclass correlation coefficient (ICC) was calculated. **Results:** Mean ADC values of the right adrenal glands were  $1.44 \times 10^{-3}\text{ mm}^2/\text{s}$  for PreP group, and  $1.23 \times 10^{-3}\text{ mm}^2/\text{s}$  for PostP. Mean values of the left adrenal glands were  $1.58 \times 10^{-3}\text{ mm}^2/\text{s}$  and  $1.32 \times 10^{-3}\text{ mm}^2/\text{s}$ , respectively. ADC values were higher in PreP compared to PostP ( $P < 0.05$ ). Agreement between readers was almost perfect (ICC, 0.84–0.94;  $P < 0.05$ ). **Conclusion:** These data demonstrate feasibility and reproducibility of performing ADC measurements of normal adrenal glands. Moreover, it may support feasibility of ADC measurement for small structures.

**Keywords:** Adrenal glands; Diffusion-weighted magnetic resonance imaging; Diffusion magnetic resonance imaging; Magnetic resonance imaging.

## 6.2 Introduction

Diffusion-weighted magnetic resonance imaging (DWI) has increasingly become routine in body magnetic resonance (MR) protocols. DWI is a MR technique with the ability to provide qualitative, and quantitative information at a cellular level based on molecular diffusion<sup>1</sup> that partially reflects tissue cellularity and presence of intact cellular membranes.<sup>2</sup> Technical advances in MR, such as development of parallel imaging, high amplitude gradients, and multichannel coils, have enabled DWI for abdominal studies.<sup>3,4</sup> DWI can provide useful additional information in characterization of abdominal lesions. In addition, quantitative information provided by apparent diffusion coefficient (ADC) measurements is now recognized as potential biomarker,<sup>5,6</sup> with significant correlation with tissue cellularity, extra-cellular space tortuosity and integrity of cellular membranes.<sup>2,7</sup>

Some abdominal organs have been extensively studied by DWI,<sup>8-10</sup> either for assessing focal or diffuse lesions. In adrenal glands, ADC values were mainly used for differentiation of malignant and benign lesions.<sup>11-15</sup> However, to the best of our knowledge, ADC quantification of the normal adrenal glands has not been published. The purpose of this study was to assess the feasibility and reproducibility of ADC measurements of the adrenal glands in subjects with no endocrinological disorder or adrenal disease.

## 6.3 Materials and methods

### *Study population*

The study design was prior approved by the Institutional Review Board and a signed informed consent was waived. Between November 2011 and December 2012, 1330 subjects underwent abdominal MR at our institution, including DWI as part of routine protocol. Radiological charts were reviewed in order to exclude subjects with abnormal findings (n=1273). From the remaining 57 subjects, clinical charts were reviewed. Five subjects were excluded for hormonal disturbances, 6 for history of neoplasm, 3 for suspicious of chronic inflammatory bowel disease, 4 for suspicious of storage disease and 7 subjects that were above normal body mass index range for age. In total, 32 healthy subjects, normal-weighted, without hormonal disturbance, chronic or systemic diseases were included (Figure 6.1).

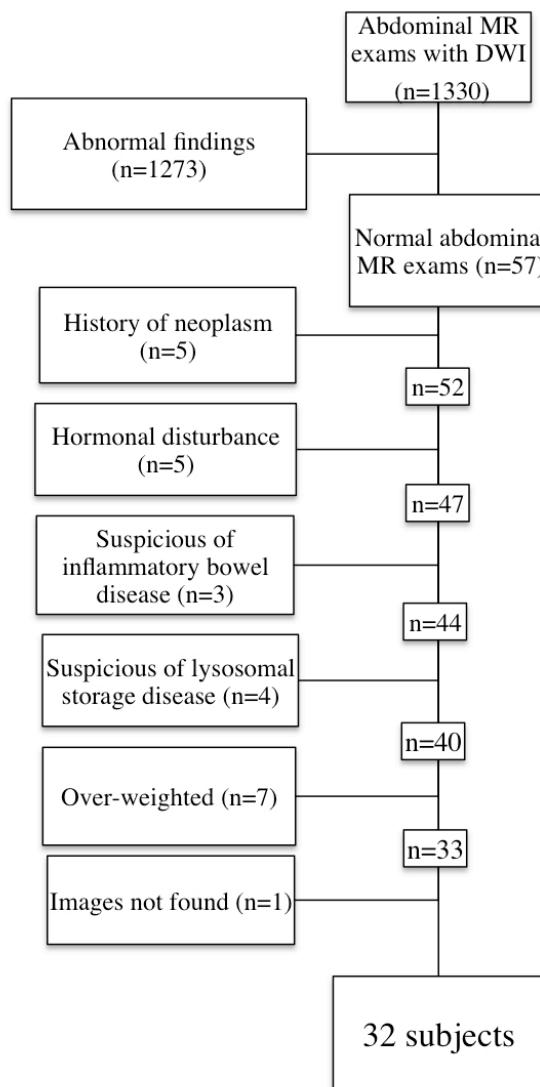


Figure 6.1 – Flowchart summarizes inclusion of subjects between November 2011 and December 2012.  
*MR, magnetic resonance; DWI, diffusion-weighted magnetic resonance imaging.*

Subjects were divided in two groups: a pre pubertal group (PreP), composed of 12 preadolescents and infants (Stage I of Tanner scale)<sup>16,17</sup> aged from 2 months to 12.5 years-old (4 males, 8 females; median age, 11 years-old); and a post-pubertal group (PostP) composed of 20 adolescents (stages II, III, IV or V of Tanner scale)<sup>16,17</sup> and adults aged from 11.9 to 61 years-old (5 males, 15 females; median age, 41 years-old ) (Table 6.1).

Table 6.1 – Subjects characteristics

<b>Group</b>	<b>N</b>	<b>Gender</b>	<b>Age</b>
Prepubertal	12	4 male	6.8 years-old
		8 female	(range, 0–12.5)
Postpubertal	20	5 male	35.4 years-old
		15 female	(range,
Total	32	9 male	24.7 years-old
		23 female	(range, 0–61)

*N, number of subjects*

### *MR imaging*

MR imaging was performed with a 1.5-T MR imager (Achieva, © Koninklijke Philips N.V., Eindhoven, The Netherlands) with an anterior sixteen-channel phased-array body coil. A standard protocol for abdominal imaging, including DWI, was used. All exams were collected and saved in the picture and archiving communication system (PACS) for posterior analysis.

Transverse diffusion-weighted multisection echo-planar MR imaging was performed with chemical shift fat saturation technique using a respiratory-gated sequence, without intravenous contrast administration. Sequence parameters: diffusion gradient *b* values of 0, 20, 500 and 1000 s/mm<sup>2</sup>, applied in three orthogonal directions (x, y and z) and subsequently averaged to minimize the effects of diffusion anisotropy; parallel imaging reduction factor, 2; repetition time/ echo time / echo planar imaging factor (TR/TE/EPI factor), 5128/73/69; bandwidth, 10355/21; section thickness, 5 mm; intersection gap, 0–1 mm; matrix size, 172 x 133; field of view, 345 x 321 mm; number of excitations acquired, 2. The whole sequence consisted of 20–25 sections, with an acquisition time of 3 minutes and 15 seconds in average. ADC maps were automatically generated by the MR system, with a multiexponential model. Calculated ADC values are expressed in square millimeters per second (x 10<sup>-3</sup> mm<sup>2</sup>/s).

### *Image analysis*

Images of all subjects were independently, retrospectively and blindly evaluated on a workstation by two different radiologists with 5 and 3 years of experience (S. R. T. and A. F. M., respectively) in abdominal imaging. The former has additional 2 years of experience in pediatric imaging. The images were reviewed in a randomized fashion to avoid learning bias.

DWI and ADC maps were converted into MINC format and analyzed using a free

software package (Display version 1.4.2, David McDonald, Brain Imaging Centre of the Montreal Neurological Institute, Montreal, Canada).

ADC measurements were performed on a pixel-by-pixel basis, by manual segmentation of the adrenal glands on the original DWI, b value of 500 s/mm<sup>2</sup>. As shape of the adrenal glands is often irregular, threshold values were established to exclude adjacent fat from the region of interest (ROI). By summing and posteriorly dividing by two the values of the closest voxel to the adrenal gland with the highest value and the voxel with the lowest value in the adrenal gland defined the threshold for the maximum value of the voxels of the ROIs. Definition of the ROI was then performed by selecting the outermost surrounding voxels with the same signal level of the thresholds in each slice and by further selecting the interior of the surrounded area. After adrenal glands segmentation, images were fused with the ADC map using a script. By this method, ADC value of the ROI is automatically calculated by average of the pixels manually chosen in each slice (Figure 6.2).

Margins of the adrenal glands were clearly defined on DWI for all subjects. Reviewers were unaware of the age, sex, and puberty stage of the subjects. They were also blind to the other observers' results. To become familiar with the software, both radiologists have applied the methodology in 10 adrenal glands before starting this study and these data were not included in the analyses. Each radiologist measured the adrenal glands once. Measurements lasted around 5 min per case.

The intraobserver agreement was assessed in 10 subjects, 10 right adrenal glands and 10 left adrenal glands. Adrenal ADC measurements were repeated 2 months after first measurements by a single observer (S.R.T.). Interobserver agreement was determined by comparing ADC values obtained by each radiologist of the right and of left adrenal glands separately.

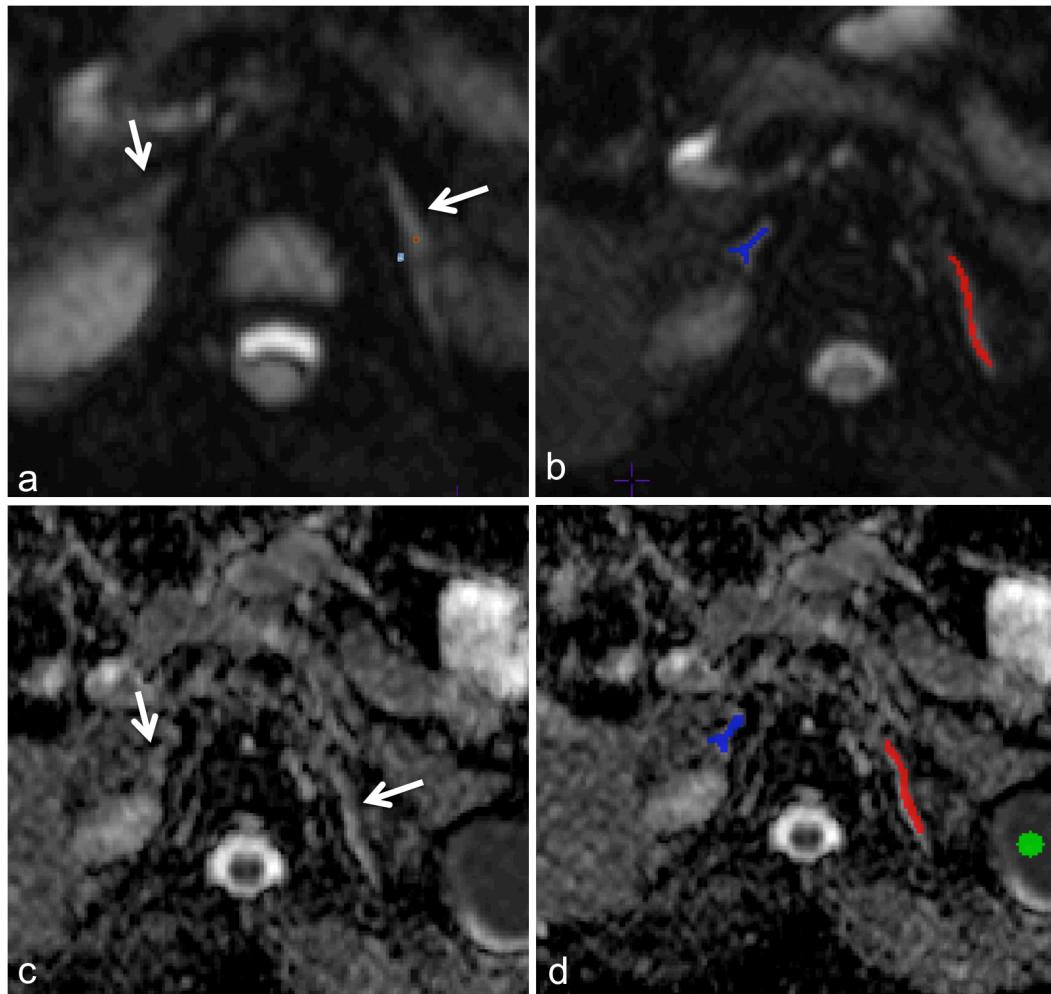


Figure 6.2. – Example of how to segment the adrenal glands and fuse diffusion-weighted magnetic resonance images (DWI) with apparent diffusion coefficient (ADC) map. Axial DWI,  $b = 500 \text{ s/mm}^2$  without (a) and with (b) labels on the adrenal glands, respectively. Axial ADC map on the same level as (a) and (b) without (c) and with (d) labels on the adrenal glands, respectively. After setting thresholds, the adrenal glands [arrows on (a) and (c); blue and red labels on (b) and (d)] are manually segmented. Then, the labels segmented are fused with the ADC map. The software automatically calculates mean ADC values of the glands based on the regions labeled.

### *Statistical Analysis*

The measured values were checked for distribution using the Shapiro-Wilk test before statistical analysis. Data were represented as means  $\pm$  standard deviation (SD) or median and quartiles (25th–75th) as required. Univariate analysis for differentiating PreP from PostP was performed using the Student-t test or Mann-Whitney test for covariates with or without normal distribution, respectively. Measurements of the two reviewers were treated

independently. For assessment of intra and interobserver agreements, we calculated the intraclass correlation coefficient (ICC) that takes into account both systematic and random errors.<sup>18</sup> *P* values under 0.05 were considered statistically significant. Statistical analysis was performed with R release 2.15.0 (R Development Core Team) and IBM SPSS statistics release 19 (IBM Corporation) software packages.

## 6.4 Results

### *ADC*

Mean ADC values of the right adrenal glands were  $1.44 \times 10^{-3} \text{ mm}^2/\text{s}$  (SD 0.23) for PreP group and  $1.23 \times 10^{-3} \text{ mm}^2/\text{s}$  (SD 0.21) for PostP. Mean values of the left adrenal glands were  $1.58 \times 10^{-3} \text{ mm}^2/\text{s}$  (SD 0.22) and  $1.32 \times 10^{-3} \text{ mm}^2/\text{s}$  (SD 0.23), respectively (Figure 6.3).

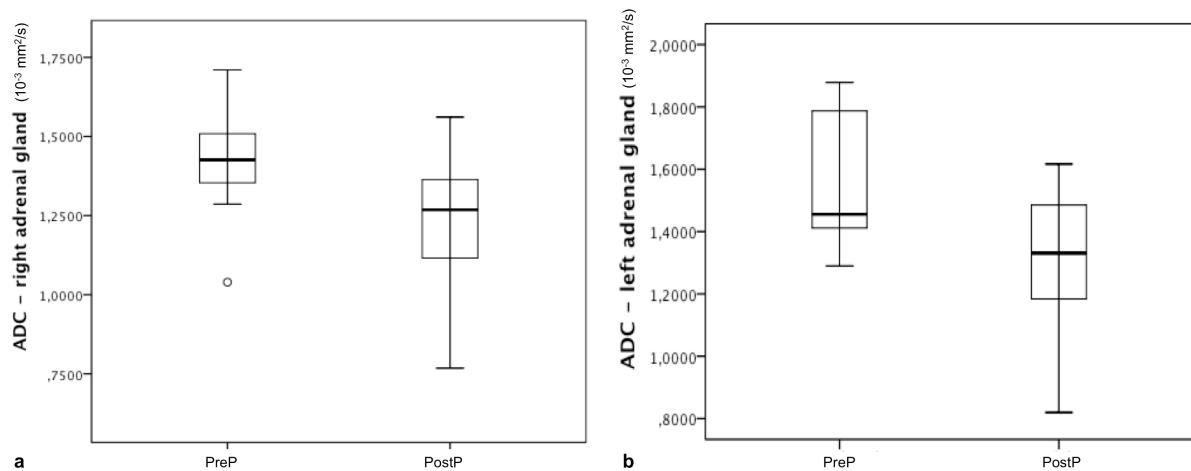


Figure 6.3 – Box-and-whisker plot of apparent diffusion coefficient (ADC) measurements of right (a) and left adrenal glands (b). Boxes represent interquartile range. Whiskers represent range of all values. Horizontal line within box is median value. There is a slight overlap of “boxes” of pre pubertal group (PreP) and post-pubertal group (PostP) but means were significantly different ( $P = 0.013$  for the right side;  $P = 0.003$  for the left side) and higher in the PostP group.

There was a significant difference of ADC values between PreP and PostP groups, both for the right and the left adrenal glands with a 95% confidence interval (CI) of 0.044–0.338 ( $P = 0.013$ ) for the right side; and 0.095–0.404 ( $P = 0.003$ ) for the left side. There was no substantial difference between ADC values of the right and left adrenals within the groups (95% CI ranging from -0.3369188 to 0.0514484,  $P = 0.142$  for PreP; and 95% CI ranging

from -0.0916099 to 0.704502,  $P = 0.201$  for PostP). Differences between genders were also not significant (95% CI, range -0.323–0.003;  $P = 0.104$  for right side; 95% CI, range -0.365–0.0389,  $P = 0.116$  for left side).

### *Intra and Interobserver agreement*

Intraobserver agreement for ADC measurements was almost perfect (ICC = 0.95, 95% confidence interval [CI] 0.82–0.98 for the right side; ICC = 0.97, 95% CI 0.91–0.99 for the left side; ICC = 0.97, 95% CI 0.93–0.99, for both sides). Agreement between the first and second reviewers was also consistent regarding ADC values. ICC was similar on comparison of different groups or different sides (Table 6.2) (Figure 6.4).

Table 6.2 – Interobserver agreement for ADC measurements of the adrenal glands

	Groups PreP and PostP			Group PreP			Group PostP		
	R	L	R/L	R	L	R/L	R	L	R/L
<b>ICC</b>	0.84	0.94	0.89	0.84	0.94	0.88	0.91	0.91	0.87
<b>95% CI</b>	0.63–0.93	0.85–0.97	0.81–0.94	0.46–0.95	0.59–0.99	0.68–0.95	0.76–0.98	0.76–0.97	0.74–0.94
<b>N</b>	25	25	50	12	12	24	16	16	32

ADC, apparent diffusion coefficient; ICC, intraclass correlation coefficient; CI, confidence interval; N, number of subjects analyzed; PreP, pre pubertal group; PostP, postpubertal group; R, right adrenal gland; L, left adrenal gland; R/L, right and left adrenal glands.

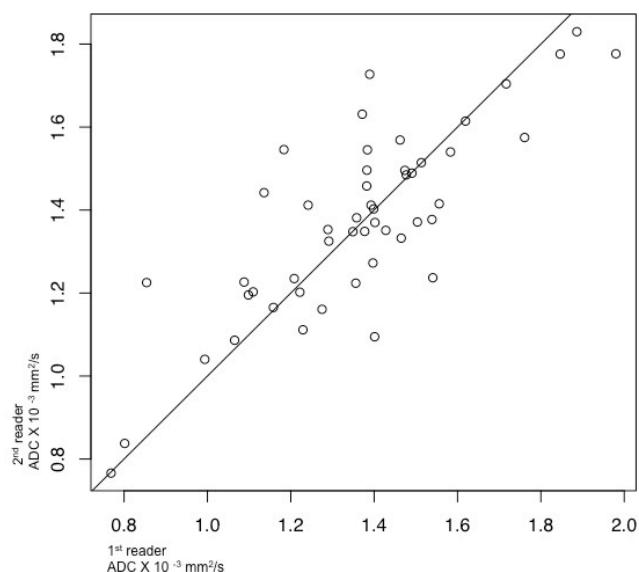


Figure 6.4. – Interobserver agreement. Intraclass correlation coefficient (ICC) for apparent diffusion coefficient (ADC) values measured in both groups, PreP and PostP. X axis, plotted measurements performed by the one radiologist; Y axis, plotted measurements performed by the other radiologist. ICC = 0.89 for right and left sides;  $P < 0.001$ .

## 6.5 Discussion

Intravoxel incoherent motion images, DWI, are quantified by ADC.<sup>1</sup> DWI is a non-invasive technique, both qualitative and quantitative, that is very useful in differentiating various pathological conditions. It has been used in clinical routine mainly in neuroimaging. With development of EPI, fast and low artifacts sequences, abdominal DWI measurements became possible. Since Muller et al<sup>4</sup> have described the feasibility of performing DWI in abdominal MR exams, it has been increasingly used as a biomarker in oncology<sup>19</sup> and to evaluate focal and diffuse diseases.<sup>20</sup> Additional roles of DWI include prediction of treatment outcomes<sup>21</sup> and detection of lymph nodes involvement in cancer staging.<sup>22</sup>

DWI provides information on diffusion and perfusion at the same time. Low b values are influenced by both perfusion and diffusion. When applying only high b values, the influence of perfusion is largely cancelled out and the ADC value approximates true diffusion.<sup>1</sup> ADC values may be extrapolated using only two b-values. However, sequences with multiple b values are more precise, with less perfusion contamination.<sup>23,24</sup> The drawback of multiple b values sequences is temporal resolution. Generally for that, breath-hold techniques are not suitable and respiratory-gated sequence is required. In addition, some abdominal organs may show important intrinsic water diffusion restriction, as spleen and prostate, and for differentiation of normal and pathological tissues high b values should be used in abdominal MR exams.<sup>25</sup> Therefore, we have used b values up to 1000 s/mm<sup>2</sup>.

Small lesions, especially those smaller than 1 cm, are very difficult to detect on ADC maps.<sup>15</sup> Normal adrenal glands show bright signal on DWI, although their small size makes direct ADC evaluation difficult.<sup>14</sup> But with the aforementioned approach, in which DWI sequence was fused with ADC map, it was possible to obtain reliable ADC values. Fusion of DWI with other sequences has been proposed for better evaluation of anatomic landmarks in lesions with irregular margins,<sup>26</sup> but not in small lesions or structures. Review of fusion images, evaluation of co-registration process and referring to other sequences in addiction to DWI improves confidence in ADC values obtained.<sup>22,27</sup>

Regarding the interobserver agreement of ADC measurements, our results have shown an almost perfect agreement, differently from that described by Sandrasegaran et al,<sup>15</sup> probably due to our methodology. We aimed to evaluate normal adrenal glands, whereas they have studied large heterogeneous adrenal masses. Also, we have used a pixel-by-pixel method followed by calculation of mean of all pixels, improved by an easier adrenal depiction in a

sequence with better anatomical and contrast resolution, posteriorly fused with ADC map. In their study, although lesions were larger than normal adrenal glands, they placed ROIs directly on ADC maps.

ADC values of some adrenal lesions were already assessed,<sup>11-15,28-31</sup> leading to controversies. Some authors concluded that ADC values could not be used to differentiate benign from malignant lesions,<sup>12-15</sup> although it could identify benign pheochromocytomas.<sup>12,14</sup> However, others have shown that ADC might be a useful tool to evaluate indeterminate lesions.<sup>15</sup> Fraction of anisotropy is another DWI related parameter with potential to differentiate benign and malignant adrenal neoplasms.<sup>11</sup> Although data were generated under different protocols, and therefore they are not truly comparable, when we analyze the ADC values found in previous studies, malignant tumors tend to have lower values compared to ADC values of the normal adrenal glands obtained in our study. Actually, the obtained ADC values of the normal adrenal glands are more similar to that reported for benign tumors, most of them adenomas.

We have found higher ADC values in PreP subjects compared to PostP group, which may be due to adrenarche stage. The expansion of the zona reticularis is a hallmark of the adrenarche.<sup>32</sup> Moreover, it has been proposed that globular expansion of the mitochondrial cristae in the zona fasciculata correlates to steroidogenesis.<sup>33</sup> Both processes may lead to structural changes in the adrenal cortex resulting in decrease of diffusion.

ADC values have also already been calculated for normal abdominal organs.<sup>8-10,34</sup> But to the best of our knowledge, there has been no published data investigating ADC values of the normal adrenal glands. Our results support reproducibility and feasibility of the method. After validation of this method, ADC values of normal adrenal glands may be used for comparison and follow-up of different abnormalities, particularly those with diffuse involvement of the adrenal glands. DWI was performed without breath holding, thus allowing examination of children, severely ill, old or obese patients who might be unable to cooperate during examination. Parameters of the sequence were according to standard protocols used in literature.<sup>5</sup>

This study has some limitations. First, as a retrospective design, we have included patients with normal MR exams and not healthy volunteers, although exclusion of subjects with risk of having adrenal or endocrine disorders, either acute or chronic diseases, was probably sufficient to minimize the confounding factors related to adrenal pathology. Another limitation of this study is the limited number of subjects. But for our purposes, this group was sufficient to show that adrenal ADC measurement is possible and reproducible. And last, the

spatial resolution provided by this technique, and MR imaging as well, prevents any conclusion regarding possible variations in ADC values due to histological difference among the two adrenal regions, cortex and medulla. Rather, our results represent a mixture of pixels from these two histological and functional distinct zones.

In conclusion, our preliminary results demonstrate the feasibility and reproducibility of performing ADC measurements of normal adrenal glands. We believe that this finding may add information for tissue characterization by MR imaging, and may be used in the future to compare adrenal small lesions to normal adrenal glands. Moreover, it adds information regarding feasibility of ADC measurements of irregular and small structures.

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## **7. AVALIAÇÃO QUANTITATIVA DAS GLÂNDULAS SUPRARRENAIS POR RESSONÂNCIA MAGNÉTICA EM PACIENTES COM HIPERPLASIA CONGÊNITA DE SUPRARRENAL**

O artigo “*Quantitative magnetic resonance imaging in the evaluation of adrenal glands in children and young adults with congenital adrenal hyperplasia due to 21-hydroxylase deficiency*” mostra o estudo prospectivo do tipo caso-controle no qual foram incluídos pacientes com CAH. O objetivo foi avaliar os parâmetros quantitativos por MRI, especificamente o ADC, volume e medidas lineares, que pudessem diferenciar os pacientes de controles normais e que apresentassem relação com o status hormonal dos pacientes.

## **Quantitative magnetic resonance imaging evaluation of the adrenal glands in children and young adults with congenital adrenal hyperplasia due to 21-hydroxylase deficiency**

### **7.1 Abstract**

**Context:** A morphological hallmark in congenital adrenal hyperplasia (CAH) is bilateral enlarged adrenal glands. Imaging studies have addressed mainly morphological aspects and dimensions of the adrenal glands. However, no function imaging was used to evaluate changes in the adrenal glands in patients with CAH. **Objectives:** To assess hormonal status in CAH and its correlation to MRI, particularly using apparent diffusion coefficient (ADC) derived from diffusion-weighted MRI; to show feasibility and reproducibility of measuring ADC of adrenal glands. **Design:** Prospective study between November/2011 and December/2012. **Setting:** Referral center. **Participants:** 25 patients (PG) with CAH (13males; median age 129 months, range:2–316) were compared to 23 age-matched controls (CG) (6males; median age 141 months, range:2–360). **Intervention:** MRI of the adrenal glands. **Main outcome measures:** Volume, thickness and ADC values of the adrenal glands were measured by two radiologists. To assess hormonal status, androstenedione concentrations from the same day of MRI and mean from the last year were used. **Results:** There was no difference between ADC values of PG and CG. Volumetric and linear measurements were significantly higher in PG ( $P=0.001–0.035$ ). A positive correlation was found between short-term hormonal control status and adrenal volume. Agreement between reviewers was substantial regarding ADC and volume measurements. **Conclusion:** These data provide additional evidence to the relationship between adrenal size and short-term hormonal control in patients with CAH. It supports feasibility and reproducibility in performing ADC measurements of adrenal glands. Although adrenal cell structure modifications in patients with CAH are described, they were not detectable by diffusion-weighted MRI.

**Keywords:** Adrenal hyperplasia, congenital; Magnetic resonance imaging; Diffusion magnetic resonance imaging; Adrenal; 21-hydroxylase deficiency.

## 7.2 Introduction

Congenital adrenal hyperplasia (CAH) is the most common genetic endocrine disorder characterized by an autosomal recessive trait caused by mutations in one of the enzymes required for steroidogenesis, most commonly affecting the cytochrome P450 21-hydroxylase.<sup>1</sup> Although clinical parameters such as growth velocity and bone age are gold standard to determine adequate control of CAH, clinical monitoring alone allows mainly a reactive approach. Serum markers most commonly used to monitor patients are 17OH-progesterone, androstenedione and testosterone, usually combined to clinical parameters to determine CAH control.<sup>2</sup> Therefore, clinical aspects, imaging studies as well as biochemical markers, taken all together, are adjunct tools in the follow-up of patients with CAH.

A morphological hallmark in CAH is bilateral enlarged adrenal glands that may show redundant folds, mostly in untreated or uncontrolled patients.<sup>3</sup> On histopathology studies, it was demonstrated that there is hyperplasia, thickened adrenal cortex, poorly defined zonation and intermingling of the medullary and cortical cells in patients with salt-wasting CAH.<sup>4</sup> Imaging studies<sup>3,5-7</sup> have addressed mainly morphological aspects and dimensions of the adrenal glands in CAH patients. However, no protocol has yet used diffusion-weighted magnetic resonance imaging (DWI) to evaluate more thoroughly the adrenal structure.

DWI is a MRI technique that provides both qualitative and quantitative information at a cellular level based on molecular diffusion.<sup>8</sup> Quantitative information is provided by apparent diffusion coefficient (ADC) measurements that is a recognized as a potential biomarker,<sup>9,10</sup> with significant correlation with tissue cellularity, extra-cellular space tortuosity and intra-cellular structure.<sup>11-13</sup>

The main purpose of this study was to evaluate a potential MRI parameter that could be used to assess hormonal control in patients with CAH, particularly the functional parameter derived from DWI – ADC. We also aimed to show feasibility and reproducibility of measuring ADC of small structures, such as the adrenal glands.

## 7.3 Subjects and methods

The institutional board review approved the study design. All patients or their guardians gave written informed consent.

### *Study population*

Twenty-five patients (patient group, PG) were prospectively included from November 2011 to December 2012. All patients were diagnosed as CAH due to 21-hydroxylase deficiency based on clinical presentation, established biochemical markers and genotyping. The patients were on regular and continuous hormonal follow-up during at least one year-period before MRI exam (but for cases 16, 20 and 21 that were new cases in the period) and had no other severe concomitant disease. Patients were phenotypically classified as salt wasting (n=14), simple virilizing (n=9) or non-classical (n=2). Twelve patients were female and 13 male. Median age was 129 months-old (m.o.), ranging from 2 to 316 m.o. One patient was on hydrocortisone treatment, one on dexamethasone, 5 on cortisone acetate, 12 on fludrocortisone and cortisone acetate and 5 on fludrocortisone and dexamethasone. The patients had body-mass index (BMI) within normal limits for age, except for five adolescents and young adults that had BMI of 26.1, 26.3, 28, 35.3 and 37 kg/m<sup>2</sup>. Clinical characteristics of the cohort of patients are displayed in table 7.1.

Adrenal size and ADC values were compared with 23 age-matched controls (control group, CG) who underwent abdominal MRI in the same period, with no history of chronic diseases, hormonal disorders or use of chronic medication. There were 6 male and 17 females, with a median age of 141 m.o. (range 2–360 m.o.).

Table 7.1 – Clinical characteristics of the patient cohort

Patient/ Gender	Age (mo)	Tanner stage	Form of CAH	Weight (kg)	Height (cm)	Treatment	$\Delta 4$ (nmol/L)	Hormonal status ( $\Delta 4$ )	$\Delta 4\text{-M}$ (nmol/L)	Hormonal status ( $\Delta 4\text{-M}$ )
1/M	110	1	SV	33	137	H	2.76	C	1.27	C
2/F	44	1	SW	20.8	100	A	19.72	PC	9.42	PC
3/F	160	3	SW	47.4	154	F+A	27.95	PC	14.80	PC
4/M	63	1	SW	21.6	108.5	F+A	0.14	C	0.14	C
5/M	316	4	SW	56.4	164.5	F+D	16.79	PC	62.23	PC
6/M	201	5	SV	64.9	168	F+D	2.51	C	7.12	C
7/F	65	1	SV	50	114.7	F+A	1.81	C	1.08	C
8/M	139	4	SV	44.5	157	F+A	13.05	PC	6.56	PC
9/M	190	5	SW	49.5	153	F+D	1.01	C	1.22	C
10/F	219	5	SW	85.5	155	F+D	10.78	PC	8.20	C
11/F	128	2	NC	28.8	118	A	1.61	C	2.62	C
12/M	213	5	SV	75.2	169.5	F+A	2.02	C	2.20	C
13/F	231	5	SW	79.9	146	F+D	2.69	C	5.56	C
14/M	111	2	SV	52.5	147.4	A	2.02	C	2.92	C
15/F	141	3	SW	44.6	150	F+A	11.73	PC	8.48	PC
16/M	7	1	SV	8.3	69.5	A	3.59	PC	2.97	C
17/M	148	3	SW	60.9	159	F+A	17.76	PC	8.59	PC
18/F	196	5	NC	72	166	D	2.65	C	6.70	C
19/M	142	2	SW	40.9	147	F+A	0.87	C	1.10	C
20/F	0.5	1	SW	3.4	51	F+A	137.61	PC	47.08	PC
21/F	2.3	1	SW	6.1	60	A	1.88	C	12.91	PC
22/F	114	3	SV	50.6	134.5	F+A	2.06	C	4.58	C
23/F	39	1	SW	18.4	106	F+A	0.17	C	1.35	C
24/M	123	2	SV	27.5	132	F+A	4.92	PC	2.30	C
25/M	143	2	SW	49	152	F+A	0.45	C	1.55	C

mo, months-old; SV, simple virilizing; SW, salt-wating; NC, non-classical; H, hydrocortisone; A, cortisone acetate; F, fludrocortisone; D, dexamethasone.

$\Delta 4$ , androstenedione in the day of magnetic resonance imaging (MRI);  $\Delta 4\text{-M}$ , mean adrostenedione levels in the last year before MRI; C, good control; PC, poor control

### MR image

MR imaging was performed using a 1.5-T scan (Achieva, Koninklijke Philips Electronics N.V., Eindhoven, the Netherlands) with an anterior sixteen-channel body coil. A standard protocol for abdominal imaging was used for both groups, including T2-weighted sequences (T2W) in the axial and coronal views and DWI sequences in the axial view. All MRI exams were collected and saved for posterior analysis in the picture and archiving communication system (PACS).

Images were independently and retrospectively evaluated in a randomized fashion by two different reviewers with 5 and 3 years of experience in abdominal imaging; the former has additionally 2 years of experience in pediatric imaging.

Before starting this study, both reviewers evaluated fifteen MRI examinations of children and young adults, in order to choose which sequence would be used to perform adrenal measurements. The MRI examinations comprised coronal and axial T1W sequences, coronal and axial single-shot T2W sequences, axial T2W fat suppressed sequences, and 3D

T1W ultrafast spoiled gradient echo sequences (THRIVE, Philips, the Netherlands) acquired on the axial plan, with no intravenous contrast. Overall image quality and adrenal glands conspicuity were subjectively graded by using a five-point scale.<sup>14-16</sup> Adrenal glands conspicuity was assessed on the basis of its visibility, margination and signal. Overall image quality was noted from 0 to 4, referring to “non readable”, “poor,” “fair,” “good” and “excellent” quality, respectively. The sequences that achieved grades 2, 3 or 4 in all parameters were considered diagnostic. The sequences that achieved the highest grades were chosen to perform adrenal measurements. Thus, coronal and axial T2W single shot turbo spin echo (T2 SSh TSE) acquisitions were used to perform adrenal measurements.

Parameters of the T2W sequences were: section thickness, 3.0–6.0 mm; intersection gap, 0–1 mm; field of view, 259–375 mm; matrix size, 196 x 252; one or two signal acquired; voxel size, 1.5 x 1.5 x 3–6.0 mm; repetition time msec/echo time msec, 1175/160; turbo spin echo factor, 90; 20 sections acquired; total acquisition time, 29 seconds; flip angle, 90°; parallel imaging with sensitivity encoding with a parallel imaging reduction factor of two.

Transverse DWI multisection echo-planar was performed with chemical shift fat saturation technique under free breathing, without intravenous contrast administration or cardiac motion correction technique. Sequences parameters were: diffusion gradient *b* values of 0, 20, 500 and 1000 s/mm<sup>2</sup> applied in three orthogonal directions (x, y and z); parallel imaging reduction factor, 2; repetition time/echo time/echo planar imaging factor (TR/TE/EPI factor), 5128/73/69; section thickness, 5 mm; intersection gap, 0–1 mm; matrix size, 172 x 133; field of view, 345 x 321 mm; voxel size, 2.55 mm<sup>3</sup>; number of excitations acquired, 2; reduction factor, 2. The whole sequence consisted of 20–25 sections, with an acquisition time average of 3 minutes. ADC maps were calculated automatically at the MRI workstation with a multiexponential model.

### *Image analysis*

T2W images were reviewed on the PACS workstation for standard measurements. A free magnification-targeting factor was used according to reviewers’ preferences. Thickness of the body and tails were measured as previously described<sup>17,18</sup> on T2W coronal and axial views (Figure 7.1) by one reviewer. Longitudinal measurements of the adrenal glands were not performed as the authors agree to others<sup>19</sup> that the accuracy to measure a curvilinear structure would not be appropriate, and it is not guaranteed that the whole tail of one gland would be present in the same image. Morphological evaluation was done based on the

presence or absence of adrenal nodules, by both reviewers.

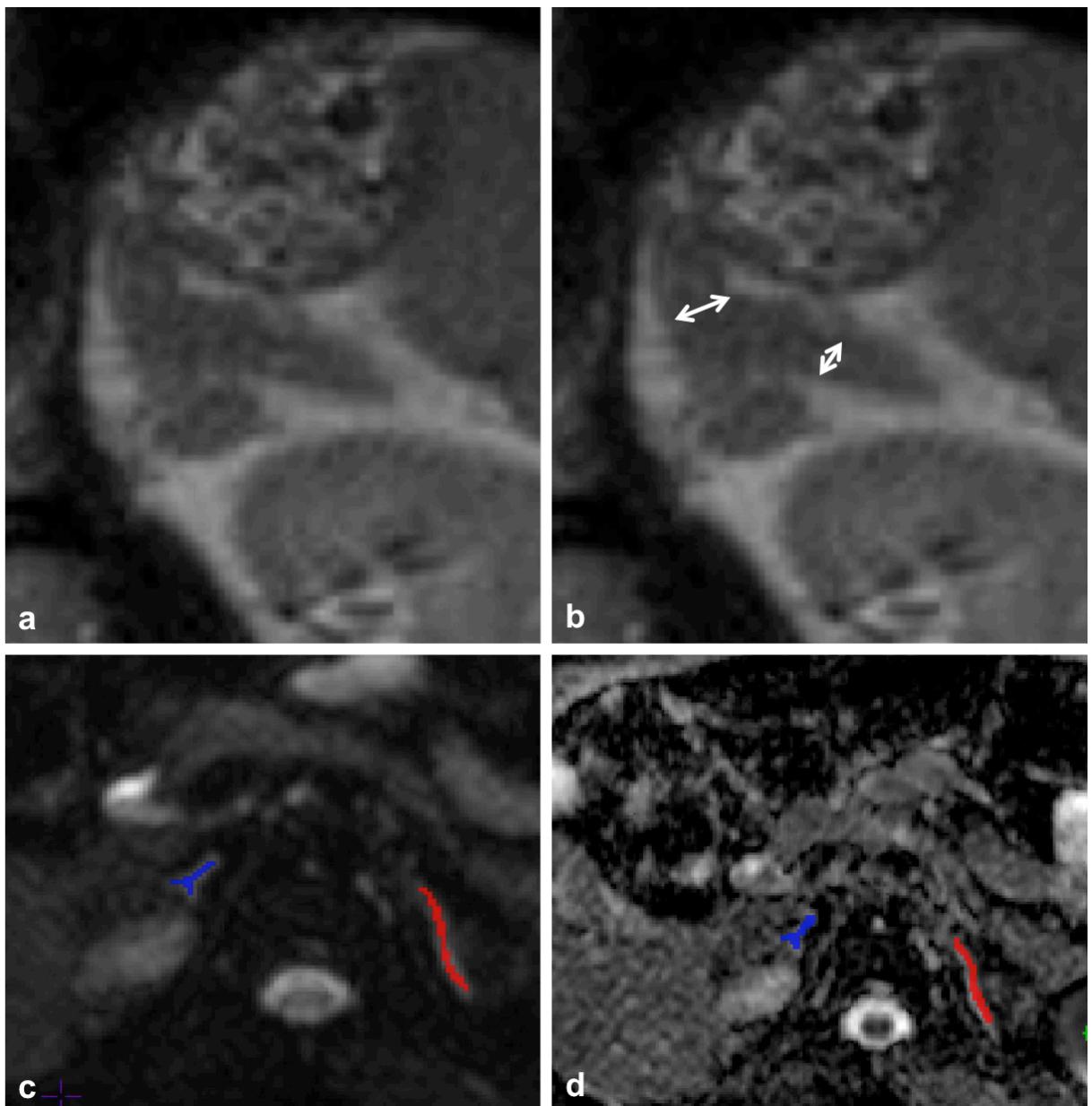


Figure 7.1 – Measurements of the adrenal glands. Figures “a” and “b”, T2-weighted magnetic resonance imaging of the left adrenal gland, coronal view. Continuous arrows in “b” are showing the thickness of the body and lateral tail of the adrenal gland (Adapted from reference 20). Figure “c”, transverse DWI,  $b = 500 \text{ s/mm}^2$ ; Figure “d”, transverse ADC map. Blue label, right adrenal gland; red label, left adrenal gland. Example of how to segment the adrenal glands and fuse diffusion-weighted images (DWI) with the apparent diffusion coefficient (ADC) map. After setting thresholds, adrenal glands are manually segmented on DWI (c). Then, labels segmented on DWI are fused with the ADC map (d). The software automatically calculates ADC values of the adrenal glands.

Subsequently, T2W images, DWI and ADC maps were converted into MINC format

and analyzed in a free software package (Display version 1.4.2, David McDonald, Brain Imaging Centre of the Montreal Neurological Institute, Montreal, Canada) allowing displaying of simultaneous coronal, sagittal and axial reconstruction planes.

A pixel-by-pixel volumetric analysis was performed by manual segmentation of the adrenal glands in the axial T2W images. Through this method, the volume of the region of interest (ROI) is automatically calculated by summing the area of the pixels manually chosen in each slice. Because the shape of the adrenals can be irregular, threshold values were established to exclude adjacent fat from the volume calculated. As described elsewhere<sup>20</sup> for different organs, summing and posteriorly dividing by 2 the values of the closest voxel to the adrenal gland with the highest value and the voxel with the lowest value in the adrenal gland defined the threshold for the maximum value of the voxels of the ROIs. Then, the definition of the ROI was performed by selecting the outermost surrounding voxels and by further selecting the interior of the surrounded area.<sup>20</sup> Axial views were preferred to perform volumetric analysis for having overall smaller slice thickness than coronal views. Also, it was the same plane in which DWI sequences were acquired.

ADC measurement was also performed on a pixel-by-pixel basis, by manual segmenting the adrenal glands on the original DWI, b value of 500 s/mm<sup>2</sup>, which allows good visualization of them. After adrenal glands segmentation, images were fused with the ADC map using a script. By this method, ADC value of the ROI is automatically calculated by average of the pixels manually chosen in each slice (Figure 7.1).

All patients and controls had clearly defined adrenal margins on T2W and DWI. Reviewers were unaware of the clinical data of the subjects included in the study and also of the other reviewer's results. To become familiar with the software, both radiologists applied the method in 10 adrenal glands before starting this study (data not included in the present analysis). Each radiologist measured the adrenal glands once. All measurements lasted around 6 min per gland.

Intraobserver agreement for ADC and volume measurements was assessed twice in 10 subjects bilaterally, with a time interval of two months, by a single radiologist (S.R.T). Interobserver agreement was determined by comparing ADC values and volumes obtained of all patients and controls included in the study, of the right and left adrenal glands separately.

#### *Hormonal evaluation and clinical control*

Short-term hormonal status of the patients was assessed based on serum

androstenedione concentration measured by in-house radioimmunoassay (RIA) with sensitivity, intra and interassay coefficients of variation of 0.17 nmol/L, 4.2% and 15.6%, respectively.<sup>21</sup> Normal ranges for androstenedione levels were <0.13 – 3.49 nmol/L for pre-pubertal patients and 2.09 – 8.73 nmol/L for post-pubertal patients, according to the local laboratory measurements. Poor or good control was based on androstenedione levels, above or below normal ranges respectively, according to pubertal stage. Blood was drawn in the morning, in the same day of the MRI exams ( $\Delta 4$ ).

Long-term hormonal status was assessed by mean androstenedione levels ( $\Delta 4\text{-M}$ ) obtained from at least two prior dosages within the last year prior to the MRI exam. A wide range of values was observed for both hormonal parameters:  $\Delta 4$ , median 2.65 nmol/L, range < 0.13 – 137.61 nmol/L;  $\Delta 4\text{-M}$ , median 4.58 nmol/L, range < 0.13 – 62.23 nmol/L. Ten patients (40%) had poor hormonal control versus 15 (60%) with good control in the day of the MRI; eight (32%) patients were in a poor chronic hormonal status versus 17 (68%).

Although CAH patients are monitored for hormonal status throughout serum androstenedione and testosterone measurements, androstenedione is the most sensitive indicator of inadequate adrenal suppression in CAH.<sup>2</sup> Additionally, androstenedione concentrations have been shown to be a good index to assess hormonal control in patients with CAH at all stages of puberty<sup>22,23</sup> being the earliest androgen to rise in case of inadequate adrenal suppression and less affected by circadian variations.<sup>24</sup> Serum testosterone concentrations may also be used for evaluating hormonal control. However, in pubertal male patients it reflects testicular production rather than adrenal androgen production.<sup>22</sup> Finally, dehydroepiandrosterone sulfate (DHEA-S) is not a good marker as it may be low either in patients with good control or poor control.<sup>23</sup> Therefore, hormonal status was based solely on androstenedione serum concentrations.

Adequacy of long-term clinical control was judged based on previously described criteria<sup>25</sup> which includes bone age, signs of virilization or adrenal crisis and hormonal profile. Bone age was estimated according to Greulich and Pyle. Signs of virilization or adrenal crisis were assessed by clinical history. Clinical control was coincident with the chronic hormonal control assessed by  $\Delta 4\text{-M}$  in all of the patients.

#### *Statistical Analysis*

Data were checked for distribution before statistical analysis using the Shapiro-Wilk test. Data are represented as means  $\pm$  standard deviation (SD) or median and interquartiles

(25th–75th) as required. For group comparisons univariate analysis was performed using the Student *t* test or Mann-Whitney *U* test for variables with or without normal distribution, respectively. The measurements of the two reviewers were treated independently. For correlation analysis between adrenal measurements and hormonal control status, Spearman's correlation coefficient was used for qualitative control and variables without normal distribution; Pearson's correlation coefficient (*r*) was used for continuous variables with normal distribution. *P* values less than 0.05 were considered statistically significant. For assessment of intra and interobserver agreement, we calculated the intraclass correlation coefficient (ICC) that takes into account both systematic and random errors.<sup>26</sup> Statistical analysis was performed with IBM SPSS statistics release 19 (IBM Corporation) software.

## 7.4 Results

### *Intra and interobserver agreements*

Agreement between first and second readers was substantial regarding ADC. In the control group ICC was 0.62 [95% confidence interval (CI) 0.001 – 0.86] for the right gland and 0.72 (95% CI 0.25 – 0.89) for the left gland. In the patient group, results were similar. ICC was 0.69 (95% CI 0.30 – 0.86) for the right gland and 0.78 (95% CI 0.50 – 0.90) for the left gland. Concerning volume measurements, in the control group a moderate agreement was found on the right side (ICC = 0.41; 95% CI -0.75 – 0.80) and a substantial agreement on the left side (ICC = 0.66; 95% CI 0.01 – 0.88). In the patient group, ICC was 0.76 (95% CI 0.22 – 0.93) for the right gland and 0.90 (95% CI 0.69 – 0.97) for the left gland.

Intraobserver reliability was almost perfect regarding volume and ADC measurements. ICC was 0.91 (95% CI 0.82 – 0.98) and 0.95 (95% CI 0.82 – 0.98) for the right adrenal gland; ICC was 0.94 (95% CI 0.85 – 0.97) and 0.97 (95% CI 0.91 – 0.99) on the left side, respectively.

### *Adrenal measurements and comparison between groups*

Mean ADC values, volumes, linear measurements and comparison between patient and control groups are shown in table 7.2. Regarding ADC values, there was no substantial difference between patients and controls (*P* = 0.8 for the right gland and *P* = 0.6 for the left gland). In contrast, all other measurements of the adrenal glands were different between

patients and controls, being higher in the PG. Exceptions were the volume of the left adrenal gland and the thickness of the right adrenal gland measured on coronal view. Morphological evaluation of the adrenal glands revealed no nodules (Figure 7.2).

Table 7.2 – Measurements of the adrenal glands and comparison between patient and control groups

<b>View</b>	<b>Side</b>	<b>Parameter</b>	<b>Patient group</b>	<b>Control group</b>	<b>P-value*</b>
			(SD)	(SD)	
n.a.	Right	ADC	1.39 ( $\pm$ 0.34)	1.37 ( $\pm$ 0.22)	0.9
	Left	ADC	1.53 ( $\pm$ 0.33)	1.49 ( $\pm$ 0.23)	0.7
n.a	Right	Volume	3.85 ( $\pm$ 2.78)	2.5 ( $\pm$ 1.25)	0.04
	Left	Volume	4.45 ( $\pm$ 4.93)	2.85 ( $\pm$ 1.57)	0.13
Axial	Right	Body thickness	0.53 ( $\pm$ 0.23)	0.28 ( $\pm$ 0.13)	<0.001
		Medial tail thickness	0.47 ( $\pm$ 0.55)	0.18 ( $\pm$ 0.06)	<0.001
		Lateral tail thickness	0.34 ( $\pm$ 0.14)	0.14 ( $\pm$ 0.09)	<0.001
		Medial tail length	3.54 ( $\pm$ 0.72)	3.01 ( $\pm$ 0.71)	0.02
		Lateral tail length	2.93 ( $\pm$ 0.98)	1.94 ( $\pm$ 1.33)	0.01
	Left	Body thickness	0.56 ( $\pm$ 0.27)	0.34 ( $\pm$ 0.14)	<0.001
		Medial tail thickness	0.37 ( $\pm$ 0.20)	0.19 ( $\pm$ 0.06)	<0.001
		Lateral tail thickness	0.40 ( $\pm$ 0.19)	0.20 ( $\pm$ 0.06)	<0.001
		Medial tail length	3.35 ( $\pm$ 0.80)	2.68 ( $\pm$ 0.67)	0.003
		Lateral tail length	3.46 ( $\pm$ 0.97)	2.41 ( $\pm$ 0.92)	<0.001
Coronal	Right	Body thickness	0.43 ( $\pm$ 0.19)	0.31 ( $\pm$ 0.11)	0.02
		Medial tail thickness	0.34 ( $\pm$ 0.15)	0.25 ( $\pm$ 0.08)	0.02
		Lateral tail thickness	0.28 ( $\pm$ 0.15)	0.22 ( $\pm$ 0.06)	0.10
		Medial tail length	2.27 ( $\pm$ 0.78)	1.69 ( $\pm$ 0.54)	0.01
		Lateral tail length	2.31 ( $\pm$ 0.84)	1.74 ( $\pm$ 0.64)	0.01
	Left	Body thickness	0.49 ( $\pm$ 0.21)	0.29 ( $\pm$ 0.10)	<0.001
		Medial tail thickness	0.33 ( $\pm$ 0.19)	0.23 ( $\pm$ 0.07)	0.01
		Lateral tail thickness	0.36 ( $\pm$ 0.21)	0.25 ( $\pm$ 0.08)	0.04
		Medial tail length	2.32 ( $\pm$ 0.73)	1.65 ( $\pm$ 0.45)	<0.001
		Lateral tail length	2.87 ( $\pm$ 1.11)	1.78 ( $\pm$ 0.47)	<0.001

\* Comparison between patient and control groups.

ADC, apparent diffusion coefficient; SD, standard deviation; n.a., non-applicable.

ADC values are given in mm<sup>2</sup>/s, volume in cm<sup>3</sup>, and thickness and length in cm.

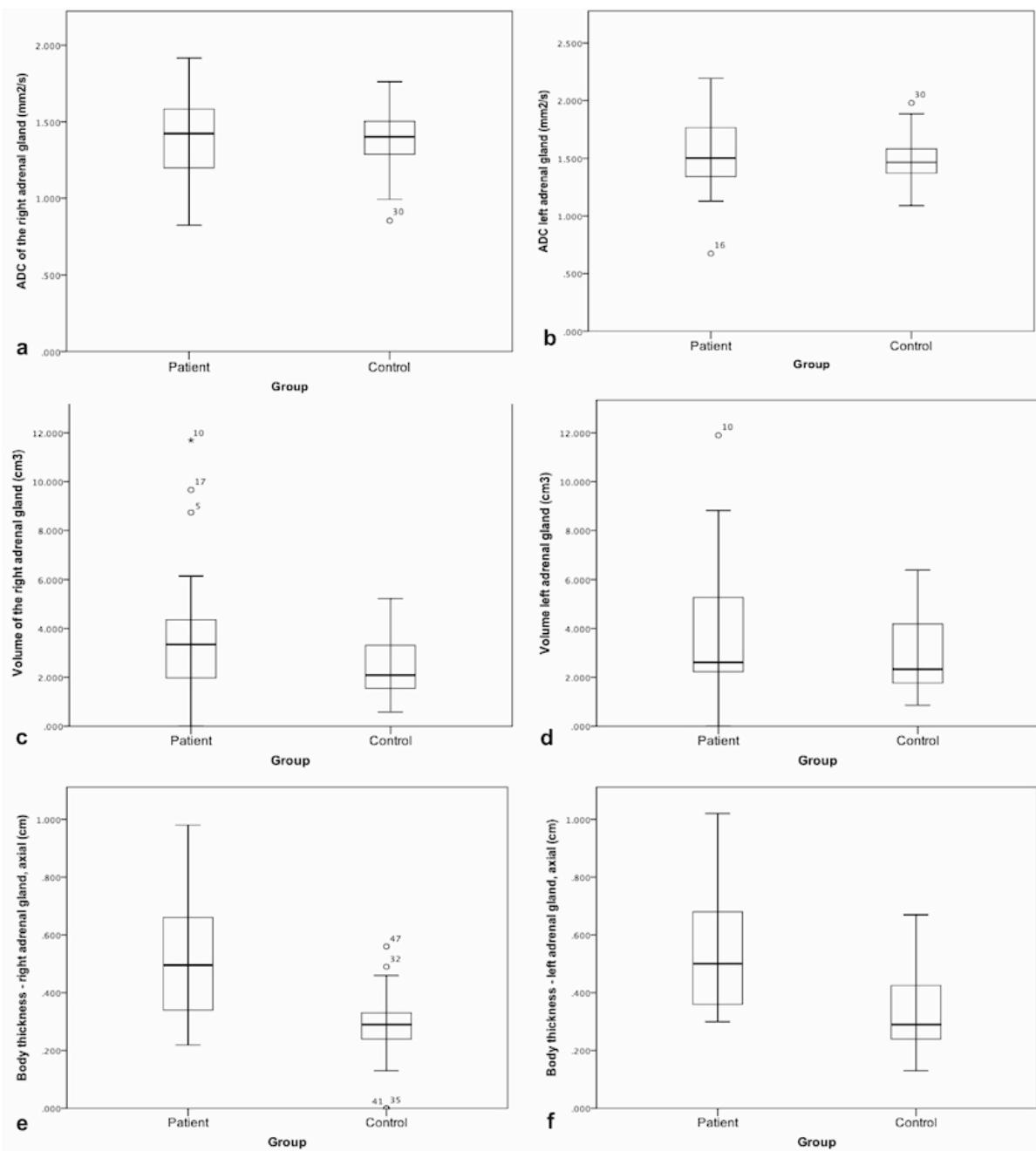


Figure 7.2 – Box-and-whisker plot of measurements of the adrenal glands according to the groups, patient and control. Apparent diffusion coefficient (ADC) of the right (a) and left adrenal glands (b); volume of the right (c) and left (d) adrenal glands; body thickness of the right (e) and left (f) glands measured on the axial view. Boxes represent interquartile range. Whiskers represent range of all values. Horizontal line within box is median value. ADC values are given in  $10^{-3} \text{ mm}^2/\text{s}$ , volume in  $\text{cm}^3$ , and body thickness in cm. ADC values were not different when comparing the groups. Measurements of the adrenal glands are higher in the patient group compared to controls.

### *Adrenal measurements and hormonal status in the patient group*

Table 7.3 displays mean ADC values, volumes and linear measurements of the adrenal glands in the patient group, and comparison between controlled and poor controlled patients according to hormonal status.

Within patients, ADC values were not significantly different when comparing individuals with poor and good control based on  $\Delta 4$  values ( $P = 0.9$ , right gland;  $P = 0.7$ , left gland). On the other hand, volume of the adrenal glands was significantly higher in poor controlled patients, although the volume of the left adrenal gland was not statistically different between different hormonal statuses ( $P = 0.04$  vs  $0.13$ , right vs left gland). Despite this fact, there was a positive correlation between hormonal control status and adrenal volumes, either for the right or for the left gland ( $r = 0.50 - 0.57$ ,  $P < 0.01$ ) (Figure 7.3).

The thickness of the medial tail measured on axial view and the thickness of the medial and lateral tails measured on coronal view of the left adrenal gland, and the lateral tail thickness of the right adrenal gland measured on coronal view were statistically different and higher in poor controlled compared to controlled patients according to  $\Delta 4$ . For other linear measurements this difference was not significant but still, measurements were higher in poor controlled patients.

When hormonal status was assessed using  $\Delta 4\text{-M}$ , none of the adrenal measurements (ADC, volume and linear measurements) were statistically different between the different hormonal control statuses of the patients ( $P = 0.06 - 0.9$ ). For all adrenal measurements, no significant differences were observed comparing the right and the left sides ( $P = 0.10 - 0.12$ ) or between genders ( $P = 0.08 - 0.9$ ).

Table 7.3 - Measurements of the adrenal glands in the patient group

View	Side	Parameter	Hormonal Status ( $\Delta 4$ )			Hormonal Status ( $\Delta 4\text{-M}$ )		
			Controlled (SD)	Poor Controlled (SD)	P-value *	Controlled (SD)	Poor Controlled (SD)	P-value *
n.a.	Right	ADC	1.42 ( $\pm 0.34$ )	1.33 ( $\pm 0.35$ )	0.87	1.42 ( $\pm 0.36$ )	1.31 ( $\pm 0.29$ )	0.42
	Left	ADC	1.63 ( $\pm 0.26$ )	1.37 ( $\pm 0.37$ )	0.56	1.56 ( $\pm 0.34$ )	1.45 ( $\pm 0.31$ )	0.45
n.a.	Right	Volume	2.86 ( $\pm 1.44$ )	5.33 ( $\pm 3.65$ )	0.04	3.33 ( $\pm 2.64$ )	4.96 ( $\pm 2.92$ )	0.20
	Left	Volume	2.67 ( $\pm 1.34$ )	7.13 ( $\pm 6.97$ )	0.01	3.8 ( $\pm 2.69$ )	6.96 ( $\pm 7.49$ )	0.08
Axial	Right	Body thickness	0.50 ( $\pm 0.19$ )	0.56 ( $\pm 0.28$ )	0.46	0.51 ( $\pm 0.23$ )	0.56 ( $\pm 0.23$ )	0.64
	Medial tail thickness	0.50 ( $\pm 0.69$ )	0.43 ( $\pm 0.26$ )	0.74	0.32 ( $\pm 0.14$ )	0.80 ( $\pm 0.91$ )	0.05	
Left	Lateral tail thickness	0.36 ( $\pm 0.13$ )	0.30 ( $\pm 0.15$ )	0.28	0.36 ( $\pm 0.13$ )	0.28 ( $\pm 0.16$ )	0.36	
	Medial tail length	3.53 ( $\pm 0.63$ )	3.54 ( $\pm 0.86$ )	0.59	3.53 ( $\pm 0.70$ )	3.56 ( $\pm 0.82$ )	0.93	
Left	Lateral tail length	3.07 ( $\pm 0.80$ )	2.73 ( $\pm 1.25$ )	0.66	3.10 ( $\pm 0.75$ )	2.51 ( $\pm 1.43$ )	0.26	
	Body thickness	0.53 ( $\pm 0.18$ )	0.61 ( $\pm 0.37$ )	0.31	0.55 ( $\pm 0.21$ )	0.59 ( $\pm 0.37$ )	0.75	
Left	Medial tail thickness	0.32 ( $\pm 0.13$ )	0.43 ( $\pm 0.27$ )	0.03	0.33 ( $\pm 0.13$ )	0.44 ( $\pm 0.30$ )	0.34	
	Lateral tail thickness	0.40 ( $\pm 0.13$ )	0.41 ( $\pm 0.25$ )	0.51	0.40 ( $\pm 0.13$ )	0.42 ( $\pm 0.28$ )	0.81	
Left	Medial tail length	3.27 ( $\pm 0.88$ )	3.50 ( $\pm 0.66$ )	0.03	3.32 ( $\pm 0.79$ )	3.43 ( $\pm 0.87$ )	0.79	
	Lateral tail length	3.35 ( $\pm 1.01$ )	3.64 ( $\pm 0.93$ )	0.19	3.42 ( $\pm 0.88$ )	3.55 ( $\pm 1.22$ )	0.80	
Coronal	Right	Body thickness	0.39 ( $\pm 0.12$ )	0.49 ( $\pm 0.26$ )	0.06	0.38 ( $\pm 0.12$ )	0.53 ( $\pm 0.28$ )	0.06
	Medial tail thickness	0.30 ( $\pm 0.14$ )	0.40 ( $\pm 0.17$ )	0.10	0.30 ( $\pm 0.13$ )	0.41 ( $\pm 0.19$ )	0.19	
Left	Lateral tail thickness	0.23 ( $\pm 0.12$ )	0.35 ( $\pm 0.18$ )	0.03	0.24 ( $\pm 0.12$ )	0.36 ( $\pm 0.19$ )	0.14	
	Medial tail length	2.30 ( $\pm 0.74$ )	2.22 ( $\pm 0.86$ )	0.87	2.28 ( $\pm 0.74$ )	2.26 ( $\pm 0.90$ )	0.95	
Left	Lateral tail length	2.17 ( $\pm 0.61$ )	2.56 ( $\pm 1.13$ )	0.10	2.22 ( $\pm 0.69$ )	2.54 ( $\pm 1.17$ )	0.41	
	Body thickness	0.44 ( $\pm 0.17$ )	0.58 ( $\pm 0.25$ )	0.14	0.44 ( $\pm 0.17$ )	0.59 ( $\pm 0.27$ )	0.20	
Left	Medial tail thickness	0.27 ( $\pm 0.09$ )	0.44 ( $\pm 0.26$ )	0.03	0.28 ( $\pm 0.09$ )	0.45 ( $\pm 0.28$ )	0.35	
	Lateral tail thickness	0.30 ( $\pm 0.15$ )	0.44 ( $\pm 0.26$ )	0.05	0.31 ( $\pm 0.14$ )	0.46 ( $\pm 0.30$ )	0.20	
Left	Medial tail length	2.13 ( $\pm 0.61$ )	2.66 ( $\pm 0.84$ )	0.03	2.20 ( $\pm 0.56$ )	2.57 ( $\pm 0.99$ )	0.36	
	Lateral tail length	2.41 ( $\pm 0.88$ )	3.57 ( $\pm 1.09$ )	0.01	2.66 ( $\pm 1.00$ )	3.34 ( $\pm 1.26$ )	0.21	

\* Comparison between controlled and poor controlled patients according to androstenedione concentrations.

ADC, apparent diffusion coefficient; SD, standard deviation; n.a., non-applicable.

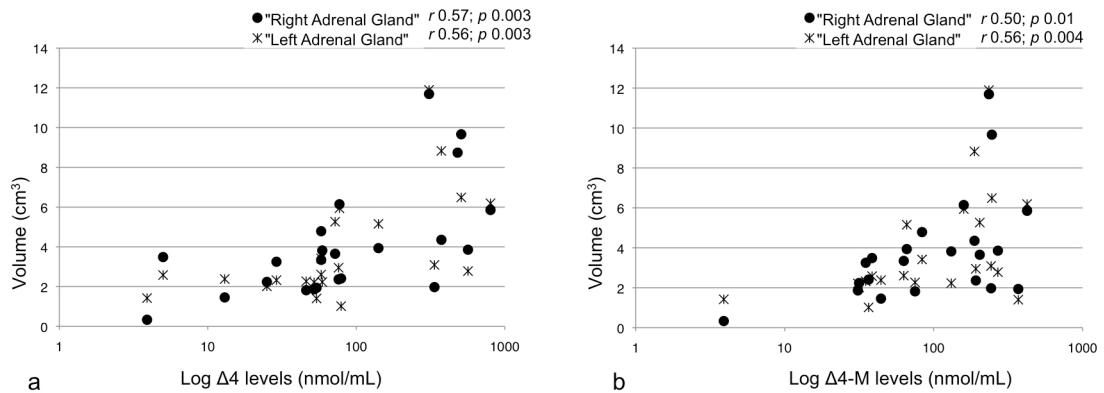


Figure 7.3 – Correlation between adrenal gland volumes and androstenedione concentrations in the same day of magnetic resonance imaging (MRI) (a); correlation between adrenal gland volumes and mean androstenedione concentrations in the last year prior to MRI (b).

*r, Pearson's correlation coefficient.*

## 7.5 Discussion

Previous studies using sonography have described the imaging pattern of adrenal glands in CAH neonates.<sup>27,28</sup> Reisch N and colleagues showed a positive correlation between adrenal gland volumes measured on MRI and hormonal levels.<sup>5</sup> However, studies using MRI to evaluate adrenal volume in children with CAH are lacking. Moreover, to the best of our knowledge, ADC of the adrenal glands in this context has not yet been studied.

Adrenal size and volume measured by MRI were statistically different and higher in patients compared to controls. Additionally, a positive correlation between adrenal volume measurements and hormonal control status was also found in our series. Our data not only are in accordance with previous studies performed in adult patients,<sup>5</sup> but also extends the evidence that short-term parameters assessing hormonal control have a significant correlation with the gland size. We have shown that children and young adults had the same correlation pattern; in agreement with the physiologic knowledge of the disease, probably reflecting the prompt adaptation of the adrenal glands size to hormonal control.

Adrenal linear measurements and volumes were not statically different between controlled and non-controlled patients, when assessed by long-term parameter Δ4-M. However, when hormonal control was assessed using Δ4, non-controlled patients presented significant higher adrenal volumes compared to controlled patients. It is important to point out that our negative results using the mean hormonal value as a long-term hormonal control parameter might have misled the true hormonal status since, during the 12 months taken into

account, patients could have oscillate between controlled and non-controlled status. Nevertheless, the results tailing measurements assessed by immediate hormonal control status ( $\Delta 4$ ) are substantial considering the relative small group studied.

Regarding slice thickness on T2W used to perform measurements, it was demonstrated that, in other organs such as the hippocampus, no clinical significant difference of volume measurements were observed using slices from 1 to 5 mm.<sup>29</sup> Nevertheless, these findings should be further validated by larger studies with children and young adults with CAH and in abdominal organs.

Although adrenal nodules are more frequent throughout adulthood in CAH patients<sup>5</sup> and adrenal incidentalomas prevalence increases with aging,<sup>30</sup> in our series of young patients, none of the adrenal glands had nodules identified on imaging. The shorter lifetime exposure to the high ACTH concentrations could be accounted for those findings.

ADC is a quantitative parameter derived form DWI that can provide information about intracellular and extracellular space.<sup>8,11-13</sup> In CAH secondary to 21-hydroxilase deficiency, there is hyperplasia of the adrenocortical region, dysplasia of the medulla, poorly defined zones, irregular zona glomerulosa and extensive intermingling of cortical and chromaffin cells.<sup>4</sup> Despite this ultrastructure remodeling and dysplasia, differences between ADC measurements of patients and controls were not found in our study. Possibly, the abnormally large amount of cytoplasm with dilated smooth endoplasmic reticulum and large, round mitochondria, encountered in the subcellular adrenocortical structure<sup>4</sup> do not reflect in true different water motion. The methods we applied to assess ADC values could also not be sufficiently sensitive to depict these subtle alterations. Moreover, modifications in the cell structure of the adrenal glands in CAH may occur with preservation of connective tissue and not allowing it to form dense cell packs that would restrict water motion. In addition, due to the low spatial resolution of the DWI sequences we could not separate ADC of the different regions (medulla and cortex) of the adrenal glands.

The results concerning feasibility and reproducibility of measuring adrenal ADC values showed good interobserver reliability. Different techniques have already been applied to calculate ADC of adrenal lesions. Most of the researchers used two radiologists to perform ADC measurements and gave results as means of values or consensus between readers,<sup>31-33</sup> though in some studies ADC measurements were performed by a single radiologist.<sup>34-36</sup> Of note, ICC was described only in one paper<sup>37</sup> lower than the one found in our patients (ICC = 0.47 vs 0.74, respectively). One should point out that in this cited paper the authors drew a manual ROI as large as possible within large heterogeneous adrenal lesions, whereas our

purpose was to measure ADC value of the entire organ in a pixel-by-pixel basis. The difference between these two techniques could be responsible for the more accurate measurements leading to similar results between readers described in our patient series.

With respect to adrenal volumes, the apparent lower ICC found for the right compared to the left adrenal gland in controls could be due to the proximity of the former with the liver making it more difficult to delimitate adrenal margins. Although variations due to different readers have already been demonstrated<sup>38</sup> they should be considered as having a minor clinical impact, thus rendering volume measurement of small structures by MRI a valuable tool.

One major limitation of our study was the number of patients. CAH is a rare disease rendering difficulties in recruiting patients, even in areas with a higher prevalence of the disease. In addition, the wide range of age may raise issues for interpreting the results. But by performing a case-control study with age-matched controls may overcome this difficult and diminish bias. For the purpose of showing feasibility and reproducibility of measuring ADC values of small structures such as the adrenal glands it did not raised concerns. But for differentiating patients from controls or showing correlation of ADC values with hormonal status, this population was not sufficient.

In conclusion, our data provide additional evidence to the relationship between adrenal size, particularly adrenal volume, and short-term hormonal control in patients with CAH. It also supports feasibility and reproducibility of performing ADC measurements of the adrenal glands. Although cell structure modifications in the adrenal glands in patients with CAH are described, it was not detectable by DWI.

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## 8. DISCUSSÃO GERAL

Apesar do diagnóstico de CAH ser baseado em dosagens hormonais e análises genéticas e existirem programas de rastreamento neonatal em alguns países<sup>2</sup>, inclusive no Brasil, métodos de imagem são importantes ferramentas auxiliares no manejo de pacientes com CAH. Além da RX para avaliar a idade óssea, US, MRI, CT e outros métodos podem adicionar informações importantes.

Em recém-nascidos, o achado na US de uma glândula suprarrenal com padrão cerebriforme é específico para o diagnóstico de CAH,<sup>12,19</sup> o que possibilita a instituição do tratamento antes mesmo dos resultados laboratoriais confirmarem o diagnóstico. O mesmo sinal pode ser encontrado no período intra-útero.<sup>18</sup> A MRI é o exame de escolha para detecção e caracterização de nódulos adrenais. Além disso, tanto neste estudo quanto em outros,<sup>11</sup> foi demonstrada significativa correlação das medidas da suprarrenal na MRI com os parâmetros hormonais, semelhante a estudos realizados com US em recém-nascidos e lactentes.<sup>76</sup> A CT é basicamente usada para caracterização de nódulos adrenais, porém com a desvantagem do uso de radiação ionizante.

A US é o método de escolha para avaliação da presença de TARTs.<sup>85,86</sup> É recomendado periodicamente e, segundo alguns autores, deveria ser realizada ainda no período pré-puberal.<sup>85</sup> A MRI é recomendada nos casos em que se planeja uma cirurgia com preservação parcial do testículo.<sup>87</sup>

Em casos de genitália ambígua, a US é o primeiro método de imagem a ser solicitado a fim de demonstrar a presença de derivados müllerianos.<sup>13</sup> A MRI fornece informações detalhadas em relação à anatomia pélvica além de ser operador-independente. Deve ser realizada nos casos em que a US não for suficiente para mostrar as estruturas pélvicas, principalmente na avaliação antes da cirurgia de feminização.<sup>13,88</sup> A RXC pode ser usada para auxiliar o planejamento cirúrgico.<sup>88</sup>

Em relação à técnica de DWI, neste estudo foi usada uma técnica habitualmente empregada nos exames de protocolos de rotina clínica. Optou-se por assim o fazer para facilitar a reprodução das sequências e medidas na prática clínica diária. Apesar de aumentar o tempo da sequência de DWI, para o cálculo do mapa de ADC, múltiplos valores de b e valores altos<sup>89</sup> entre 500 e 1000 s/mm<sup>2</sup> são recomendados por serem mais precisos e reduzir a contaminação da perfusão.<sup>62,63</sup>

Lesões pequenas, principalmente as menores que 1,0 cm, podem ser difíceis de serem detectadas nos mapas de ADC.<sup>68</sup> A glândula suprarrenal apresenta alto sinal na DWI porém, também é difícil a sua identificação direta nos mapas de ADC.<sup>70</sup> Portanto, a medida do ADC das glândulas suprarrenais neste estudo foi realizada após corregistro de uma sequência com maior resolução espacial (DWI,  $b = 500 \text{ s/mm}^2$ ) com o mapa de ADC. Esta técnica já foi empregada para medir o ADC de lesões com margens irregulares<sup>64</sup> já que permite uma avaliação morfológica mais adequada da estrutura a ser avaliada e aumenta a confiança nos valores obtidos de ADC.<sup>90,91</sup> Além disso, o método é factível e reproduzível, com alta concordância entre os observadores e intra-observador [coeficiente de correlação intraclasses (ICC) inter-observadores variando de 0,62 a 0,78; ICC intra-observador variando de 0,91 a 0,94;  $P < 0,05$ ). É importante salientar que até o momento da confecção dessa tese não existiam estudos prévios publicados direcionados para aspectos técnicos e valores de ADC em glândulas suprarrenais normais, bem como em pacientes com CAH.

Em pacientes sem doença hormonal conhecida, o ADC é mais baixo a partir da adrenarca. Soma-se a este fato o conhecimento das modificações celulares que ocorrem na CAH.<sup>8</sup> Todavia, estas alterações não foram detectadas pelas medidas de ADC no nosso estudo. Uma das hipóteses seria: devido à baixa resolução espacial inerente à DWI não se distingue a medula do córtex da adrenal o que leva a uma mescla das medidas do ADC das duas diferentes zonas com diferentes estruturas celulares, e não à verdadeira medida do ADC do córtex adrenal. Outra hipótese seria a de que possam existir mecanismos diferentes em relação ao estímulo da adrenal entre a adrenarca fisiológica e a hiperestimulação patológica em CAH, com arranjos citoarquiteturais distintos. Na adrenarca fisiológica, há uma expansão da zona reticular<sup>92</sup> e em ratos, foi proposto que exista um enlongamento e expansão globular da crista mitocondrial da zona fasciculada que está relacionado a esteroidogênese.<sup>93</sup> Por outro lado, na CAH, o córtex adrenal é hiperplásico e espessado, com perda de diferenciação das zonas corticais e entrelaçamento das células da medula e do córtex.<sup>8</sup>

O tamanho das glândulas suprarrenais na MRI avaliado tanto por volume quanto por suas medidas lineares está direta e positivamente relacionado ao status hormonal recente de crianças e adultos jovens com CAH. Estes dados estão de acordo com o que se conhece da doença e já foi mostrado em outro estudo<sup>11</sup> realizado apenas em adultos. Possivelmente há uma adaptação e resposta rápida da suprarrenal ao tratamento. Porém em relação ao status hormonal crônico, não houve relação entre o tamanho das glândulas e o status hormonal do paciente. As oscilações hormonais que ocorreram durante o período ficam atenuadas quando

se faz uma média das dosagens séricas dos últimos 12 meses. Este fato reforça ainda mais a hipótese de que existe uma rápida resposta da suprarrenal à instituição do tratamento.

A presença de nódulos na CAH aumenta com a idade, sendo, portanto, mais frequente em adultos.<sup>3,11</sup> Não foram encontrados nódulos em nenhum dos pacientes avaliados neste estudo, crianças ou adultos jovens, o que está de acordo com a premissa de que quanto maior o tempo de exposição a altos níveis de ACTH, maior a prevalência de nódulos adrenais.

Para avaliação das glândulas suprarrenais em pacientes com CAH, métodos de imagem observador-independente e que permitam o cálculo volumétrico e medidas das glândulas sem radiação ionizante, como a MRI, podem auxiliar no acompanhamento dos pacientes e mostrar rapidamente os efeitos da exposição a altos níveis de ACTH. Talvez, com o auxílio desta ferramenta, seja possível predizer a presença de nódulo adrenal no futuro e monitorar mais de perto os sinais de transformação maligna dos nódulos. A desvantagem da MRI ainda é o seu alto custo, baixa disponibilidade e a necessidade de sedação em pacientes selecionados.

## 9. CONCLUSÃO

Em recém-nascidos e no período pré-natal, a US é o método de escolha para avaliar a suprarrenal e pode sugerir com alta especificidade o diagnóstico de CAH enquanto se aguarda a confirmação diagnóstica laboratorial. Além disso, o rastreamento precoce de TARTs por US ainda no período pré-puberal é justificado. A US é o primeiro método de imagem a ser solicitado nos casos de genitália ambígua e a MRI é indicada quando aquela não for suficiente ou para o planejamento de cirurgia de feminização.

Medir o ADC das suprarrenais normais é factível e reproduzível. Estes dados podem acrescentar informações para caracterização tecidual por MRI e no futuro poderão ser usados para comparação com lesões adrenais pequenas e doenças difusas. Além disso, o método pixel-a-pixel com correção de imagens empregado para medir o ADC das suprarrenais poderá ser usado em outros órgãos, lesões ou regiões de pequenas dimensões e de contornos irregulares.

As dimensões das glândulas suprarrenais – volume e medidas lineares – em pacientes com CAH avaliadas por MRI podem ser utilizadas como ferramenta auxiliar no acompanhamento dos pacientes e mostrar rapidamente os efeitos da exposição a altos níveis de ACTH. As dimensões das glândulas suprarrenais estão diretamente e positivamente relacionadas ao status hormonal recente dos pacientes com CAH. Apesar de ocorrerem modificações celulares na CAH e de ter sido mostrado neste estudo que em pacientes sem doença hormonal conhecida o ADC é mais baixo após a adrenarca, estas alterações não foram detectadas pelas medidas de ADC das suprarrenais em pacientes com CAH.

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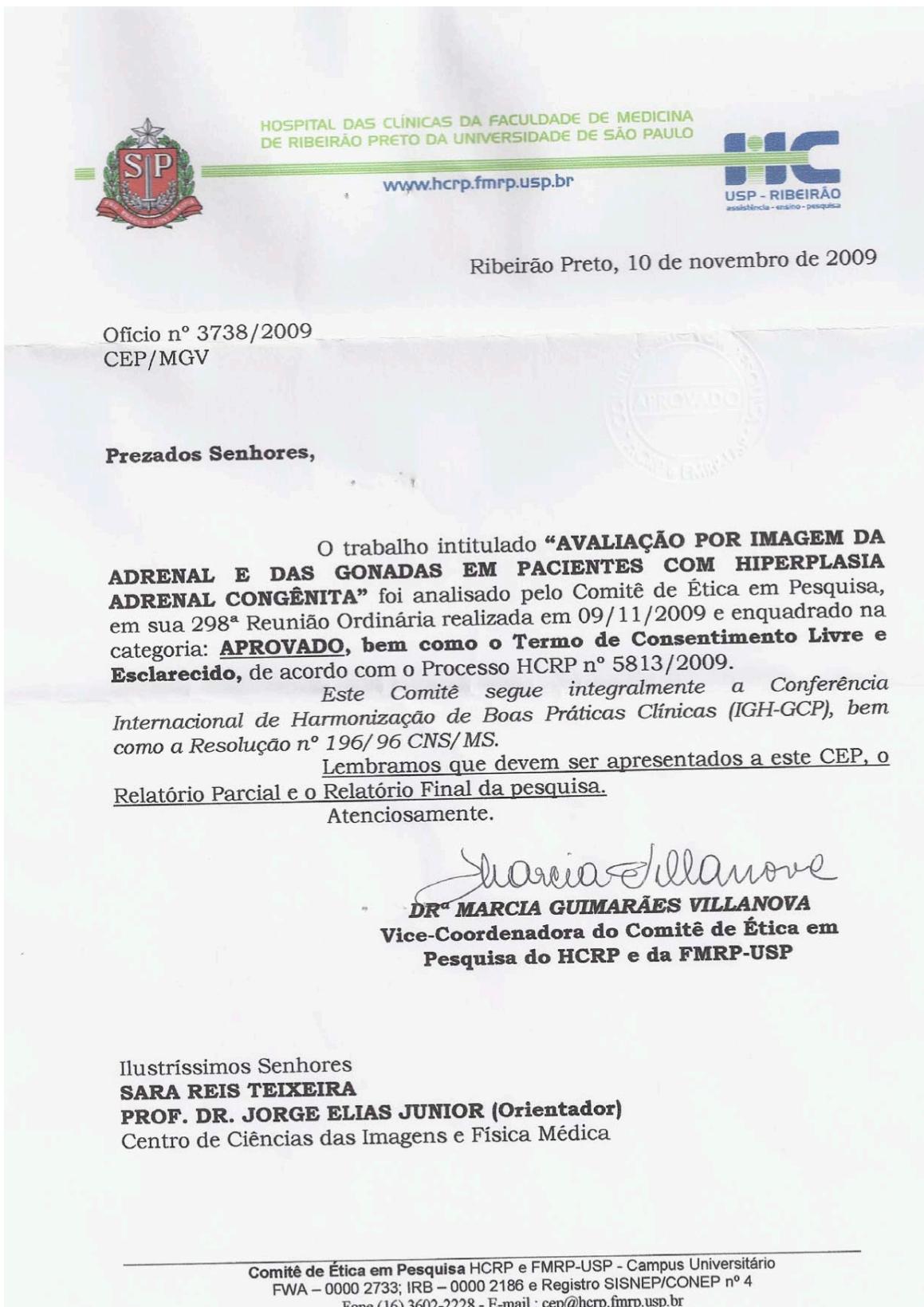
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## ANEXOS

### Anexo A – Documento de aprovação do Comitê de Ética e Pesquisa



**Anexo B – Modelo do termo de assentimento livre e esclarecido****HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DE  
RIBEIRÃO PRETO - UNIVERSIDADE DE SÃO PAULO****Termo de consentimento livre e esclarecido**

**Nome da pesquisa:** Avaliação por imagem da adrenal com ultrassonografia e ressonância magnética

**Pesquisadores:** **Sara Reis Teixeira- Médica Pós Graduanda**

**Jorge Elias Junior- Professor Doutor do Centro de Ciências das Imagens e Física Médica.**

**Telefones para contato: 3602 2640 ou 3602 2361**

**Convidamos você para participar de um estudo sobre avaliação por ultrassonografia e ressonância magnética da glândula adrenal.**

A hiperplasia adrenal congênita é causada pela falta de uma substância no corpo que é importante para que o corpo funcione normalmente. Em crianças com esta doença, pode ocorrer aumento de um órgão dentro da barriga, a glândula adrenal. Também podem ocorrer alterações nos testículos e ovários, órgãos que possibilitam que cresçamos e tenhamos filhos.

Ainda não sabemos o que ocorre direito com estes órgãos dentro do corpo quando a pessoa tem esta doença. Por isso, vamos estudar quais são estas modificações que ocorrem através de dois exames que tiram fotos de dentro da barriga.

Durante o estudo, faremos estes exames neste primeiro dia de encontro, 6 meses e 12 meses após. No primeiro exame, chamado de ressonância magnética, você entrará em uma sala com pouca luz junto com seus pais, deitará no aparelho e ouvirá sons altos parecendo batidas na porta. Estes barulhos são

da máquina tirando fotos da barriga. Dura em média 20 minutos. Depois deste exame você vai para outra sala sem barulho e deitará em uma cama. Nós vamos passar outro aparelho pequeno na sua barriga e gel para tirar outros tipos de fotos. Este exame é mais rápido e dura cerca de 5 minutos. Ele se chama ultrassom.

Já falamos com seus pais e eles deixaram que você pudesse participar do estudo. Por favor, fale com seus pais ou com o seu médico sobre o estudo antes de decidir participar. Você pode querer ou não participar do estudo. Não tem problema não participar, você poderá continuar as consultas médicas e a vir ao hospital como sempre. Se você tiver qualquer pergunta, pode nos procurar ou a seu médico ou telefonar.

Se você deseja participar do estudo, escreva seu nome nesta página e assine. Você receberá uma cópia desta folha depois de assinar.

Ribeirão Preto, \_\_\_\_ de \_\_\_\_\_ de \_\_\_\_\_

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Paciente

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Dra Sara Reis Teixeira (pesquisadora responsável)

Tel: (16) 3602-2640 ou (16) 3602-2361

**Anexo C – Modelo do termo de consentimento livre e esclarecido**

**HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA  
DE RIBEIRÃO PRETO - UNIVERSIDADE DE SÃO PAULO**

**Termo de Consentimento Livre e Esclarecido**

**Nome da pesquisa:** AVALIAÇÃO POR IMAGEM DA ADRENAL COM ULTRASSONOGRAFIA E RESSONÂNCIA MAGNÉTICA

**Pesquisadores:** Sara Reis Teixeira – Médica Pós Graduanda  
Jorge Elias Junior – Professor Doutor do Centro de Ciências das Imagens e Física Médica.

**Telefones para contato:** 3602 2640 ou 3602 2361

**Prezado pai ou mãe ou responsável legal pelo(a) paciente,  
Venho por meio deste documento convidar o seu filho(a) ou menor em sua responsabilidade para um estudo sobre avaliação por ultrassonografia e ressonância magnética da glândula adrenal.**

A hiperplasia adrenal congênita é causada pela deficiência de uma substância da adrenal, importante na produção de vários hormônios. Em crianças não tratadas podem ocorrer alterações das glândulas em tamanho e forma. Em alguns casos há restos do tecido da adrenal nas gônadas, que pode confundir com outras doenças como tumores. Não existem estudos até o momento que mostrem pela ultrassonografia e Ressonância Magnética as alterações da glândula.

O estudo pretende avaliar as alterações da adrenal e se é possível visualizar estes tecidos nas gônadas pelos métodos de imagem. Durante o estudo, estão previstos exames neste primeiro dia de encontro, 6 meses e 12 meses após.

O seu filho(a) ou menor sob sua responsabilidade poderá deixar a pesquisa a qualquer momento sem nenhum prejuízo ao seu seguimento no Hospital das Clínicas. Não haverá benefício direto para o seu filho (a) ou menor sob sua responsabilidade mas será um estudo que poderá auxiliar no diagnóstico e tratamento de outros pacientes no futuro. Até o momento não existem outros métodos para avaliação por imagem da adrenal. Como desconforto seu filho(a) ou menor sob sua responsabilidade poderá sentir a picada da agulha do contraste para ressonância magnética e o tempo dispendido para realização do ultrassom e ressonância que será em torno de 50 minutos no total.

Para qualquer dúvida que houver relacionado à coleta ou à participação na pesquisa você poderá entrar em contato com um dos médicos responsáveis pela pesquisa. Seu nome e de seu filho(a) ou menor em sua responsabilidade será mantido

em sigilo durante a pesquisa e qualquer informação sobre o andamento do estudo será fornecida.

**Aceito o convite dos pesquisadores Dr Jorge Elias Junior e Dra Sara Reis Teixeira para que meu filho(a) ou menor em minha responsabilidade e concordo inteiramente com as condições que me foram apresentadas para participar na pesquisa. Livremente, manifesto a minha vontade e declaro que tenho conhecimento dos meus direitos abaixo relacionados:**

- A garantia de receber a resposta a qualquer pergunta ou esclarecimento de qualquer dúvida durante a realização do estudo;
- A liberdade de retirar o meu consentimento e deixar de participar do estudo a qualquer momento, sem que isso traga prejuízo à continuidade do meu tratamento;
- A segurança de que não serei identificado e que será mantido o caráter confidencial da informação relacionada a minha privacidade;
- O compromisso de que me será prestada informação atualizada durante o estudo, mesmo que essa possa afetar a minha vontade de continuar dele participando;
- O compromisso de que serei devidamente acompanhado durante todo o período de minha participação no projeto.

Declaro, ainda, que concordo inteiramente com as condições que me foram apresentadas e que, livremente, manifesto a minha vontade em participar do referido projeto.

Ribeirão Preto, \_\_\_\_ de \_\_\_\_\_ de \_\_\_\_\_

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Pai, mãe ou responsável legal do paciente (Nome e assinatura)

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Dra Sara Reis Teixeira (pesquisadora responsável)

Tel: (16) 3602-2640