ISSN: 2318-8413 DOI: 10.18554/refacs.v4i3.1778

REFACS
Revista Família, Ciclos de Vida e Saúde no Contexto Social

Transitory hiperthyrotropinemia and alteration of 17-OH-progesteron on neuropath infant

Hipertireotropinemia transitória e alteração da 17-OH-progesterona em lactente com neuropatia

Hipertireotropinemia transitoria y alteración de la 17-OH-progesterona en lactante con neuropatía

Received: 05/04/2016
Approved: 10/07/2016
Published: 01/09/2016

Jussara Silva Lima[1]
Valéria Cardoso Alves Cunali[2]
Luciana de Azevedo Tubero[3]
Vandui da Silva dos Santos[4]

The present paper has the objective to report the case of a neuropath infant that presented transitory hiperthyrotropinemia and alteration of 17-OH progesterone after surgical stress aggravated with septic shock and distributive. The information were obtained by medical records' revision, interview with patient's parents, by accompaniment of its evolution, registering of diagnosis methods, those that the patient was submitted during many admissions, and literature's reviews. The reported case and the literature review show that are frequent changed and instable TSH values, as well as alterations of 17-OH-progesteron, due to many factor, among which surgical stress and inflammatory ones. In this patient's case, neurological factors as inborn errors of metabolism even when not diagnosed can interfere on the child's homeostasis.
Descriptors: Hypothyroidism; Adrenal; Metabolism inborn errors, Infant.

O presente trabalho tem como objetivo relatar o caso de um lactente com neuropatia que apresentou hipertireotropinemia transitória e alteração de 17-OH-Progesterona após estresse cirúrgico complicado com choque séptico e distributivo. As informações foram obtidas por meio de revisão de prontuário, entrevista com os pais, por acompanhamento de evolução, registro dos métodos diagnósticos dos quais o paciente foi submetido durante várias internações e, revisão da literatura. O caso relatado e o levantamento da literatura mostram que são frequentes os valores de TSH alterados e instáveis, bem como alterações de 17-OH-Progesterona, devido a vários fatores, dentre os quais estresse cirúrgico e inflamatório. No caso desse paciente, os fatores neurológicos como os erros inatos do metabolismo mesmo quando não diagnosticados podem intervir na homeostase da criança.
Descritores: Hipotireoidismo; Suprarrenal; Erros inatos do metabolismo; Lactente.

El presente trabajo tiene como objetivo relatar el caso de una lactante con neuropatía que presentó hipertirotropinemia transitoria y alteración de 17-OH-Progesterona luego de estrés quirúrgico complicado con choque séptico y distribuido. Las informaciones fueron obtenidas por medio de revisión de prontuario, entrevista con los padres, por acompañamiento de evolución del paciente, registro de los métodos diagnósticos y revisión de la literatura. El caso relatado y el levantamiento de la literatura muestra que son frecuentes los valores de TSH alterados e inestables, bien como alteraciones de 17-OH-progesterona, debido a varios factores, entre los cuales estrés quirúrgico e inflamatorios. En el caso de este paciente, los factores neurológicos como los errores innatos del metabolismo, aun cuando no diagnosticados, pueden intervenir de sobremanera en la homeostasis del niño.
Descriptores: Hipotiroidismo; Suprarrenal; Errores innatos del metabolismo; Lactante.

[1] Physician. Specialist in Health System Auditions. Specialist in Medical Assessment. Specialist in Health Services Administration. Specialist in Occupational Medicine. Specialist in Homeopathy. Master's degree in Medical Sciences. Master's degree in Pathology. Doctor's degree in Health Care General Hospital of the Federal University in the Triângulo Mineiro (GH-UFTM). jussaralima@netsite.com.br. Brazil.
[2] Physician. Master's in child and adolescent health. Doctorate in Infectology. Assistant Professor of Pediatrics at the UFTM. vcunali@gmail.com. Brazil.
[3] Graduated in Medicine at UFTM. luciana.tubero@gmail.com. Brazil.
[4] Medicine Undergrad from UFTM. vandui.santos@gmail.com. Brazil.

INTRODUCTION

Neurological pathologies present intriguing associations with thyroid anomalies. Thyroid dysfunction is prevalent in the general population, depending, among other things, on the underlying pathology. The most frequent thyroid change in these patients is from elevation of the thyroid-stimulating hormone (TSH), without changes in other thyroid hormones. This condition is known as subclinical hypothyroidism, and it does not have a detectable etiology[1].

Transient TSH elevation has been documented in children with neuropathy, and there is not a consensus regarding how much it is detrimental to their development, since the cause of that elevation has not been defined[2].

Primary adrenal insufficiency rarely manifests itself during childhood. It can, however, appear insidiously, especially in the presence of a triggering stressful event. Clinical signs are nonspecific and may include variables of different degrees of severity[3].

The present study aims at reporting the possible prevalence of altered TSH and 17-OH-progesterone levels in a nursing infant with neuropathy, including its possible consequences and clinical worsening.

METHOD

The information presented in this report were obtained through the analysis of medical records, as well as through an interview with the parents, a clinical examination of the patient, the revision of sequential laboratory exams of every hospitalization, and photographic research of some diagnostic methods to which the patient was subjected, in addition to a review of the literature on the subject.

The patient her described was admitted to the Pediatrics ward of the General Hospital of the Federal University in the Triângulo Mineiro (GH-UFTM) in 10/15/2015 and was discharged in 11/6/2015. A second hospitalization occurred from 12/16/15 to 1/1/2016. A third hospitalization happened from 1/7/16 to 5/15/16. The analyzed child is currently being monitored by a multidisciplinary team in the outpatient pediatric ward of UFTM.

Those responsible for the infant gave their express documented consent for the preparation and publishing of this work, as well as provided the images of the patient.

RESULTS

Describing the case

Infant, aged 7 months and 20 days, hospitalized in the pediatric ward of UFTM for 4 months, referred to them through the outpatient ward for the investigation of progressive weight loss and dysphagia accompanied by coughs and chokes. The initial diagnosis indicated gastresophageal fistula, however, a bronchoscopy only showed hyperplasia in the pharyngeal tonsil tissues, a discrete laryngomalacia, and no fistulas.

Then, a gastrostomy was recommended, together with an anti-reflux valve using the Nissen technique (eponymous - it has the name of the surgeon who invented the technique). In the preoperative procedures it evolved with distributive shocks (both septic and neurogenic), presenting seizures. Even after septic clinical improvement, the patient was in severe refractory dehydration, pre-renal renal failure, symptomatic hypoglycemia, and semi-obstructive abdomen, difficult to control seizures evolved to bilateral amaurosis, with pale retina, flushed papilla bounded in both eyes, of probable neurogenic origin, together with 17-OH-progesterone changes occurring during the first two months of hospitalization, in addition to cortisol changes and TSH increase.

Obstetric antecedents

Birth weight 3.070 Kg. Apgar: 9/10 Gestational age of 39 weeks and 4 days. Mãe G3, P3, C1, com quadro de ITU na 2º, 3º e 8º mês de gestação, com relato de uso de formol (progressiva) durante a gestação.

Morbid personal history

Admission at 18 days of age, presenting daily fever which started when 11 days old. The

patient was then admitted in order for a non-specific neonatal sepsis treatment to be performed, and presented hypoglycemia, daily fever, refractory to antibiotic therapy, and metabolic acidosis.

Exams

The patient also presented altered TSH and cortisol levels, with regular levels of 17-OH-progesterone. Neonatal heel prick results normal. Investigations of innate metabolism malfunctions already started in two different occasions, both with a normal result. After the first hospitalization, the patient presented hypotonia, daily fever, intense irritability and difficulty to suck. During outpatient follow-up, 17-OH-progesterone and cortisol were also maintained. The conducted exams are in table 1.

Table 1. Infant according to laboratory exams. Uberaba, 2016.

Exam	Oct/15	Dec/15	Jan/16	Mar/16
170H-progesterona	1408.9	1485	94.6	87.2
Testosterone	---	---	---	2.5
Cortisol	30.3	---	---	11.03
TSH	9.65	---	---	4.24
Free T4	1.4	---	---	0.996
Karyotype	---	---	---	Normal
Serologies	Negative	---	---	---
Neonate triage	Normal	---	---	---
Innate Metabolism Errors	Negative	---	---	Negative
Bronchoscopy	---	---	No fistula, discrete, laryngomalacia	---
Video-fluoroscopic swallow study	---	Normal	---	---
Endoscopy	---	Gastroesophageal reflux	---	---
Skull CT scan	Fronto-parietal and occipital infarction to the right, changes in the white matter.	---	---	---
Back of the eye	---	---	---	Pale retina, colored papillae, normal macula.

The infant evolved with 2 episodes of aspiration pneumonia, and then the reflux was investigated through an esophagus-stomach-duodenum (ESD) test, with contrast, and through a video-fluoroscopic swallow study, by the time the infant was 2 months old, with the presence of gastroesophageal reflux and skull CT scan, already presenting front-parietal and occipital infarction areas to the right, with white matter changes. Along this period, progressive weight gain was worsened.

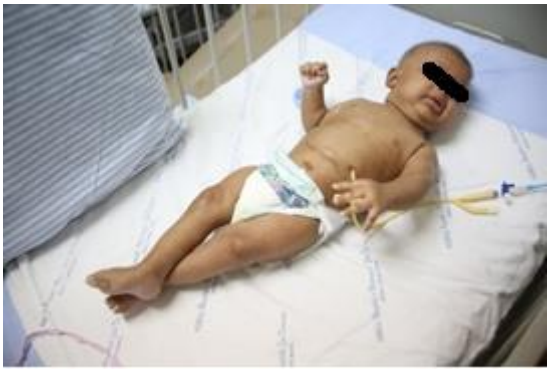
In the physical examination conducted when the infant was seven months old, the infant were lethargic, in a regular general state, daily fever, brachygnathia, skin hyperpigmentation (Image 1), especially around the eyes, malnourished, weighing 5.070Kg (Z score -2), and cephalic perimeter

with a Z score below -3 Cardiovascular system without changes with 2BRNF-no murmurs, normal wrist amplitude and intensity normal, good peripheral perfusion, hemodynamically stable. Lungs: presence of vesicular murmur, symmetrical, bilaterally, without adventitious breath sounds, clear lung sounds at a respiratory rate of 46. Abdomen: gastrostomy healed well, no signs of inflammatory process. Nervous system: generalized hypotonia (Image 2), which evolved with hypertonia, minimal fontanelle, with overlaying suture, with visible hypertonia, claw-feet and hands, movements using the whole body, limbs asymmetry, nystagmus, spastic quadriplegia.

Initially, it was chosen not to use thyroid hormones, but laboratory and clinical changes was not altered, and hemodynamic control was difficult, which led to the replacement with regular doses of clinical hypothyroidism, bringing a clear improvement starting at the twelfth day.

Image 1. Infant with lethargy, brachygnathia and hyperpigmentation of the skin. Uberaba, 2016.

Image 2. Infant with generalized hypertonia, claw-feet and hand, movements using the whole body, spastic quadriplegia. Uberaba, 2016.



DISCUSSION

Congenital adrenal hyperplasia can be caused by the deficiency of various enzymes and can be diagnosed by the transient elevation of 17-OH-progesterone, as clinical consequences of growth retardation, successive dehydrations, serious or recurring. In turn, the high concentrations of sexual steroids caused by this abnormality, can induce the early closure of epiphysis and suppress growth[3].

Several enzymes are involved in the synthesis of adrenal cortisol, which can also generate different clinical symptoms. During the neonatal period, clinic can be suggestive, presenting symptoms such as dehydration, vomiting, and hyponatremia[2], as was the case of this particular patient.

The acute crises that happened during the neonatal period can occur in situations of stress or infection, with maintained hypoglycemia and hypokalemia, with hypovolemia [4].

The changes in 17-OH-progesterone and cortisol experienced by the patient could

be triggered not by primary adrenal changes, but also in the presence of a triggering stress, such as sepsis and surgical stress. In addition, there are reports of an autoimmune multi-glandular syndrome , much more rare, which brings about malabsorption and seems to be related to the mutation of the FOXP3 gene, as well as syndromes related to polyneuropathies, organomegalies and endocrinopathies related to the M protein. Other diseases, determinants of adrenal dysgenesis or of steroidogenesis defects must also be addressed[5].

In patients with neuropathy, whatever the etiology, TSH elevated values are frequent, and strict monitoring is of vital importance, due to the high risk of the evolution of the manifest thyroid disease[2].

The prevalence of thyroid dysfunction is greater than in the general population, depending on the studied pathology. The most common thyroid change in these patients is the isolated elevation of the thyroid-stimulating hormone (TSH), without changes of other thyroid hormones, known as sub-clinic hypothyroidism, serum TSH levels being just above the reference values (between 5 and 10 μ units/ml) and sometimes without a detectable etiology[1,2,6].

The isolated elevation of TSH in children with neuropathy could be an early sign of primary auto-immune hypothyroidism[7].

Autoimmune factors related to the pathogenesis of hyperthyrotropinemia can be related to cellular sensitivity to interferon, presence of HDR antigens associated with auto-immune thyroiditis, or changes of the dismutase superoxide. In this particular clinical case, it was not possible to establish a clear etiology for these changes, however, it is evident that these changes have contributed to the worsen the homeostasis, transforming the case in a graver one.

Changes in the TSH and free T4 hormones can also be affected by maternal factors and mostly affect the premature child. The neonatal transplacental passage of maternal auto-antibodies is already known to be the cause of transient neonatal dysfunction, especially against the TSH receptor and, more rarely, the anti-TPO or anti-thyroid drugs[7]. When it comes to this particular patient, there was no evidence of thyroid change in the neonatal period, nor of the use of anti-thyroid drug by the mother.

Changes in the TSH, even transactional ones, can affect the infant's growth and development in varying levels. But this child had other factors that might have contributed to the transient hypothyroidism. The child had hypoglycemia on several occasions, hypotonia and hypoactivity shortly after birth, severe systemic deterioration after surgical stress with evolution to hypertonia, repeated seizures, and worsened food refusal, which was already verified since the child had 11 days of life and worsened dramatically over the course of their clinical evolution. And still, in addition to that, the general deterioration of the senses, vision alterations, led the examiners to think more than once in the diagnosis "innate metabolism errors" (IME) which, however, has not been confirmed so far, even if the evolution of the child can still show other characteristics which can evolve with time[8].

The range of alterations in these patients is broad and can only be completed after a thorough metabolism evaluation, because it is necessary to discard disorders related to food-poisoning, which could involve the energetic metabolism or complex molecules, and that is not always possible[9]. The infant's karyotype was normal.

Later exams, such as a comparative genomic hybridization (ARRAY-CGH), which is still not available to this service, could boost the diagnoses through cytogenetics and through the genomic hybridization technique, as it presents a resolution much greater than that of conventional techniques, allowing for the viewing of changes 100 times smaller than those observable in conventional microscopy. This is already a gold standard technique with patients who (as in this particular case) presented late neuropsychomotor

development without any other causes, accompanied by growth retardation due to multiple congenital abnormalities. These analysis of abnormality could even explain the changes in the case just described[10-15].

The treatment for patients with sub-clinical hypothyroidism is controversial, and a greater number of prospective studies are necessary in order for an adequate therapeutic protocol to be established. In addition, evaluating the thyroid function in patients with neuropathy is suggested.

CONCLUSION

In neuropathic patients, as the one in the case just described, slightly elevated and instable levels of TSH are reported, even though its etiology is variable and/or unknown. The clinical and laboratory follow-up proved to be very important in the choice of therapy, due to the potential risk of evolution to a manifest thyroid disease.

Similarly, monitoring and establishing correlations between clinical and laboratory findings allow for this patient to be taken to a hemodynamic stabilization and to a briefer form of homeostasis.

The diagnostic investigation regarding the causes of the neuropathy is paramount in order for the gravely ill patient to receive the most precise and effective treatment. An initial diagnostic approach with a few biochemical essays as its basis, it could be argued, can be used rationally in the clinical suspicion of a neurological pathology.

This description of a clinical case raises the question of whether or not the evaluation of the thyroid function in the neuropathic patients should be given special attention from health professionals. This is a rare case, in which different clinical conditions are superimposed, such as neuropathy, adrenal and thyroid changes, in addition to grave infections, showing that the control of the thyroid changes, even in a patient with sub-clinical hypothyroidism, contributes to a significant improvement in the general situation of a patient.

REFERENCES

1. Ghasemi M, Hashemipour M, Hovsepian S, Heiydari K, Sajadi A, Hadian R, et al. Prevalence of transient congenital hypothyroidism in central part of Iran. J Res Med Sci. [Internet]. 2013; 18(8):699-703 [cited 25-05-2016]. Available in: http://www.ncbi.nlm.nih.gov/pubmed/24379847

2. Dias VM, Nunes JC, Araújo SS, Goulart EM. Avaliação etiológica da hipertirotropinemia em crianças com síndrome de Down. J pediatr [online]. 2005; 81:79-84 [cited 25-05-2016]. Available in: http://www.scielo.br/pdf/jped/v81n1/v81n1a15.pdf

3. Alves C. Desafios no manejo da hiperplasia adrenal congênita causada pela deficiência da 21-hidroxilase. Rev paul pediatr [Internet]. 2007; 25(3):200-1 [cited 25-05-2016]. Available in: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0103-05822007000300001&lng=en. http://dx.doi.org/10.1590/S0103-05822007000300001.

4. Gonçalves M, Teles A, Coelho E, Pontes M, Mendes I, Rego A. Hiperplasia congénita da suprarrenal no período neonatal. Sociedade Portuguesa de Neonatologia [Internet]. Consensos 2014 [cited 25-05-2016]. Available in: http://www.lusoneonatologia.com/site/upload/consensos/2014-Hiperplasia_SR_congenita.pdf

5. Longui CA. Insuficiência adrenal primária na infância. Arq Bras Endocrinol Metabol [Internet]. 2004; 48(5):739-45 [cited 25-05-2016]. Available in: http://www.scielo.br/pdf/abem/v48n5/a20v48n5.pdf

6. Bhering AR; Almeida ACG, Gomes BX, Lopes LCS, Moreira PAM, Silva APO, et al. Estudo epidemiológico da evolução de neonatos com hipertireotropinemia no Estado de Minas Gerais – Brasil. Rev Med Minas Gerais [Internet]. 2015; 25(Supl 5):S26-S29 [cited 25-05-2016]. Available in: http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&src=google&base=LILACS&lang=p&nextAction=lnk&exprSearch=771276&indexSearch=ID

7. Silva LO, Dias VMA, Silva IN, Chagas AJ. Hipotiroidismo congênito transitório: perfil das crianças identificadas no programa estadual de triagem neonatal de Minas Gerais, Brasil. Arq Bras Endocrinol Metab [Internet]. 2005; 49(4):521-8 [cited 25-05-2016]. Available in: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-

27302005000400009&lng=en. http://dx.doi.org/10.1590/S0004-27302005000400009.
8. Saudubray JM, Sedel F, Walter JH. Clinical approach to treatable inborn metabolic diseases: An introduction. J Inherit Metab Dis [Internet]. 2006; 29(2-3):261-74 [cited 25-05-2016]. Available in: http://www.ncbi.nlm.nih.gov/pubmed/16763886
9. Jardim LB, Prolla PA. Erros inatos do metabolismo em crianças e recém-nascidos agudamente enfermos: guia para o seu diagnóstico e manejo. J Pediatr [Internet]. 1996; 72(2):63–70 [cited 25-05-2016]. Available in: http://www.jped.com.br/conteudo/96-72-02-63/port.pdf
10. Bastos R, Ramalho C, Dória S. Prevalence of Chromosomal Abnormalities in Spontaneous Abortions or Fetal Deaths. Acta Med Port [Internet]. 2014; 27(1):42-8 [cited 25-05-2016]. Available in: http://actamedicaportuguesa.com/revista/index.php/amp/article/view/3952
11. Ministério da Saúde (Br). Agência Nacional de Saúde Suplementar. Rol de procedimentos e eventos em saúde 2014. [Internet]. Rio de Janeiro (RJ): Ministério da Saúde; 2014 [cited 25-05-2016]. Available in: http://www.ans.gov.br/images/stories/Materiais_para_pesquisa/Materiais_por_assunto/ProdEditorialANS_Rol_de_Procedimentos_e_eventos_em_saude_2014.pdf
12. Vermeesch JR, Brady PD, Sanlaville D, Kok K, Hastings RJ. Genome-Wide Arrays: Quality criteria and platforms to be used in routine diagnostics. Human Mutation [Internet]. 2012; 33(6):906-15. [cited 25-05-2016]. Available in: http://www.academia.edu/17992648/Genomewide_arrays_Quality_criteria_and_platforms_to_be_used_in_routine_diagnostics
13. Ministério da Saúde (Br). Protocolo de Tratamento e Acompanhamento Clínico de Crianças com Hipotireoidismo Congênito do Programa de Triagem Neonatal de Minas Gerais. Belo Horizonte: NUPAD/FM/UFMG, 2012.
14. Bareto N. Análise de CNVs e indicação clínica em indivíduos com deficiência intelectual e outros distúrbios do desenvolvimento diagnosticados por CGH Array. [Dissertação de mestrado]. Florianópolis (SC):Universidade Federal de Santa Catarina/UFSC; 2015. 127p.
15. Souza KRS. Avaliação citogenômica em indivíduos com cardiopatias congênitas conotruncais. [Dissertação de mestrado]. Porto Alegre (RS): Universidade Federal do Rio Grande do Sul/UFRGS; 2015. 33p.

CONTRIBUTIONS

Jussara Silva Lima was responsible for the bibliographical survey and for the writing of the article, in addition to data collection from the medical record. **Valéria Cardoso Alves Cunali** was responsible for the bibliographical survey and for the writing of the article**. Luciana de Azevedo Tubero** reviewed the medical records, took part in the bibliographical survey and in the writing of the article. **Vandui da Costa** took part in the bibliographic survey and in the writing of the article.

How to cite this article (Vancouver):
Lima JS, Cunali VCA, Tubero LA, Santos VS. Transitory hiperthyrotropinemia and alteration of 17-OH-progesteron on neuropath infant. REFACS [Online]. 2016 [cited in *(insert day, month and year of access)*]; 4(3):254-260. Available in: *(access link)*. DOI: 10.18554/refacs.v4i3.1778.

How to cite this article (ABNT):
LIMA, J.S.; CUNALI, V.C.A.; TUBERO, L.A.; SANTOS, V.S. Transitory hiperthyrotropinemia and alteration of 17-OH-progesteron on neuropath infant. **REFACS**, Uberaba, MG, v. 4, n. 3, p. 254-260, 2016. Available in: *(access link).* Access in: *(insert day, month and year of access)*. DOI: 10.18554/refacs.v4i3.1778.

How to cite this article (APA):
Lima, J.S., Cunali, V.C.A., Tubero, L.A. & Santos, V.S. (2016). Transitory hiperthyrotropinemia and alteration of 17-OH-progesteron on neuropath infant. *REFACS*, 4(3), 254-260. Recovered in: *(insert day, month and year of access)*. *(access link)*. DOI: 10.18554/refacs.v4i3.1778.