UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:
ENDOCRINOLOGIA

ASPECTOS DIAGNÓSTICOS, CLÍNICOS E PROGNÓSTICOS DE UMA COORTE DE PACIENTES COM HIPOTIREOIDISMO CONGÊNITO

EDMUNDO KREISNER

TESE DE DOUTORADO

Porto Alegre
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“Desocupado leitor, não preciso de prestar aqui um juramento para que creias que com toda a minha vontade quisera que esse livro, como filho do entendimento, fosse o mais formoso, o mais galhardo e discreto que se pudesse imaginar: porém, não esteve em minhas mãos contravir à ordem da natureza, na qual cada coisa gera outra que lhe seja semelhante; que podia portanto o meu engenho, estéril e mal cultivado, produzir neste mundo, senão a história de um filho magro, seco e enrugado, caprichoso e cheio de pensamentos vários, e nunca imaginados de outra alguma pessoa?(.....) Acontece muitas vezes ter um pai um filho feio e extremamente desengraçado, mas o amor paternal lhe põe uma venda nos olhos para que não veja as próprias deficiências; antes as julga como discrições e lindezas, e está sempre a contá-las a seus amigos, como agudezas e donaires. Porém eu, que, ainda que pareço pai, não sou contudo senão padrasto de Don Quixote, não quero deixar-me ir com a corrente do uso, nem pedir-te, quase com lágrimas nos olhos, como aí fazem muitos, que tu, leitor caríssimo, me perdoes ou desculpes as faltas que encontrares e descobrires nesse livro; e porque não és seu parente nem seu amigo, e tens a tua alma no teu corpo, e a tua liberdade de julgar muito à larga e a teu gosto, e estás em tua casa, onde és senhor dela como el –rei das suas alcavalas, e sabes o que comumente se diz ´que debaixo de meu manto ao rei mato`. Isso tudo te isenta de todo o respeito e obrigação e podes do mesmo modo dizer dessa história tudo quanto te lembrar sem teres medo de que te caluniem pelo mal, nem te premiem pelo bem que dela disseres.”

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LISTA DE ABREVIATURAS

HC - hipotireoidismo congênito

MF - malformações congênitas

QI - quociente de inteligência

SNC - sistema nervoso central

US - ultra-sonografia

INTRODUÇÃO

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Aspectos clínicos e epidemiológicos do hipotireoidismo congênito

Dentre as diversas patologias endócrino-metabólicas responsáveis pelo estabelecimento de uma deficiência mental, o hipotireoidismo congênito (HC) primário se destaca como a principal causa, ocorrendo numa incidência de cerca de 1 em cada 3000 a 4000 recém-nascidos, com predomínio no sexo feminino, numa proporção em torno de 2:1 (33,46). Essa incidência pode variar de acordo com a raça ou grupo étnico, sendo menos comum na comunidade negra e mais comum entre hispânicos e asiáticos (11,72,77). Em aproximadamente 85% dos casos, o HC permanente decorre de anomalias no desenvolvimento da tireóide (33,49). Essas disgenesias são representadas por hipoplasia, hemiagenesia, agenesia ou ectopia da glândula, sendo essas últimas, as formas de apresentação mais freqüentes. A etiopatogenia dessas disgenesias permanece ainda hoje indefinida. Embora na imensa maioria dos casos ocorram de forma esporádica, ocasionalmente descrevem-se casos familiares (28,43,71,76,82), tendo-se também registrado uma maior freqüência de anomalias assintomáticas do desenvolvimento da tireóide em familiares em primeiro grau de pacientes com HC (51). Além disso, alguns poucos casos de

disgenesia da tireóide têm como causa mutações de genes da PAX 8, TTF 1 e TTF 2, que se constituem em fatores transcricionais, cuja expressão é essencial ao processo de embriogênese (33,53). Sob esse aspecto as disgenesias seriam, pelo menos em parte, um distúrbio genético. Por outro lado, a concordância na ocorrência de disgenesia da tireóide em gêmeos idênticos de pacientes com HC é muito baixa, sugerindo serem as disgenesias resultado de fenômenos epigenéticos (73).

Outros 10% dos casos são decorrentes de distúrbios da síntese e secreção dos hormônios tireóideos, as chamadas disormonogêneses (34), bastante estudadas em nosso meio (57). Esses casos, ao contrário das disgenesias, ocorrem na presença de uma tireóide tópica e são transmitidos por herança de caráter autossômico recessivo.

Ocasionalmente, o HC primário pode ser transitório devido a um bloqueio na síntese dos hormônios tireóideos por uso de produtos com iodo ou pelo uso de drogas antitireóideas e, principalmente, pela presença de anticorpos maternos bloqueadores do receptor de TSH (3), podendo responder por 5% dos casos identificados pelos programas de rastreamento neonatal (49).

Hormônios da tireóide e o desenvolvimento do sistema nervoso central

A importância do HC se deve ao fato de os hormônios da tireóide exercerem um papel fundamental no processo de desenvolvimento e diferenciação do sistema nervoso central (SNC), durante uma fase crítica do desenvolvimento que envolve o período intra-útero e os primeiros 2 anos de vida (12,42,74). Embora se desconheça em detalhes os mecanismos de

ação dos hormônios da tireóide nesse processo, já se evidenciou em ratos que sua presença é imprescindível para a expressão de genes responsáveis pela produção de fatores aí envolvidos, tais como o fator de crescimento neural tipo A (58) e neurogranina (59).

De acordo com Porterfield e Hendrich, o processo de inter-relação entre as ações dos hormônios tireóideos e o desenvolvimento do SNC obedece a 3 fases.

Na primeira fase, que se estende até a 12ª semana de gestação, o desenvolvimento do sistema nervoso se caracteriza essencialmente pela neurogênese e migração cerebral. Nesse período, o hormônio tireóideo presente é de origem exclusivamente materna (74).

Numa segunda fase, que se estende da 12ª semana ao nascimento, completa-se a gênese neural e a migração cerebral. Nesse período, inicia-se a diferenciação dos neurônios e o desenvolvimento dos axônios, dendritos e sinapses. Também correspondem a essa fase o processo de diferenciação, migração e maturação do cerebelo. Observa-se, ainda, o início do processo de mielinização. Nesse período, aos hormônios tireóideos de origem materna, somam-se os hormônios produzidos pela tireóide fetal (74).

A terceira fase se inicia com o nascimento e se estende até em torno dos 2 anos de vida. Nessa etapa, completam-se todos os eventos iniciados na fase anterior e é nessa última fase que ocorre, com maior intensidade, o processo de mielinização. O sucesso desse processo depende, agora, exclusivamente da função tireóidea do recém-nascido (74).

Quando esse processo evolutivo é rompido em qualquer dessas fases, pela deficiência dos hormônios tireóideos, a reposição hormonal pós-natal pode trazer uma compensação parcial, mas com possíveis alterações na composição e na arquitetura celular. As possíveis seqüelas daí decorrentes serão de maior ou menor gravidade na dependência da precocidade, intensidade e duração dessa deficiência hormonal durante esse período.

Manifestações clínicas e dificuldades de diagnóstico precoce

O diagnóstico e o tratamento precoces do HC são fundamentais na tentativa de preservação do potencial neurológico e intelectual desses pacientes. Os primeiros registros de uma melhora no prognóstico mental de indivíduos com HC, a partir de um tratamento precoce, remontam à década de 30 (32,52). Na década de 50, Smith et al. confirmaram uma significativa melhora no prognóstico mental das crianças tratadas antes dos 7 meses de vida (91). Em 1972, Klein et al. e Maenpaa obtiveram, em seus pacientes, quociente de inteligência (QI) superior a 85 em 81% e 85%, respectivamente, ao instaurarem a reposição hormonal antes dos 3 meses de vida (45,54). Os resultados posteriores de Hulse foram ainda mais extraordinários, com prevenção da deficiência mental em 100% dos pacientes tratados antes de completadas 6 semanas de vida (41).

Infelizmente, a sutileza das manifestações clínicas no período neonatal dificulta, com freqüência, o diagnóstico em tempo hábil. Na Suécia, antes da implantação dos programas de triagem neonatal, 52% de um total de 112 pacientes com HC, tiveram seu diagnóstico estabelecido após os 3 meses de idade (105). De acordo com Grant et al., 25% dos pacientes identificados através de um rastreamento neonatal apresentaram-se sem manifestações clínicas quando do diagnóstico (38). A considerável transferência do T4 materno para o feto pode contribuir para a atenuação do quadro clínico inicial, dificultando o diagnóstico precoce (27,101,104).

Os programas de rastreamento neonatal foram introduzidos a partir da década de 70 (26,44), de modo a possibilitar um diagnóstico e um tratamento precoce. Esses programas, com suas variadas estratégias, mostraram-se extremamente eficazes, sendo hoje

universalmente utilizados como parte das políticas de saúde pública, com o objetivo de prevenção das graves seqüelas neurológicas decorrentes de um diagnóstico tardio (3).

Uma vez identificado o HC, a determinação de sua etiologia é extremamente importante, devido às diferentes implicações no que concerne à necessidade de tratamento imediato e permanente, bem como no que concerne à possibilidade de herança e prognóstico. As disgenesias da glândula tireóide, nas suas diferentes apresentações, representam formas permanentes de deficiência hormonal, de ocorrência esporádica. As formas associadas à presença de glândula em localização habitual podem representar defeitos permanentes de síntese ou secreção, transmitidos por herança autossômica recessiva, ou defeitos transitórios da função endócrina. Os programas de rastreamento neonatal, baseados nas dosagens de TSH e T4, não são capazes de distinguir essas diferentes formas de apresentação, com suas diferentes implicações.

A cintilografia da tireóide, tanto com ^{123}I ou com tecnécio pertecnetato (^{99m}Tc), tem sido classicamente utilizada como método de escolha para a confirmação diagnóstica e etiológica em pacientes com evidências clínicas e laboratoriais de HC (87,99,103). Trata-se, no entanto, de um exame nem sempre disponível de forma imediata, e com custo relativamente alto. Além disso, ocasionalmente não se identifica a presença de tecido funcional em pacientes com HC transitório submetidos à cintilografia de tireóide com ^{99m}Tc (60,87) e com I^{123} (85). O uso de ^{99m}Tc tem sido recomendado por sua facilidade de execução, custo mais baixo, boa tolerância e maior disponibilidade (87).

A ultra-sonografia (US), por seu turno, tem sido sistematicamente utilizada na avaliação de pacientes adultos com diferentes patologias da tireóide (10,98). Esse exame tem sido considerado como o melhor método não invasivo para avaliação anatômica da glândula tireóide. Como resultado dos avanços tecnológicos, o uso de transductores de alta freqüência

permite a identificação de estruturas adjacentes tão pequenas quanto 2 mm, a uma profundidade de até 5 cm (10). Essas características oferecem, teoricamente, um método simples e útil para a identificação e análise anatômica da glândula tireóide em recém-nascidos, crianças e adolescentes (4). No entanto, somente alguns poucos relatos foram até agora publicados, com alguma atenção à utilidade do estudo de US no diagnóstico etiológico do HC (20,21,61,69,75,93,97).

De acordo com alguns desses relatos, a US se constituiu num excelente método de avaliação diagnóstica inicial em pacientes com suspeita de HC. No entanto, o número de pacientes com suspeita de HC arrolados, na maioria desses estudos, foi pequeno (4,20,75,93,97) e, em geral, sem a simultânea realização de estudo de cintilografia para comparação (20,75,97). Bachrash et al., estudando 55 pacientes com idade entre 6 dias e 19 anos com diferentes tipos de patologia, detectaram presença de glândula tópica à US em 2 casos nos quais a cintilografia, com ausência de captação, sugeria agenesia (4). Ueda et al., examinando 23 pacientes com HC, obtiveram excelentes resultados com o uso da US, considerando-a como importante método diagnóstico na avaliação inicial de recém-nascidos que apresentam resultados anormais no teste de rastreamento neonatal (97).

Na mesma linha, Pöihönen et al., utilizando a US, identificaram facilmente a presença de glândula em neonatos normais, contrastando com ausência da mesma em 15 pacientes recém-nascidos com HC (75).

Takashima et al. compararam os resultados de estudos de US e cintilografia em 37 pacientes suspeitos de HC (93). A US detectou 6 de 8 casos de ectopia revelados pela cintilografia; tal sensibilidade de detecção de ectopias pela US não fora, até então, registrada. A concordância entre os dois métodos foi boa, com a US identificando corretamente 1 caso com falsa agenesia, 3 casos de hemiagenesia e 25 casos com glândula presente em localização

usual.

Mais recentemente, Onishi et al. defenderam a utilidade da US na confirmação diagnóstica das disgenesias pela ausência da glândula tireóide em sua localização habitual, enquanto a presença de glândula de tamanho normal ou aumentado exigiria ulterior investigação para se estabelecer um diagnóstico definitivo (69).

Outros autores, no entanto, consideram a US como um método limitado de avaliação de pacientes com HC (21,61). Muir et al. observaram uma pobre correlação entre esses dois métodos (61). De acordo com os resultados descritos, quando uma tireóide cervical era identificada pela cintilografia, a glândula se mostrava igualmente presente à US. Porém, em 4 pacientes sem concentração do radioisótopo à cintilografia, sugerindo agenesia, observou-se a presença de uma aparente glândula normal ao estudo de US. Com base nesses resultados discordantes, os autores consideraram o exame US como não fidedigno quando uma glândula cervical não era demonstrada na cintilografia. No estudo de De Bruyn et al., a US foi capaz de identificar a presença de glândula em localização habitual em apenas 7 de 10 casos e de ectopia em 5 de 26 casos (21). Em 3 de 18 pacientes, a US identificou a presença de uma glândula anatomicamente normal na ausência de concentração do isótopo a cintilografia.

Numa análise preliminar, de comparação dos nossos resultados de US e cintilografia da tireóide na investigação de pacientes com HC (13,48), observamos ser a US um excelente método de investigação inicial de casos suspeitos.

Apesar das controvérsias e das limitações metodológicas dos relatos disponíveis, a US parece oferecer um importante papel na investigação inicial dos pacientes identificados como suspeitos de HC. O prosseguimento dos estudos, envolvendo um número maior de pacientes, com execução de ambos os exames, poderá nos trazer maiores subsídios quanto a acurácia da

US como instrumento de investigação etiológica e de confirmação diagnóstica do HC.

Hipotireoidismo congênito e malformações congênitas

Com a implantação de programas de triagem neonatal a partir dos anos 70, os pacientes com HC passaram a ser atendidos em centros de referência, com o desenvolvimento de bancos de dados e uma maior sistematização dos conhecimentos acumulados.

Como decorrência disso, a partir da década de 80 surgiram vários relatos na literatura médica, com registros de uma maior prevalência de malformações congênitas (MF) extra-tireóideas associadas ao HC (2,5,6,15,17,24,29,36**,**37**,**50,56**,**63,70,77,89,92). As MF aí descritas não obedeceram a nenhum padrão definido, atingindo diferentes órgãos e tecidos, porém, com nítido predomínio de MF cardíacas. A prevalência dessas MF, em geral, tem variado entre 3,4% e 24% e entre 2,4% e 16% quando consideradas apenas as formas cardíacas.

Essa variação tão ampla poderia ser devida, em parte, aos diferentes métodos e critérios empregados no estudo dessa associação ou, talvez, a uma efetiva diferença entre as populações estudadas (89). Investigações baseadas em notificações e registros (5,36,37,50,70) apontam uma menor prevalência, possivelmente subestimada, quando comparadas com aquelas observadas em estudos de casos (2,6,29,56,89). Além disso, diferentes critérios de classificação das MF, como a eventual inclusão de pacientes com Síndrome de Down, sabidamente associada a ambos os problemas, e de persistência do canal arterial em pacientes com prematuridade (2,6,29), que representa por si só causa dessa alteração cardíaca (94), poderiam contribuir para essa variabilidade.

A etiopatogenia dessa curiosa associação tem sido motivo de especulações e estudos. Estudos de biologia molecular têm revelado que alguns casos de disgenesia da tireóide são provocados por mutações em genes codificadores de fatores de transcrição para o desenvolvimento de células foliculares como TITF 1, TITF 2, PAX 8, ou do receptor de TSH (1,8,18,31,53,67).

Esses fatores de transcrição encontram-se amplamente distribuídos por diferentes tecidos e parecem exercer um papel fundamental no processo de organogênese. Dentro desse contexto, a descrição de mutações do gene codificador do TTF 2 associadas à agenesia da tireóide e palato fendido em camundongos (22) e à disgenesia da tireóide, palato fendido e atresia das coanas em seres humanos (16,18), representa um modelo biológico altamente ilustrativo.

As mutações, até agora descritas, são responsáveis por apenas um número limitado de disgenesias. No entanto, reforça-se a idéia de que essas e outras proteínas e fatores transcricionais, amplamente distribuídos pelos diversos tecidos e com importante papel na embriogênese, representem o elo etiopatogênico entre disgenesias de tireóide e MF congênitas de distintos padrões.

A ausência de um padrão uniforme de apresentação dessas MF, observada nos diferentes estudos, pode estar relacionada aos fenômenos epigenéticos envolvidos tanto na etiopatogenia das MF (55) como das disgenesias da tireóide (73). Dependendo do momento em que esses fatores (cromossômicos, gênicos ou ambientais) atuem, diferentes tipos ou combinações de MF podem se fazer presentes.

Recentemente, no entanto, o caráter genuíno dessa associação entre HC e MF ou pelo menos sua real prevalência foram colocados em dúvida. Essas dúvidas surgiram a partir da

descrição de uma elevação transitória do TSH em recém-nascidos com diferentes tipos de MF (68), bem como de uma associação também significativa entre MF e formas transitórias de hipotireoidismo (92). De acordo com Oakley et al., a alta prevalência das malformações associadas ao HC poderia ser resultado de uma falha em se distinguir entre um verdadeiro HC primário permanente e elevações transitórias do TSH observadas em vigência de situações de estresse, tais como prematuridade, septicemia, asfixia neonatal e síndrome de angústia respiratória (68,88). Essa elevação transitória do TSH neonatal, observada na presença dessas MF, poderia induzir a um falso diagnóstico de HC primário permanente. Em verdade, as publicações associando HC e MF, de uma maneira geral, não avaliaram a etiologia do hipotireoidismo, não definindo, portanto, seu caráter permanente ou transitório.

A fim de se verificar a real prevalência de MF em pacientes com HC primário permanente, impõe-se a realização de mais estudos que contemplem a identificação etiológica do HC, assegurando seu caráter permanente, bem como uma clara definição das MF maiores a serem consideradas, evitando a inclusão de anomalias congênitas de surgimento em período ulterior à organogênese, como a luxação congênita de quadril, que não se constituem em MF.

Tratamento do HC e desenvolvimento neuropsicomotor e intelectual dos pacientes

A experiência geral tem confirmado que o tratamento do HC deve ser iniciado o mais precocemente possível, a fim de otimizar os resultados da intervenção terapêutica. A introdução dos programas de rastreamento neonatal para HC, a partir da década do 70 e a possibilidade de um tratamento precoce, resultaram numa marcada melhora no prognóstico neurológico e intelectual desses pacientes (64,65,66,90).

No entanto, a literatura tem mostrado que, apesar dessa marcada melhora no prognóstico com a intervenção mais precoce, um número significativo de pacientes mantém alterações neurológicas, particularmente nas áreas de motricidade, linguagem, atenção e memória (79,95,102). Essas alterações podem se fazer presentes até mesmo em pacientes tratados tão precocemente quanto com 6 dias de vida (100). De acordo com as estimativas de Tillotson et al., aproximadamente 10% dos pacientes identificados em programas de rastreamento neonatal necessitará de educação especial (95).

Derksen-Lubsen, em um estudo de metanálise, concluiu que pacientes com HC apresentam um QI médio inferior ao observado em grupos controle, a despeito de um diagnóstico e tratamento precoces (23).

Vários estudos têm registrado uma associação entre o desfecho desfavorável e a gravidade da doença, medida pela baixa concentração de T4 (7,30,47,80,90,95,100) e de T3 (62) no diagnóstico, imaturidade óssea (35,80) e agenesia da tireóide (40,47,80). Uma vez que os hormônios da tireóide exercem um papel fundamental no desenvolvimento do SNC, as seqüelas resultantes seriam devidas à deficiência hormonal mais intensa no período pré-natal, com o tratamento precoce não sendo suficiente para compensar totalmente tal deficiência.

Outros autores têm observado uma significativa associação entre o prognóstico neurológico e a qualidade do tratamento (9,25,30,84,86,90). De acordo com esses autores, a utilização de doses maiores de L-tiroxina, entre 10 e 15 μg/kg, instituídas de forma precoce, preferencialmente antes dos 14 dias de vida, reduziria o hiato no desenvolvimento intelectual desses pacientes em relação aos indivíduos sadios.

Na contrapartida, outros grupos recomendam doses menores, entre 5 e 10 μg/kg, como apropriadas para início de tratamento, sem observarem diferenças no desfecho em relação às

crianças tratadas com doses maiores (14,83,96).

Rovet et al., estudando o temperamento de crianças com HC, observaram uma associação entre dificuldades de temperamento e concentrações mais elevadas de T4 e T3 nos primeiros 3 meses de vida (81). Nessa mesma linha de pesquisa, crianças tratadas com doses iniciais de L-tiroxina mais elevadas, apresentaram um melhor desempenho cognitivo, particularmente nas áreas de habilidade e memória verbais. No entanto, uma dose inicial maior, especialmente maior que 10 μg/Kg, foi acompanhada de uma maior freqüência de problemas de comportamento incluindo ansiedade, comportamento anti-social e baixa capacidade de concentração (78).

Dessa maneira, ainda que diferentes protocolos recomendem doses iniciais maiores, buscando manter a concentração de T4 no limite superior da normalidade e TSH normal, a dose ótima de tratamento e a concentração ideal dos hormônios circulantes na vigência do tratamento, não estão de todo estabelecidas.

Nos países desenvolvidos, a possível importância de diferenças sócio-demográficas, como fatores independentes para o desenvolvimento intelectual desses pacientes, tem recebido escassa atenção (19,30,39,95,100). De acordo com Fuglle et al. e Tillotson et al., pacientes cujos pais exerciam atividade de sustento manual apresentaram desempenho intelectual inferior ao dos filhos de pais com atividade profissional não manual (30,95). De acordo com Connelly et al., a maior idade e o maior nível educacional maternos estiveram positivamente associados ao desenvolvimento intelectual dos pacientes (19). Por outro lado, Heyerdahl et al. e Virtanen et al. não observaram diferença significativa entre pacientes oriundos de diferentes classes sociais, o que poderia ser reflexo de uma menor diferença entre as classes sociais dos países escandinavos (39,100).

A resposta para as diferenças de resultados observados nos diferentes programas, o papel de cada uma das variáveis acima citadas e a real utilidade dos diversos fatores potencialmente predictivos da evolução intelectual e neurológica dos pacientes, poderão ser melhor esclarecidas com o prosseguimento de estudos nessa linha de pesquisa.

Com a organização de programas de rastreamento neonatal, vinculados em sua maioria a serviços de saúde pública e/ou instituições de ensino médico, modificou-se radicalmente o panorama de atendimento a esses pacientes, antes disperso e agora concentrado em centros de referência. Em nosso meio, a centralização desse atendimento e o conseqüente desenvolvimento de bancos de dados tem possibilitado uma maior sistematização das informações e dos conhecimentos acumulados. Isto oferece uma oportunidade ímpar no sentido de se desenvolver investigações com o objetivo de responder a questões como as anteriormente levantadas, contribuindo para um contínuo progresso na compreensão global dessa patologia e na otimização da intervenção médica e de seus resultados.

Nas linhas de investigação aqui desenvolvidas, procurou-se verificar o valor da US como instrumento de confirmação diagnóstica e etiológica do HC. Buscou-se, também, verificar a prevalência de MF maiores em uma coorte de pacientes com HC primário com caráter permanente bem definido. Além disso, procurou-se a identificação de possíveis fatores pré-natais, pós-natais e, em especial, sócio-demográficos que pudessem estar associados ao prognóstico intelectual desses pacientes.

As respostas obtidas nessas e em futuras investigações poderão, eventualmente, servir de subsídio para a implantação de políticas de saúde e de rotinas que auxiliem no aperfeiçoamento dos programas estatais de rastreamento neonatal ora em desenvolvimento no país.

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ARTIGO 1 – ACCURACY OF ULTRASONOGRAPHY TO ESTABLISH THE DIAGNOSIS AND ETIOLOGY OF PERMANENT PRIMARY CONGENITAL HYPOTHYROIDISM

Accuracy of ultrasonography to establish the diagnosis and etiology of permanent primary congenital hypothyroidism*

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Abstract

Objective: To compare ultrasonography and ^{99m}Tc thyroid scintigraphy for the etiologic diagnosis of permanent congenital hypothyroidism (CH).

Study design: 88 consecutive patients with CH were recruited at an endocrinology outpatient clinic and submitted to high-frequency ultrasonography and to ^{99m}Tc scintigraphy.

Results: 76 patients were diagnosed with permanent CH and 12 with transitory CH. The agreement between ultrasound and scintigraphy was very high (Kappa coefficient = 0.866; P<0.001) for the entire group. In permanent CH patients, ultrasonography identified 67 cases of dysgenesis (absence of thyroid gland in the usual anatomical location in 66 and hemiagenesis in 1), and this diagnosis was confirmed by scintigraphy (absence of functional thyroid tissue in 43 and ectopia in 24). In the other 9 permanent CH patients the thyroid was in the usual anatomical location on ultrasonography but scintigraphy did not identify functional tissue in one patient. In the 12 transitory CH patients, a normally shaped thyroid was detected by ultrasound in the usual location, whereas scintigraphy showed absence of functional tissue in two identical twins and scarce concentration of isotope in a third patient.

Conclusion: Ultrasonography is an accurate method to establish the presence of dysgenesis and might be used as the first imaging tool in patients with CH, whereas scintigraphy should be used mainly to distinguish agenesis from ectopia. Further examination is required to differentiate permanent CH with a normally located and shaped gland from transitory hypothyroidism.

Introduction

Permanent primary congenital hypothyroidism (CH) affects approximately one in every 4000 newborns (Klett, 1997); this number may vary depending on race/ethnicity (Brown et al., 1981; Rosenthal et al., 1988). In 85% of the cases**,** permanent CH results from some type of thyroid dysgenesis. This form, which is considered to be sporadic, generally results from nonheritable postzygotic events (Perry et al., 2002). However, genetic factors may play a role in some cases; mutations in genes related to thyroid development (TTF1, TTF2, PAX-8 and TSHR) have been associated with thyroid dysgenesis (Macchia, 2000). Another 10% of permanent CH cases are caused by defects in thyroid hormone synthesis or secretion (dyshormonogenesis) transmitted by autosomal recessive inheritance (La Franchi, 1999).

In dysgenesis, the gland may be ectopic, completely absent (agenesis) or partially absent (hypoplasia), or it may be morphologically abnormal (hemiagenesis). In dyshormonogenesis, the thyroid gland is frequently present in the usual anatomical site (normally shaped and located thyroid gland). However, in some cases of decreased TSH responsiveness, the thyroid gland may be hypoplastic suggesting an abnormality of thyroid gland development. A transitory form, transitory CH, accounts for approximately 5% of the cases of CH (La Franchi, 1999).

It is extremely important to determine the etiology of CH due to the implications for inheritance, prognosis, and treatment decisions (Heyerdahl et al., 1991; Rove et al., 1992; Kooistra et al., 1994). The usual CH screening programs based on high levels of thyrotropin (TSH) and low levels of T4 are not capable of distinguishing permanent CH from transitory CH or transitory high TSH levels; in the latter, treatment is not always required, at least permanently. Furthermore, such screening programs cannot differentiate patients with

sporadic dysgenetic forms of permanent CH from patients presenting permanent CH with dyshormonogenesis.

Thyroid scintigraphy (^{123}I or ^{99m}Tc) has long been used as the method of choice for diagnostic confirmation and determination of CH etiology in patients with clinical and laboratory evidence of this disease (Wells et al., 1986; Verelst et al., 1991; Sfakianiakis et al., 1999). However, the cost of this exam is relatively high, and it is not always available. In addition, scintigraphy sometimes requires interruption of treatment, and it has been associated with fear of radiation (Beekhuis et al., 1983; American Academy of Pediatrics, 1993). Furthermore, occasionally no gland is visualized by scintigraphy in infants with transitory CH (Mitchell et al., 1995; Sfakianakis et al., 1999).

Ultrasonography, in turn, has been used systematically to study adults with various thyroid diseases. This technique is considered as the best non-invasive method for the anatomical assessment of the thyroid gland (Van Erle et al., 1982; Blum et al., 1997). As a result of technological improvements, the high frequency transducers currently available for ultrasonography allow the identification of adjacent structures as small as 2 mm, located as deep as 5 cm (Blum et al., 1997). This provides a simple method for the identification of the thyroid gland in newborns, children, and adolescents (Bachrash et al., 1983). However, only a few controversial reports so far have addressed the usefulness of ultrasound to diagnose and determine the etiology in CH (Pöyhönen et al., 1984; Dammacco et al., 1985; Muir et al., 1988; De Bruyn et al., 1990; Ueda et al., 1992; Takashima et al., 1995; Onishi et al., 2002).

The objective of the present study was to compare the role of thyroid ultrasonography and ^{99m}Tc scintigraphy for diagnostic confirmation and etiological investigation in a sample of 88 patients with CH.

Patients and Methods

Eighty-eight patients with a diagnosis of CH (54 females and 34 males) were recruited between 1979 and 2002 at the Pediatric Endocrinology outpatient clinic at Hospital Materno Infantil Presidente Vargas, a district hospital. Patients included in the study were diagnosed right after birth or until 2 years of age. All patients were followed by the same investigator (EK). Informed consent was obtained from the parents of the children included in the study and the protocol was approved by the institution's Ethics Committee. In 64 patients, the initial diagnosis of CH was established by routine neonatal screening. The other 24 patients were referred to the Pediatric Endocrinology Unit since they presented clinical manifestations compatible with CH, such as hoarse cry, umbilical hernia, abdominal distention, protruded tongue and puffy face. Although these patients did not undergo routine screening right after birth, they were submitted to the same diagnostic evaluation as the other 64 patients.

The screening program started in 1991 as a non-governmental, non-mandatory effort. TSH and T4 were measured in blood spot collected by heel puncture on filter paper after the 5^{th} day of life. TSH was measured by a chemoluminescence method developed in our laboratory (Camargo-Neto, 1991), with intra and interassay variation coefficients no higher than 5.2% and 9.1%, respectively, and a sensitivity of 2mIU/l. T4 was measured by radioimmunoassay (ICN Biomedical; Los Angeles, CA, USA). Patients with TSH values higher than 20 mIU/l and/or T4 lower than 77.2 nmol/l were referred to the pediatric endocrinologist and submitted to serum dosages to confirm the diagnosis. Diagnostic confirmation was made through measurements of serum T4, free T4, TSH and T3 by chemoluminescence methods, using Automated Chemiluminometric System kits (ACS 180™, Chiron, Walpole, MA, USA). In 6 patients diagnosis was established before the beginning of the screening program, with TSH and T4 measured by radioimmunoassay (Diagnostic

Product Corporation, Los Angeles, CA, USA).

Real time sonography was carried out using a rectilinear scanner (Aloka SSD-650) with a 7.5 MHz high-frequency transducer. Infants were placed in supine position with the head in hyperextension, and images were obtained through transverse scanning at the neck. The images were classified into three groups: 1) absence of thyroid gland; 2) normal or enlarged gland in usual anatomical location; and 3) morphologically abnormal gland in usual anatomical location. In patients with a normally located gland, the maximum thickness and width of the right and left lobes were measured on transverse scans and the sum of these measurements was considered (Ueda et al., 1992).

Thyroid scintigraphy was carried out with ^{99m}Tc, 10 to 15 minutes after administration of 37 to 90 mBq sodium pertechnetate, using a single-photon emission computed tomography (SPECT) camera (GE Star Cam 2000 or Gammatome II CGR). With help from the parents, patients were placed on their back with hyperextension of the neck. Images were obtained using a gamma camera with parallel-hole collimator, so as to allow an ample view of the region, and/or complementary pinhole imaging. Depending on the concentration and distribution of the tracer, the images obtained were classified as absence of uptake, uptake in ectopic area (ectopic gland), or presence of functional tissue in the usual anatomical location.

Statistical analysis

The Student t test was used for comparisons between group means. Agreement between ultrasonographic and scintigraphic studies for the diagnosis of normally located and shaped thyroid glands was measured by Kappa statistics. The level of significance was 5%.

Results

Based on the ultrasonographic and scintigraphic studies, patients were classified into two main categories: 1) developmental anomalies or dysgenesis; 2) gland in usual location. In the dysgenesis group, agenesis was characterized by absence of the thyroid gland on both ultrasonography and scintigraphy; ectopia was characterized by detection of any thyroid tissue outside the usual anatomical location; and hemiagenesis was characterized by identification of a single thyroid gland lobe on ultrasonography, with or without radioisotope uptake. No patient was recognized by either ultrasonography or scintigraphy as presenting hypoplasia.

In patients with unequivocal sonographic identification of a normal or enlarged thyroid gland in the usual anatomical location, with or without uptake of tracer on scintigraphy, L-thyroxine replacement therapy was interrupted when the patient reached 2 years of age to allow distinction between transitory forms of neonatal hypothyroidism and permanent forms with a normally placed and shaped thyroid gland. In these patients, transitory CH was characterized by repeated normal measurements of TSH and T4 after interruption of L-thyroxine. L-thyroxine was not interrupted if levels of TSH were consistently high during therapy. In these cases, the patients were classified as having permanent CH with a normally placed and shaped gland, and no specific tests were performed to determine the presence and type of dyshormonogenesis, or to identify other less common causes of permanent CH with an anatomically preserved gland, such as TSH receptor mutations or resistance.

Seventy-six patients were considered to have permanent CH (47 females and 29 males, age range: 16 days to 2 years). In 12 patients a diagnosis of transitory CH was established (7 females and 5 males, age range: 17 to 85 days).

The results of the ultrasonographic and scintigraphic studies of the 76 patients with

permanent CH are described in table 1. Sixty-seven of these patients had a final diagnosis of dysgenesis and the other 9 were diagnosed with permanent CH with a normally placed and shaped gland. In the group with dysgenesis, there were 42 cases of agenesis, 24 cases of ectopia and 1 case of hemiagenesis. In the group of patients with ectopia, there was one instance of familial occurrence (brother and sister). In the 9 patients with permanent CH with normally placed and shaped gland, familial history of congenital hypothyroidism was identified in 7 cases and consanguineous marriages in 5 cases. One of these patients presented a clinically palpable goiter. Ultrasonography identified dysgenesis in 67 of the 76 patients. In 66, the examination revealed absence of the gland in the usual anatomical site. Hemiagenesis was identified in 1 case. In the remaining 9 patients, the presence of the gland in the usual anatomical site, plus permanent dysfunction, led to a diagnosis of permanent CH with normally placed and shaped gland.

Scintigraphy led to a diagnosis of dysgenesis in 68 patients, and of permanent CH with normally placed and shaped gland in 8. In 44 cases, uptake was undetectable on scintigraphy. Ectopic tissue was found in 24 cases, and an anatomically normal gland was present in 8 cases.

There was only one case of disagreement between ultrasonography and scintigraphy, in which a normal thyroid gland was identified by ultrasonography in the usual anatomical location, whereas scintigraphy did not identify any uptake on the thyroid area. This led to an ultrasonographic diagnosis of permanent CH with normally placed and shaped gland versus a scintigraphic diagnosis of agenesis.

In all the 12 patients with transitory CH, ultrasound identified a thyroid gland of normal size and shape in the usual site. Scintigraphy revealed a normal scan in 9 patients, absence of functional tissue in 2 identical twins and scarce tracer distribution over the gland in one

patient. In one case of transitory CH, a consanguineous marriage was registered. The maximum values for thyroid gland width and thickness in patients with permanent CH and a normally placed and shaped thyroid gland were not different from the values obtained for patients with transitory CH (width: 22.3 mm ± 4.7 vs. 19.1 ± 1.5 mm; P=0.064; thickness: 23.6 ± 5.6 mm vs. 21.2 ± 2.7 mm; P=0.262).

In all 88 patients, the agreement between ultrasound and scintigraphic results for the identification of normally located and shaped thyroid glands was very high (Kappa coefficient =0.866; P<0.001).

Discussion

In the present study, ultrasound correctly identified all cases of thyroid dysgenesis, which were confirmed by scintigraphy. The agreement of these methods for the identification of a normally located and shaped thyroid gland was high. Despite this fact, the absence of radioisotope uptake on scintigraphy resulted in 4 erroneous diagnoses (4.9%), suggesting agenesis in 3 patients with transitory CH and in 1 patient with permanent CH and a normally placed and shaped thyroid gland.

Similar results with ultrasound have been observed in other studies including a small number of patients, although concomitant scintigraphy was not performed in most of them (Pöyhönen et al., 1984; Dammacco et al., 1985; Ueda et al., 1992; Takashima et al. 1995). More recently, Ohnishi et al. (2002) argued that ultrasonography is useful mainly to confirm the diagnosis of thyroid dysgenesis when the thyroid gland is not in the usual location, whereas normal size or enlarged glands require further examination to allow a definitive diagnosis. Differently from our study, most patients included in that study did not have

permanent CH.

Nevertheless, other authors consider the usefulness of ultrasound scans of limited value for the evaluation of CH (Muir et al., 1988; Bruyn et al., 1990) because of a discrepancy between the presumed absence of thyroid tissue (athyreosis) on thyroid scintigraphy and the presence of an anatomically normal gland on ultrasonography. This discrepancy could be, in part, explained by the fact that ultrasonography reflects the anatomical status of the thyroid gland, whereas scintigraphy relies mainly on the functional status of the gland. Because ultrasonography does not take into consideration functional aspects, it may occasionally identify an anatomically normal but non-functioning gland. This presentation could be the result of maternal TSH receptor blocking antibodies suppressing fetal thyroid function in patients with transitory CH (Sfakianakis et al., 1999). Alternatively, it could be due to an iodine/iodide transport defect (Pohlenz et al., 1997), or to a mutation of the TSH receptor gene causing loss of function (Gagne et al., 1998) in patients with permanent CH.

In our experience, ultrasound allowed identification of all cases of dysgenesis, and also of all cases with a normally located gland. The accuracy of this exam was similar to that of scintigraphy for the identification of CH-related developmental anomalies. The absence of the gland in the usual anatomical location on ultrasonography ensures a diagnosis of permanent CH resulting from dysgenesis, even if it does not identify the type of dysgenesis. Also, although ultrasonography does not always identify ectopic thyroid tissue in patients with dysgenesis, recent studies show that the use of specific equipment and performance of ultrasonographic sections at the medial sagittal and posterior coronal lines of the mouth floor could be useful to identify sublingual ectopic thyroid (Takashima et al., 1995; Ueda et al., 1998). In addition, ultrasonography allows the identification of an anatomically normal gland, which is not always identified by scintigraphy. In these cases, the differential diagnosis

between dyshormonogenesis and transitory forms of neonatal hypothyroidism should be made. For that, other tests should be performed, such as measurement of thyroglobulin, perchlorate discharge test, and saliva/plasma ^{131}I ratio.

In conclusion, ultrasonography of the thyroid gland with a high-frequency transducer is a simple, sensitive and noninvasive diagnostic tool, and should be included as part of the initial evaluation of newborns with abnormal thyroid function tests on neonatal screening. The absence of a gland in the usual location virtually confirms the diagnosis of thyroid dysgenesis, and consequently, of permanent CH. The presence of the gland in the usual location requires further examination to differentiate permanent CH with normally placed and shaped gland from transitory hypothyroidism or neonatal transitory hyperthyrotropinemia. The focus of scintigraphy should be the discrimination between different types of dysgenesis identified by ultrasound.

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Table 1. Etiological diagnosis according to ultrasound and scintigraphy in 76 patients with permanent primary congenital hypothyroidism*

Etiology	Final diagnosis	Ultrasonographic diagnosis	Scintigraphic diagnosis
Normally located and shaped gland	9*	9	8
Dysgenesis	67	67	68
Agenesis	42	66†	44
Ectopia	24	00	24
Hemiagenesis	01	01	00

*Numbers in each column indicate the number of patients with each diagnosis.
†Includes patients with agenesis or ectopia**.**

ARTIGO 2 – HIGH PREVALENCE OF EXTRATHYROID MALFORMATIONS IN A COHORT OF BRAZILIAN PATIENTS WITH PERMANENT PRIMARY CONGENITAL HYPOTHYROIDISM

High prevalence of extrathyroid malformations in a cohort of Brazilian patients with permanent primary congenital hypothyroidism

Short title: Extrathyroid malformations in permanent primary congenital hypothyroidism

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Keywords: hypothyroidism congenital, malformations congenital, abnormalities

Summary

Objective: To evaluate the prevalence of major congenital malformations in a cohort of children with permanent primary congenital hypothyroidism.

Design: Cross-sectional cohort study.

Patients: Seventy-six consecutive, unselected children with permanent primary congenital hypothyroidism (PCH) were recruited from an outpatient clinic of a district hospital. **Measurements:** Malformations were identified by clinical examination. The prevalence of major congenital malformations observed in these patients was compared with the prevalence of malformations reported for live newborns at Hospital de Clínicas de Porto Alegre (HCPA), a tertiary care center. The etiology of hypothyroidism was established by scintigraphy and ultrasonography.

Results: Hypothyroidism was caused by thyroid dysgenesis in 67 patients (1 case of hemiagenesis, 24 of ectopia and 42 of agenesis); the gland was normal and well shaped in 9 patients. Ten patients (13.2%) had major congenital malformations (1316/10000 patients), mostly cardiac. Malformations occurred only in patients with congenital hypothyroidism due to some kind of dysgenesis: thyroid agenesis (n=7), and sub-lingual ectopic thyroid (n=3). The prevalence rate of malformations was significantly higher (RR=2.6; CI 95%: 1.3 to 4.8; *P*=0.005) than the rate for live newborns in Hospital de Clínicas de Porto Alegre (509/10000 patients).

Conclusions: A high rate of extrathyroid congenital malformations, mostly cardiac, was found for patients with permanent PCH. Malformations were all associated with some type of thyroid dysgenesis.

Introduction

The association between congenital hypothyroidism and congenital extrathyroid malformations has been reported since the beginning of the 1980s (Goujard *et al.*, 1981; Bamforth *et al.*, 1986; Fernhoff *et al.*, 1987; Grant & Smith, 1988; Lazarus & Hughes, 1988; Rosenthal *et al.*, 1988; Siebner *et al.*, 1992; Majeed-Saidan *et al.*, 1993; Cassio *et al.*, 1994; Balestrazzi *et al.*, 1994; Al-Jurayyan *et al.*, 1997; Chao *et al.*, 1997; Devos *et al.*, 1999; Stoll *et al.*, 1999; Olivieri *et al.*, 2002). These malformations may increase morbidity and mortality (Fernhoff *et al.*, 1987; Grant & Smith, 1988; Cassio *et al.*, 1994; Al-Jurayyan *et al.*, 1997). They may dominate the presenting clinical picture in such a way that screening for congenital hypothyroidism and, consequently, its early detection and treatment may be delayed (Fernhoff *et al.*, 1987). More recently, however, several authors have raised questions about the genuineness of this association (Oakley *et al.*, 1998) and about its actual prevalence rate (Fernhoff, 1998; Oakley *et al.*, 1998; Stoll *et al.*, 1999). These questions arose from observations of a significantly higher rate of malformations in patients with transient congenital hypothyroidism (Stoll *et al.*, 1999) and, above all, from findings of transient neonatal elevations of TSH in newborns with different types of malformations (Oakley *et al.*, 1998). Transient elevations of neonatal TSH, observed in patients with those types of malformations, could induce a false diagnosis of permanent primary congenital hypothyroidism (PCH).

Furthermore, studies reporting on an association between congenital hypothyroidism and congenital malformations have not consistently evaluated the etiology of hypothyroidism (Bamforth *et al.*, 1986; Fernhoff *et al.*, 1987; Grant & Smith, 1988; Lazarus & Hughes, 1988; Rosenthal *et al.*, 1988; Siebner *et al.*, 1992; Majeed-Saidan *et al.*, 1993; Cassio *et al.*, 1994; Balestrazzi *et al.*, 1994; Al-Jurayyan *et al.*, 1997; Chao *et al.*, 1997; Olivieri *et al.*, 2002).

Consequently, the permanent or transient character of hypothyroidism has not been defined in relation to the genuine character of this association.

The purpose of this study was to verify the prevalence of malformations in a cohort of patients with permanent PCH evaluated according to a well-defined etiology.

Patients and Methods

Cohort

Seventy-six consecutive, unselected patients with a diagnosis of permanent PCH (47 females and 29 males; age range: 16 days to 2 years) were recruited between 1979 and 2002 in the Pediatric Endocrinology outpatient clinic at Hospital Materno-Infantil Presidente Vargas, a district hospital in Porto Alegre, Brazil. All patients were followed up by the same investigator (EK) for 2 to 20 years. Informed consent was obtained from the parents of the children included in the study, and the study was approved by the hospital's Ethics Committee. The initial diagnosis of congenital hypothyroidism was established by routine screening in 52 patients. The other 24 patients were referred to the Pediatric Endocrinology Unit (13 before the age of 3 months) because they presented with clinical signs compatible with congenital hypothyroidism, such as hoarse cry, umbilical hernia, abdominal distension, protruded tongue and puffy face. Although these patients did not undergo routine screening right after birth, they underwent the same diagnostic evaluation.

Screening program and hormone measurements

The screening program started in 1991 as a non-governmental, non-mandatory program.

TSH and T4 were measured by filter paper blood spot, collected after the 5th day of life by puncturing the heel. TSH was measured by a chemoluminescence method developed in our laboratory (Camargo-Neto, 1991), with intra and interassay variation coefficients no higher than 5.2% and 9.1% and a sensitivity of 2 mIU/l, and T4 was measured by radioimmunoassay, using ICN Pharmaceutical (Los Angeles, CA, USA) kits. Patients with TSH values higher than 20 mIU/l and/or T4 lower than 77.2 nmol/l were referred to the pediatric endocrinologist and underwent serum dosages to confirm the diagnosis. Diagnoses were confirmed by measurements of serum T4, free T4, TSH and T3 by chemoluminescence methods, using an Automated Chemiluminometric System (ACS: 180^{TM}, Chiron, Walpole, MA, USA) kits.

For 6 patients diagnosed before the beginning of the screening program, diagnoses were confirmed by dosages of T4 and TSH using RIE, with Diagnostic Product Corporation (Los Angeles, CA, USA) kits.

The diagnosis was confirmed when a value of TSH ≥ 20 μUI/ml was found. The patients were underwent a standardized clinical evaluation that included a structured questionnaire. The clinical data collected included information about the pregnancy, weight at birth, neonatal clinical status, consanguinity, and family history of congenital hypothyroidism. The etiology of all the patients was investigated by ultrasound and thyroid scintigraphy studies.

Investigation of the etiology of congenital hypothyroidism

The etiology of congenital hypothyroidism was performed as previously described (Kreisner *et al.*, 2003). In brief, patients underwent a real-time ultrasonography using a rectilinear scanner (Aloka SSD-650) with a 7.5 MHz high-frequency transducer. The images

obtained were classified into 3 groups: 1) absence of image; 2) normal or enlarged gland in normal anatomic location; and 3) gland in normal anatomic location with morphologic abnormalities. Thyroid scintigraphy was also carried out with ^{99m}Tc in a camera using single photon emission computed tomography (GE Star Cam 2000 or Gammatome II CGR). The images were classified as absence of uptake, uptake in an ectopic area (ectopic gland) or presence of functional tissue in the usual anatomic location.

Based on ultrasound and scintigraphic findings, patients were classified according to etiology into a developmental anomalies (dysgenesis) group or a normally placed and shaped group. In the dysgenesis group, agenesis was characterized by absence of the gland on both ultrasound and scintigraphy; ectopia, by the detection of any thyroid tissue outside the usual topography; and hemiagenesis by a single lobe on ultrasound, with or without radioisotope uptake during the functional exam. Patients with a normally located gland were characterized by unequivocal sonographic identification of a normal or enlarged thyroid gland in the usual anatomic location, with or without uptake of the tracer on scintigraphy. The permanent nature of the disease in the normally placed and shaped group was confirmed by persistently high TSH levels (>10 mIU/l) after one year of treatment, or by TSH >20 mIU/l after hormone replacement was interrupted at the age of 2 years. In these cases, a family history of congenital hypothyroidism and blood kinship between the parents was investigated. In cases of permanent congenital hypothyroidism with an anatomically preserved thyroid gland, no other tests were conducted to identify specific forms of dyshormonogenesis or to differentiate it from other less common forms of permanent congenital hypothyroidism with an anatomically preserved thyroid gland, such as TSHR gene mutations or resistance. Therefore, these patients were classified as having permanent congenital hypothyroidism with a normally placed and shaped gland.

Patients with transient congenital hypothyroidism were not included in this study; and neither were patients with hypothyroxinemia without TSH elevation from different causes, such as prematurity, congenital thyroxine-binding globulin deficiency, or hypothyroidism secondary to TSH deficiency.

Congenital malformations

The malformations were identified by clinical evaluation. When patients had clinical signs suggestive of a cardiac malformation, a conventional one- and two-dimensional echocardiography study with Doppler and color flow mapping was performed (Toshiba SSH 140 with 5 MHz transducer). Congenital malformations were defined, according to Stevenson & Hall's (1993) criteria, as those anomalies that originate during the organogenesis phases; deformations whose origin was associated with a later period of development were excluded. Following these criteria, only major malformations, defined according to their potentially serious medical and social consequences, were listed. Minor malformations that are frequent and not very relevant medically and socially, such as hydrocele, strabismus or calcaneus valgus feet, as well as anomalies associated with the picture of congenital hypothyroidism itself, represented by umbilical hernia and deafness, were not included in this study. Patients with chromosomal anomalies, such as Down syndrome, were also not included. For the purposes of the present study, two cases were not classified as malformations: a case of a patent ductus arteriosus in a premature patient, since prematurity in itself was found to be the cause of this anomaly (Thibeault *et al.*, 1975); and a case of congenital luxation of the hip, because this is an event that occurs after organogenesis.

The prevalence of major congenital malformations and congenital heart malformations

observed in our patients was compared with the prevalence of malformations in live newborns at Hospital de Clínicas de Porto Alegre, a tertiary care center, where malformations are investigated as part of a multicenter collaborative study of congenital malformations in Latin America (Estúdio Colaborativo Latinoamericano de Malformaciones Congênitas; www.biologia.ufrj.br./eclamc/). The prevalence of cardiac malformations was also compared with the prevalence found in a population screening study of these abnormalities by means of pre-natal echocardiography (n=3980) in low risk pregnancies (Hagemann, 2001).

Statistics

The results were expressed in percentages and mean ± SD, and a 5% level of significance was adopted. The student *t* test was used to compare means. The chi-square or the Fisher exact test was used to analyze qualitative non-parametric data. The prevalence rate of malformations was assumed to have a Poisson distribution. In order to compare the occurrences in the group of hypothyroid patients with the reference population, the relative risks with their respective confidence intervals were calculated.

Results

According to ultrasonographic and scintigraphic evaluations, 9 patients with permanent PCH had a normally placed and shaped gland and 67 had some type dysgenesis. In the group with dysgenesis, there were 42 cases of gland agenesis, 24 cases of ectopia and 1 case of hemiagenesis. In the group of patients with ectopia, there was one instance of familial (brother and sister) occurrence. In the 9 patients with permanent PCH with a normally placed

and shaped gland, a familial history of congenital hypothyroidism was identified in 7 cases and consanguineous marriages in 5 cases. One of these patients had a clinically palpable goiter.

Malformations were detected in 10 (13.2%) of the 76 patients with permanent PCH. The clinical and laboratory features, etiology of hypothyroidism and type of malformations are described in Table 1. Cardiac malformations were predominant, and found in 8 of the 10 patients, in isolation or in combined patterns: atrial septal defect (ASD) (n=2/10), ventricular septal defect (VSD) (n=2/10), partial atrial-ventricular septal defect (AVSD) (n=2/10), valve anomalies (n=3/10), and other cardiac malformations (1/10). One patient (patient no. 8) had more than one MF (venticular septal defect and bifid spine) associated with other abnormalities (neurogenic bladder and an extrapyramidal syndrome). The malformations were found only in patients with some type of dysgenesis: thyroid agenesis (n=7), and sub-lingual ectopic thyroid (n=3). No patient with PCH and a normal placed thyroid gland had any malformation.

Patients with malformations were no different from patients without malformations at diagnosis regarding mean serum levels of T4 (50.31±48.76 nmol/L vs. 32.51±36.12 nmol/L; *P*=0.318) and T3 (1.68±1.40 nmol/L vs. 1.37±0.97 nmol/L; *P*=0.422), mean weight at birth (3.30±0.70 vs. 3.41±0.70 kg; *P*=0.653), age at beginning of treatment (mean 60.78±34.87 vs. 79.76±104.45 days; *P*=0.281), or sex (4 malformations in 30 males vs. 6 malformations in 46 females; Fisher exact test, *P*=1.0). Furthermore, no differences were found in the frequency of neonatal asphyxia or respiratory distress syndrome in either group (2 occurrences in 10 patients with malformation versus 4 occurrences in 66 patients without malformations; Fisher exact test, *P*=0.176).

Based on the observation of 10 cases of malformations in 76 patients with PCH, a rate

of 1316/10000 patients (95%CI: 532 to 2420) was obtained, and it was higher (RR=2.6; 95%CI: 1.3 to 4.8; *P*=0.005) than the rate of malformations observed at the Hospital das Clínicas de Porto Alegre: 2991 in 58761 live newborns, corresponding to an expected rate of events of 509/10000 live newborns (95%CI: 491 to 537).

Concerning cardiac malformations, the number of patients with permanent PCH indicated an expected rate of events of 1053/10000 patients (95%CI: 454 to 20740); at Hospital das Clínicas de Porto Alegre, a rate of 154/58761 newborns was observed, corresponding to an estimated rate of 26.2/10000 live newborns (CI 95%: 22.2 to 30.7), also significantly lower than that observed for our patients (RR=40.2; CI 95%: 20.5 to 78.8; *P*<0.001). The expected rate of cardiac malformations in patients with PCH was also higher (RR=14.0; 95%CI: 6.6 to 29.4; *P*<0.001) than the prevalence rate detected by echocardiography in children born of low risk pregnancies: 30 in 3980 studied, or 75.4/10000 (95%CI: 50.9 to 107.4).

Discussion

In this study, we observed a higher prevalence of congenital malformations (13.2%) in patients with permanent PCH than a sample of live newborns in a tertiary care center. Furthermore, our patients also had an increased proportion of cardiac malformations when compared with children born of low risk pregnancies. The malformations (MF) observed in patients with permanent PCH did not have a well-defined pattern, affecting different organs and systems, but a predominance of cardiac malformations of the septal or valvular type was observed. These malformations were associated with some type of thyroid dysgenesis.

Other authors have also observed a high prevalence of MF in patients with PCH, with

the same absence of a pattern in the MF found and with an equal predominance of cardiac MF (Goujard *et al.*, 1981; Bamforth *et al.*, 1986; Fernhoff *et al.*, 1987; Grant & Smith, 1988; Lazarus & Hughes, 1988; New England Congenital Hypothyroidism Collaborative, 1988; Rosenthal *et al.*, 1988; Siebner *et al.*, 1992; Majeed-Saidan *et al.*, 1993; Cassio *et al.*, 1994; Balestrazzi *et al.*, 1994; Al-Jurayyan *et al.*, 1997; Chao *et al.*, 1997; Devos *et al.*, 1999; Stoll *et al.*, 1999). The prevalence of malformations in general ranged from 3.4 to 24%, and of cardiac malformations, from 2.4 to 16%. This broad variation may be partly due to the different methods and criteria used in these studies or, possibly, to a real difference between the populations studied (Siebner *et al.*, 1992). Investigations based on notifications and records (Goujard *et al.*, 1981; Grant & Smith, 1988; Lazarus & Hughes, 1988; Cassio *et al.*, 1994; Balestrazzi *et al.*, 1994) indicate a lower prevalence rate - which may be affected by underestimation - than the rates reported in case studies (Bamforth *et al.*, 1986; Fernhoff *et al.*, 1987; Siebner *et al.*, 1992; Majeed-Saidan *et al.*, 1993; Al-Jurayyan *et al.*, 1997). Furthermore, different criteria for the classification of MF, such as the possible inclusion of chromosomal changes or persistence of ductus arteriosus in premature newborns (Bamforth *et al.*, 1986; Fernhoff *et al.*, 1987, Al-Jurayyan *et al.*, 1997), might contribute to this variability.

This increased prevalence of congenital malformations associated with PCH has been questioned recently. Transient elevation of TSH has been described in newborns with different types of malformation (Oakley *et al.*, 1998), and a significant association between congenital malformations and transient forms of hypothyroidism has been found (Stoll *et al.*, 1999). Therefore, this high prevalence might be partly due to the incapacity to distinguish accurately between true CH and transient thyroid-stimulating hormone elevation caused by a variety of perinatal influences (Oakley *et al.*, 1998). In fact, most authors did not investigate, and therefore did not discriminate the etiology of congenital hypothyroidism in most of the patients, thus allowing questions about the permanent or transient character of thyroid disease. In the present study, only patients with permanent PCH classified according to very strict

criteria were used to define etiology and to confirm the permanent nature of thyroid dysfunction. Therefore, the high prevalence of congenital malformations and particularly cardiac malformations in this sample of patients with permanent PCH confirms the association of congenital hypothyroidism due to thyroid dysgenesis with malformations.

Molecular biology studies have revealed that some cases of thyroid dysgenesis are provoked by mutations in coding genes of transcription factors for the development of follicular cells, such as TITF 1, TITF 2, PAX 8, or of the TSH receptor (Abramowicz *et al.*, 1997; Bieberman *et al.*, 1997; Clifton-Bligh *et al.*, 1998; Gagne *et al.*, 1998; Macchia *et al.*, 1998; Nogueira *et al.*, 1999; Tell *et al.*, 1999; Castanet *et al.*, 2002). In these studies, the descriptions of mutations of the coding gene of TTF2 associated with thyroid agenesis and cleft palate (Castanet *et al.*, 2002), and with thyroid agenesis, cleft palate and choanal atresia (Clifton-Bligh *et al.*, 1998) are very illustrative.

The mutations described so far are responsible for only a limited number of dysgeneses. However, the idea is reinforced that these and other proteins and transcription factors widely distributed throughout the various tissues, and playing a major role in embryogenesis, represent the etiopathogenic link between thyroid dysgeneses and different patterns of MF. The absence of a uniform presentation pattern for these MF, observed in this and in other studies, may be associated with epigenetic phenomena involved both in the etiopathogenesis of the MF (Martínez-Frías, 2001), and in thyroid dysgeneses (Perry *et al.*, 2002). Depending on the time when these factors (chromosomal, genetic or environmental) act, different types or combinations of congenital anomalies may be found.

In conclusion, patients with permanent PCH had a high rate of extrathyroid congenital malformations, especially cardiac ones, which were always associated with some type of thyroid dysgenesis. Patients with permanent PCH due to thyroid dysgeneses should ideally be screened for such malformations.

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Table 1. Clinical and laboratory features at diagnosis, etiology of hypothyroidism and type of malformation.

Case	Sex	Body weight (kg)	TSH spot (mUI/l)	T4 venous sample (nmol/L)	T3 venous sample (nmol/L)	Etiology of PCH	Type of malformation
1	Male	3.6	534.70	91.60	2.22	ectopia	ASD
2	Male	3.6	467.10	3.87	0.154	agenesis	ASD
3	Male	3.5	226.0	6.45	0.37	agenesis	Partial AVSD, mitral and tricuspid valve anomalies
4	Female	3.2	180.0	12.9	0.154	agenesis	AVSD
5	Female	2.9	400.0	6.45	0.462	agenesis	cleft palate and cleft lip
6	Female	3.9	204.0	140.6	2.63	ectopia	sub-aortic ring. obstruction of aortic out flow, VSD
7	Female	4.2	339.5	90.30	3.19	ectopia	Pulmonary valve stenosis
8	Female	2.3	>100.0	0.0	-	agenesis	VSD, bifid spine
9	Male	1.7	>100.0	42.44	3.70	agenesis	Pulmonary valve stenosis
10	Female	2.3	100	59.47	2.17	agenesis	cleft palate

ASD: atrial septal defect, VSD: ventricular septal defect, AVSD: atrial-ventricular septal defect

ARTIGO 3 – PREDICTORS OF INTELLECTUAL OUTCOME IN A COHORT OF BRAZILIAN CHILDREN WITH CONGENITAL HYPOTHYROIDISM

Predictors of intellectual outcome in a cohort of brazilian children with congenital hypothyroidism*

Short title: predictors of intellectual development in congenital hypothyroidism

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Summary

Objective: To identify predictors of intellectual development in a cohort of children with permanent primary congenital hypothyroidism.

Design: Cohort study with intellectual development as the outcome.

Patients and Measurements: Thirty-one consecutive newborns with permanent primary congenital hypothyroidism diagnosed by a screening program were recruited from the outpatient clinic of a district hospital and underwent psychometric evaluation with the Wechsler Intelligence Scales after a minimum follow-up of 4 years.

Results: Eight of the 31 patients (25.8%) presented impaired intellectual development (full-scale intellectual quotient < 85), and 1 of them presented mental deficiency (full-scale intellectual quotient ≤ 69). The following were associated with worse prognosis: initial serum T4 levels ≤ 32.18 nmol/L, treatment beginning after 30 days of age, less than 7 clinic visits during the first year of life, living in rural areas, non-intellectual parental occupation and little parental schooling. In a multiple regression analysis, only maternal schooling (B = 0.401; beta coefficient = 13.053, *P* = 0.063), number of clinic visits during the first year of life (.B=0.382; beta coefficient = 4.145, *P* = 0.047) and initial serum T_4 (B = 0.287; beta coefficient = 1.336, *P* = 0.089) remained significantly associated with full-scale intelligence quotient scores.

Conclusion: Maternal schooling, number of visits during the first year of life and baseline T4 levels were the main predictors of cognitive outcome in this cohort of patients.

Introduction

The introduction of neonatal screening programs for congenital hypothyroidism (CH) in the 1970s and the possibility of early treatment translated into remarkable improvement in the neurological prognosis of CH patients (Klein et al., 1972; New England Congenital Hypothyroidism Collaborative, 1984; Simons et al., 1994). Precocity and adequacy of treatment have been considered as the most relevant factors determining cognitive development. Rapid restoration of circulating T4 to high normal levels during the first year of life improves intellectual development regardless of the screening T4 concentration or the type of hypothyroidism (New England Congenital Hypothyroidism Collaborative, 1990; Dubuis et al, 1996). However, a metanalysis study has reported that patients with CH still present an IQ deficit in relation to control groups despite early diagnosis and treatment (Derksen-Lubsen, 1996). Even for treatment starting as early as age 6 days (Virtanen et al, 1989) a lower mean intelligence quotient (IQ) has been observed.

Such cognitive sequelae have been interpreted as an inevitable consequence of more intense intrauterine CH, which cannot be fully compensated during the post-natal period. In this context, the presence of very low levels of serum T4 (Virtanen et al., 1989; Fuggle et al., 1991; Rovet et al., 1992; Simons et al., 1994; Tillotson et al., 1994; Koistra et al., 1994; Bargagna et al., 2000) or serum T3 (Murphy et al., 1986) at diagnosis, immature bones (Glorieaux et al., 1985; Rovet et al., 1992) and thyroid agenesis (Heyerdahl et al., 1991; Rovet et al., 1992; Koistra et al., 1994) have been considered as markers of more intense intrauterine deficiency, and as possible predictive factors for worse intellectual prognosis. Few studies so far have taken into account the possible direct effects of socio-demographic factors on the prognosis of CH patients. (Virtanen et al., 1989; Fuggle et al., 1991; Simons et al., 1994; Tillotson et al., 1994, Heyerdahl et al., 1996).

The objective of this study was to investigate the effect of prenatal factors (CH aetiology and serum T4 and T3 levels at diagnosis), postnatal factors (age at beginning of treatment, initial hormone replacement dose, mean serum T4 and T3 levels during the first 2 years of life and number of routine medical visits during the same period), and socio-demographic factors (living in rural or urban areas, type of parental occupation, and parental schooling) on the mental, motor and full-scale IQ in a cohort of Brazilian patients with permanent CH identified by a screening program and followed for at least 4 years.

Patients and Methods

Cohort

Consecutive patients older than 4 years of age, diagnosed with permanent CH at the Pediatric Endocrinology outpatient clinic at Hospital Materno-Infantil Presidente Vargas by a screening program beginning in 1991 were selected for this study. Patients with hypothyroxinemia not presenting elevated TSH, resulting from congenital thyroxine-transporting globulin deficiency or from other causes such as prematurity, transient hypothyroidism or hypothyroidism secondary to TSH deficiency were not included. The final cohort consisted of 31 patients with permanent CH (18 females and 13 males). No patient presented any other concomitant condition that might affect intellectual outcome.

All patients were followed regularly by one of the authors (EK). Informed consent was obtained from the parents, and the protocol was approved by the Institution's Ethics Committee.

At baseline, the patients underwent a standardized clinical evaluation and the etiologic

diagnosis of CH was made by cervical ultrasonography and scintigraphy. The parents answered a structured questionnaire, which included information about pregnancy, weight at birth, neonatal clinical status, parental consanguinity and family history of CH. At follow-up, when the patients were at least 4 years old, a psychometric evaluation was performed and the socio-demographic status of the family was assessed. The nutritional status of the child was also evaluated.

Screening program and hormone measurements

The screening program began in 1991 as a non-governmental, non-obligatory effort. In the period from 1991 to 1997, 187,880 newborns were screened for congenital hypothyroidism in the state of Rio Grande do Sul, and 57 cases were identified (35 females and 22 males). This translates into an incidence of 0.030% (1:3296). Thirty-one patients (18 females and 13 males) with permanent primary congenital hypothyroidism were followed at our institution. Both incidence and gender proportion were similar to those reported by other investigators (Devos et al, 1999).

Blood was collected after the 5th day of life, on filter paper, by puncturing the heel. TSH was measured by a chemoluminescence method developed in our laboratory (Camargo-Neto, 1991), with intra and interassay coefficients of variation no higher than 5.2 and 9.1%, respectively, and a sensitivity of 2 mU/l. The results were expressed per volume of plasma. T4 was measured by RIA using an ICN Pharmaceutical kit (Los Angeles, CA, USA). In patients with TSH values higher than 20 mU/l and/or T4 lower than 77.2 nmol/l, the screening laboratory contacted parents and physician by phone**.** They were referred to a pediatric endocrinologist and submitted to diagnostic confirmation through measurements of serum T4,

free T4, TSH and T3 by chemoluminescence methods, using Automated Chemiluminescence System kits (ACS 180 MR, Chiron, Walpole, MA, USA).

The interval of time between the screening and blood collection for diagnostic confirmation of congenital hypothyroidism did not exceed 7 days. Treatment was started on the same day or on the day after confirmatory blood collection and diagnostic confirmation. The baseline T4 values used for statistical analysis were the values obtained just before the beginning of treatment. The same physician (EK) followed the patients since diagnosis, and all efforts were made to ensure compliance and proper administration of L-thyroxine by the parents. We had no objective evidence of non-compliance in taking/administering l-thyroxine.

Investigation of the aetiology of permanent hypothyroidism

Aetiology of permanent hypothyroidism was established as previously described (Kreisner et al, 2003). Briefly, real time ultrasonography (Aloka SSD-650, 7.5 MHz high-frequency transducer) was performed with the patients in supine position, with head in hyperextension. The images obtained were classified as: 1) absence of image; 2) normal or enlarged gland in usual anatomic location; and 3) gland in usual anatomic location with morphologic abnormalities (hemiagenesis).

^{99m}Tc thyroid scintigraphy was carried out in a scintillation chamber, using single-photon emission computed tomography (GE Star Cam 2000 or Gammatome II CGR). With help from the parents, the patients were placed in supine position with hyperextension of the neck. Depending on the concentration and distribution of ^{99m}Tc, the images obtained were classified as absence of uptake, uptake in a sublingual or ectopic hyoid region or presence of functional tissue in the usual topography.

Based on ultrasound and scintigraphic findings, an etiological classification was performed to categorize patients into a developmental anomalies (dysgenesis) group or a normal placed and shaped group. In the dysgenesis group, agenesis was characterized by absence of a gland on both ultrasound and scintigraphy; ectopia, by the detection of any thyroid tissue outside the usual topography; and hemiagenesis by identification of a single lobe on ultrasound. The permanent nature of the disease in the normal location and shape group was confirmed by TSH >20 mIU/l after hormone replacement was temporarily interrupted at the age of 2 years. In these cases, a family history of CH and blood kinship between the parents was investigated. During the follow-up, serum T4 and TSH levels were measured at each visit.

Psychometric evaluation

Two tests were used: the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) was applied to patients with age between 4 to not quite 6 years (n=24) (Wechsler, 1991); and the Wechsler Intelligence Scale for Children (WISC) (Wechsler, 1964) was used for the age group between 6 and 15 years and 11 months (n=7). The results were expressed as verbal IQ scores, performance IQ and full-scale IQ scores. The patients were classified as follows according to their full-scale score: mental deficiency (IQ ≤ 69), borderline (IQ ≥ 70-84), medium (IQ ≥ 85-114) and high (IQ ≥ 115) intelligence/cognitive development.

Socio-demographic and nutritional assessments

We collected information on the parents' level of schooling, type of occupation (manual

or intellectual), and place of residence (rural or urban area). Parents were divided into 2 groups according to schooling: complete or incomplete elementary school and high school or higher. As regards the type of work, intellectual occupations encompassed teachers, business people with a university degree, secretaries, bank employees, engineers, managers and individuals working for insurance companies. Manual occupations included housewives, farmers, handymen, machine operators, shop clerks, painters, drivers, security personnel, firemen and hairdressers. The rural category encompassed families who supported themselves with agricultural activities or families living in localities with less than 5,000 inhabitants (George, 1975). The urban population was defined as people living in localities with more than 5,000 inhabitants (Trewartha, 1974; George, 1975).

The nutritional status of the patients was evaluated taking into account National Center for Health Statistics (NCHS) growth curves (Hamill et al., 1979), triceps skin fold measurements (Frisancho, 1981) and, for patients over the age of 6, the body mass index (BMI) (Frisancho, 1990). Iodine intake is considered to be adequate in both urban and rural areas since the implementation of the salt iodination program in Brazil, in 1983. The average urinary iodine excretion in schoolchildren in the state of Rio Grande do Sul is 22 μg/dl (Lisboa & Gross, 2002), well above the cutoff point of 10 μg/dl considered as the minimal concentration for iodine sufficiency.

Statistical analysis

The various characteristics of the groups were expressed as percentage and mean ± standard deviation. Comparisons between the groups were made using the Student's t test. The Pearson correlation coefficient was used for testing the relationships between IQ and

different variables. The level of significance adopted was 5%. Multiple regression analysis was performed to identify the possible factors associated with intellectual development (full-scale IQ as the dependent variable). For this analysis, the level of significance was 10%.

Results

All 31 patients had their diagnosis confirmed and treatment started between 16 and 89 days of life (43.4 ± 22.6 days). The mean age at blood collection for screening was 28.9 ± 16.0 days (minimum: 5 days, maximum: 69 days) and no difference was observed between urban (n = 24; 29.1 ± 16.2 days) and rural cohorts (n = 7; 28.1 ± 16.5 days; P = 0.89). However, blood collection in children of mothers with more schooling was performed significantly sooner (n = 18; 21.9 ± 11.9) than in children of mothers with only complete or incomplete elementary school (n = 13; 38.5 ± 16.2 days, P = 0.003).

Ectopia was observed in 16 (51.6%) cases, agenesis in 11 (35.5%) and dyshormonogenesis in 4 (12.9%). In these 4 patients with normally placed and shaped gland, the permanent nature of hypothyroidism was confirmed by interruption of therapy during 15 to 19 days at or after 2 years of age with prompt replacement of l-thyroxine when TSH showed unequivocally high values.

One patient (3.2.%) was identified as having severe mental deficiency by psychometric tests. Seven patients (22.6%) had an IQ < 85, and were classified as borderline. In 20 (64.5%) patients the full-scale IQ was medium, and in 3 (9.7%) it was high. In 3 of the 7 borderline patients, treatment had been instituted before the age of 30 days (20, 26 and 29 days respectively) with an initial levothyroxine dose of 10.0, 12.5 and 11.4 μg/kg, respectively.

Table 1 depicts the mean levels of full-scale, verbal and motor IQ scores and possible predictors of cognitive impairment in the 31 patients. Full-scale and verbal IQ scores were, respectively, borderline and significantly lower in patients with baseline serum T4 ≤ 32.18 nmol/l (P = 0.055 and P = 0.030). However, full-scale IQ score and T4 levels (analyzed as continuous variables) at the start of treatment did not present a significant correlation (r = 0.243; P = 0.187). After the start of treatment and during the first year of life mean serum levels of T4 and TSH were 164.7 ± 28.3 nmol/l and 10.5 ± 6.6 mIU/l, respectively; a significant correlation (r = 0.14; P = 0.46 and r = -0.16; P = 0.42 respectively) with full-scale IQ was not observed. In patients whose treatment began before the 31st day of life, full-scale and performance IQ scores were also borderline and significantly higher than in patients whose treatment began at a later point (P = 0.054 and P = 0.036 respectively). In addition, patients with more than 6 medical visits in the first year of life showed significantly higher full-scale, verbal and performance IQ scores than patients with fewer visits ($P < 0.001$, $P < 0.001$ and P = 0.021, respectively).

In terms of demographic variables, urban patients presented significantly higher full-scale IQ (P = 0.046) and borderline higher verbal and performance IQs than rural patients (P = 0.071 and P = 0.070, respectively). Full-scale, verbal, and performance IQ scores were higher in the children of mothers with an intellectual occupation than in the children of mothers with a manual occupation (P = 0.006, P = 0.024 and P = 0.006). The same was observed for paternal intellectual vs. manual occupation (P = 0.024, P = 0.032 and P = 0.031). Higher full-scale, verbal and performance IQ scores were also observed in the children of mothers with more schooling (P = 0.004, P = 0.008 and P = 0.002) and of fathers with more schooling (P = 0.008, P = 0.022, P = 0.001). We observed that the children of mothers with a lower level of schooling began their treatment later than those whose mothers had a higher

level of schooling (n = 13, mean 58.46 ± 25.60 days, n = 18, mean 32.44 ± 11.77 days, respectively; *P*= 0.001).

No significant differences were observed concerning the other parameters assessed in this study, including mean serum levels of T4 and T3 in the first 24 months of life, baseline serum T3, levothyroxine doses at beginning of treatment, nutritional status and aetiology (data not shown).

A multiple regression analysis was performed with full-scale IQ as the dependent variable and age at the beginning of treatment, serum T4 levels at diagnosis, number of medical visits during the first year of life, and maternal level of schooling as independent variables (table 2). Baseline T4 levels (B = 0.287; beta coefficient = 1.336 and *P* = 0.089), number of medical visits during the first year of life (B = 0.382; beta coefficient = 4.145 and *P* = 0.047) and socio-demographic factors, represented by maternal schooling (B = 0.401; beta coefficient = 13.053 and *P* = 0.063), remained significantly associated with full-scale IQ.

Discussion

In this cohort of 31 patients with permanent CH from an iodine sufficient area, cognitive development was associated with baseline levels of serum T4, number of clinic visits during the first year of life, and socio-demographic variables, especially maternal schooling.

T4 levels ≤ 32.18 nmol/l at diagnosis were associated with worse prognosis. Nevertheless, we did not observe an association between cognitive impairment and baseline T3 levels or aetiology. Other studies have reported an association between less favorable

outcomes and severity of disease measured by low concentrations of T4 (Virtanen et al., 1989; Fuggle et al., 1991; Rovet et al., 1992; Simons et al., 1994; Tillotson et al., 1994; Koistra et al., 1994; Bargagna et al., 2000) and T3 at diagnosis (Murphy et al., 1986), bone immaturity (Glorieaux et al., 1985; Rovet et al., 1992) and thyroid agenesis (Heyerdahl et al., 1991; Rovet et al., 1992; Koistra et al 1994). Since thyroid hormones play an essential role in brain development during a critical period of fetal life and during the first 2 years of life (Porterfield & Hendrich, 1993), the resulting sequelae could be linked to more severe hormone deficiency during the prenatal period.

Quality of treatment measured by number of routine medical visits in the first year of life was also identified as an important predictor of cognitive impairment. Patients with less than 7 medical visits during the first year of life had a worse prognosis. Other authors have also observed an association between prognosis and quality of treatment (Fuggle et al., 1991; Simons et al., 1994; Dubuis et al., 1996; Bongers-Schokking et al., 2000). The strong association between cognitive impairment and the number of visits during the first year of life possibly reflects better adherence to treatment and better quality of treatment.

Moreover, we observed a significant association between the full-scale IQ for the entire group and the socio-demographic parameters analyzed, with a worse outcome in patients from families living in rural areas, or whose parents had non-intellectual professional occupations and less schooling (especially the mother). In developed countries, little attention has been paid to the role of these socio-demographic differences as independent factors influencing the cognitive prognosis of CH patients (Virtanen et al., 1989; Fuggle et al., 1991; Heyerdahl, 1996; Tillotson et al., 1994; Connely et al., 2001).

Some of these authors have also identified socio-demographic factors such as non-intellectual paternal occupation (Fuggle et al., 1991; Tillotson et al., 1994) and maternal age

and level of education (Connelly et al., 2001) as independent predictors of intellectual outcome. Nevertheless, Virtanen et al. (1989), Heyerdahl (1996) did not observe significant differences between patients belonging to different social classes – however, this may be reflecting the smaller gap between social classes in Scandinavia in relation to Brazil.

Although age at the beginning of treatment was not significantly associated with intellectual outcome in the multiple regression analysis, the well-known importance of early intervention to prevent mental deficiency should not be downplayed. Early treatment and a high initial dose of levothyroxine improve developmental outcome of infants with severe congenital hypothyroidism (Dubuis et al, 1996). The non-significant association between age at the start of treatment and full-scale IQ may be reflecting a strong influence of low maternal schooling favoring delayed diagnosis and treatment. In fact, blood collection in children of mothers with more schooling was performed significantly sooner than in children of mothers with only complete or incomplete elementary school.

In order to be effective, screening programs should enable early detection and treatment of infants with permanent CH. In our study we identified social factors, especially low maternal schooling, as a significant component of the delay in screening and treatment of some of these infants. This type of observation motivated the implementation of appropriate health policies favoring a more precocious identification of patients and earlier intervention in the form of a mandatory screening program supported by the Federal Government's Health Ministry. Furthermore, the participation of an interdisciplinary team, including social workers and psychologists, was also adopted to encourage proper follow-up and compliance. With the implementation of these measures, we hope to achieve much better outcomes, similar to those recorded in Europe and the US.

In conclusion, our results suggest that cognitive outcome in this cohort of Brazilian

patients with CH diagnosed by neonatal screening was influenced by several factors, including disease severity. In addition, our results underscore the importance of quality of treatment (reflected in the number of medical visits in the first year of life) and of maternal schooling, which play an important role in a timely diagnosis and treatment. The importance of socio-economic factors should be taken into consideration in the implementation of adequate health policies, especially in countries where great social inequalities are present.

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Table 1. Influence of clinical, laboratory and socio-demographic aspects on the IQ of patients with congenital hypothyroidism diagnosed by a screening program.

Variable	Full-scale IQ	Verbal IQ	Performance IQ
Baseline serum T4			
≤ 32.25 nmol /l (n=20)	91.40±14.51	91.75±15.10	92.70±12.97
> 32.25 nmol /l (n=11)	102.73±16.08	104.55±14.69	99.64±16.67
P	0.055	0.030	0.208
Age at beginning of treatment			
≤ 30 days of life (n=10)	103.30±18.27	102.20±17.67	103.00±16.95
> 30 days of life (n=21)	91.67±13.38	93.48±14.71	91.43±11.89
P	0.054	0.159	0.036
No. of medical visits in the first year of life			
> 6 (n=10)	109.10±9.71	110.00±8.79	104.40±10.09
≤ 6 (n=19)	88.58±14.64	89.53±15.21	91.42±14.94
P	< 0.001	0.001	0.021
> 6 (n=10)	109.10±9.71	110.00±8.79	104.40±10.09
Place of residence			
urban (n=24)	98.46±16.26	99.08±16.49	97.71±15.04
rural (n=7)	85.00±8.54	86.71±9.76	86.43±8.42
P	0.046	0.071	0.070
Maternal occupation			
intellectual (n=9)	107.11±15.37	106.26±17.20	105.89±12.89
manual (n=22)	90.64±13.59	92.23±13.86	90.77±12.97
P	0.006	0.024	0.006
Paternal occupation			
intellectual (n=11)	103.91±16.31	104.45±17.90	102.64±13.64
manual (n=20)	90.75±13.78	91.80±13.20	91.05±13.59
P	0.024	0.032	0.031
Maternal schooling			
Elementary (n=13)	86.15±14.81	87.62±14.34	86.23±13.32
high school or higher (n=18)	102.11±13.16	102.56±14.35	101.61±11.90
P	0.004	0.008	0.002
Paternal schooling			
Elementary (n=16)	88.38±14.51	90.06±14.18	87.25±12.06
high school or higher (n=15)	102.93±13.88	102.93±15.48	103.60±12.16
P	0.008	0.022	0.001

Table 2. Multiple linear regression model expressing the effects of selected variables on global IQ

Variable	b coefficient	beta	P
Age at beginning of treatment (days)	0.134	0.181	0.362
Number of clinic visits during first year of life	4.145	0.382	0.047
Baseline serum T4	1.336	0.287	0.089
Maternal schooling	13.053	0.401	0.063