UNUSUAL CASE OF THIAMINE RESPONSIVE MEGALOBLASTIC ANEMIA

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PRÉSENTATION INHABITUELLE D'UNE ANÉMIE MÉGALOBLASTIQUE THIAMINE SENSIBLE

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RÉSUMÉ

Prérequis : L'anémie mégaloblastique thiamine sensible est un syndrome rare définie par l'association d'une anémie mégaloblastique, un diabète et une surdité et qui répond à des degrés variables au traitement par la thiamine.

But : rapporter une observation inhabituelle de ce désordre rare.

Observation : Nous rapportons l'observation d'un enfant âgé de 4 ans qui présentait ce syndrome. Ce patient présentait en plus de la triade classique du syndrome, une leuco- neutropénie, une hépatosplénomégalie, des anomalies cardiaques incluant l'absence d'onde P et une insuffisance mitrale et tricuspidienne, une rétinite pigmentaire, un nystagmus et une lésion ischémique à l'IRM sans corrélation clinique. Le taux de lactacidémie et le rapport lactate/pyruvate étaient élevés. La mutation MELAS n'a pas été retrouvée. Le traitement par la thiamine a permis de normaliser le taux de l'hémoglobine, le chiffre des globules blancs la glycémie et le taux des lactates. Durant un suivi de 3 ans, ce patient n'a pas nécessité d'insulinothérapie.

Conclusion : Ces données signent le rôle crucial que joue la thiamine pour les cellules et les tissus et son importance dans le fonctionnement de la chaine respiratoire.

MOTS-CLÉS

diabète ; anémie mégaloblastique thiamine sensible ; enfant ; déficit de la chaine respiratoire.

SUMMARY

Background: Thiamine- responsive megaloblastic anemia syndrome is a rare autosomal recessive disorder defined by the occurrence of megaloblastic anemia, diabetes mellitus, and neurosensoriel deafness, responding in varying degrees to thiamine treatment.

Aim: Report an unusual case of this rare disorder

Case report: We report the case of a four-year-old boy who presented unusual features of thiamine- responsive megaloblastic anemia. In addition to the typical triad of the syndrome, he presented leuconeutropenia, hepatosplenomegalia, cardiac abnormalities including absent P waves, mitral and tricuspid insufficiency, retinitis pigmentosa, nystagmus, developmental delay and a brain Magnetic resonance imaging ischemic lesion. Lactate levels in serum and the lactate/ pyruvate ratio were increased. The mitochondrial mutation m.3243A>G located in MTTL1 gene encoding for transfer RNA leucine (tRNALeu(UUR)) was not found . Treatment with thiamine resulted in normalisation of the haemoglobin level, white cell count, and glucose and lactate levels. On three years follow up, the patient did not need insulinotherapy.

Conclusion: These data sign the crucial role that thiamine plays for many cells and tissues and its importance in the activity of the respiratory chain.

KEY-WORDS

child; diabetes; thiamine responsive megaloblastic anemia; respiratory chain deficiency

حالة غير عادية لفقر الدم ضخم الأرومات المتجاوب مع " التيامين "

الباحثون : تينسي . ف - بن عمر. س - كعباشي. ن - بن لسود . م - بوستي. ك - بوسنينا. س.

فقر الدم ضخم الأرومات المتجاوب مع التيامين هو متلازمة نادرة تتميز بتزامن فقر الدم ضخم الأرومات مع السكري ومع فقدان السمع وهذه الإصابة النادرة تتجاوب بمستويات مختلفة مع " التيامين."

تستعرض دراستنا حالة طفل عمره 4 سنوات مصاب بهذه المتلازمة لكنه يحمل مع الأعراض الثلاثة التقليدية أعراضا أخرى بدون تداخل سريري واضح.

العلاج بواسطة " التيامين " مكننا من الحصول على نتائج طبيعية في خصوص الهيموغلوبين وعدد الكريات البيض ونسبة السكري في الدم ونسبة اللاكطاط وخلال المتابعة لمدة 3 سنوات لم يلجأ المريض إلى العلاج بالأنسولين.

تمكننا هذه المعطيات من ملاحظة الدور الذي تقوم به " التيامين "مع الخلايا والأنسجة و أهميتها في وظيفة السلسلة التنفسية.

الكلمات الأساسية : سكري - فقر الدم ضخم الأرومات المتجاوب مع التيامين - طفل - عجز في السلسلة التنفسية.

Thiamine responsive megaloblastic anemia, first described by Roger et al [1], is an autosomal recessive disorder with childhood onset. The main clinical manifestations of the syndrome are megaloblastic anemia, diabetes mellitus, and neurosensoriel deafness. In addition to the cardinal triad features of thiamine responsive megaloblastic anemia, abnormalities of the retina and optic nerve, congenital heart disease, arythmya, have been reported in some patients [2,3,4,5].

We report the case of a four-year-old Tunisian boy who presented unusual features of thiamine responsive megaloblastic anemia.

CASE REPORT:

A four-year-old boy was admitted to the hospital for diabetes mellitus. The boy was born to consanguineous Tunisian parents at term by normal delivery after an uneventful pregnancy. There was no history of neonatal distress and his Apgar score was nine at one minute. He presented seizures at the age of eight months .He had a developmental delay. He could not speak; he had hearing loss and was an agitated and disturbed boy. He was the third child of the family. His two sisters died at the age of two and three years. One sister had diabetes mellitus and splenomegalia and the other one had anemia and splenomegalia. This patient had polyuria and polydipsia for the last one week before admission. On physical examination, the child could not hear or speak and was agitated. His weight was 17kg and height was 97cm (-1 standard deviation), temperature was 37.5°C, heart rate was 100 beats/min and blood pressure 100/60 mmHg. He had a systolic, ejection-type murmur, hepatomegalia, and splenomegalia. He had no signs of cardiac failure. Laboratory analysis showed hyperglycemia with plasma glucose level of 18 mmol/l, glucosuria and ketones in the urine, hypochromic microcytic anemia with haemoglobin level of 6.9 g/dl, mean corpuscular volume of 64.8 fl, mean corpuscular haemoglobin of 20 pg, and a low reticulocyte index of 0.5%. He had also leuconeutropenia with white blood cell count of 2700/mm3 (15.8% neutrophils, 77% lymphocytes, 7.1% monocytes) and platelet count of 169 000/mm3. The peripheral smear showed anisopoikilocytosis with macrocytosis and microcytosis. The bone marrow aspirate showed normal cellularity but abnormal erythropoiesis with megaloblastic and dyserythropoietic changes, ringed sideroblasts up to 50%. He had low iron level of 7 μg/l (reference range: 9-30μg/l). Hemoglobin electrophoresis was normal. Creatinine, electrolytes and liver enzymes were normal. Insulin islet cell antibodies and insulin antibodies were negative. Peptide C was of 0.91μg/l (reference range 1.15-4.5μg/l). An audiogram revealed a profound neurosensoriel hearing loss. His ophthalmic examination showed retinitis pigmentosa and nystagmus. Doppler cardiography showed mitral and tricuspid insufficiency and electrocardiogram revealed absent P waves. Lactate levels were increased in the serum (2.74 mmol/l and 3.32 mmol/l) and lactate/ pyruvate ratio before feeding was of 30 and one hour after feeding of 66. Plasma amino acids and urine organic acids were normal. The mitochondrial mutation m.3243A>G located in MTTL1 gene encoding for transfer RNA leucine (tRNALeu(UUR)) and associated with Maternally Inherited Diabetes and Deafness and Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes syndrome was not found. Magnetic resonance imaging of the brain showed right parietal ischemic lesion about 1cm. Hemostasis tests were normal. Thyroid functions were normal. The diagnosis of thiamine responsive megaloblastic anemia was suggested and oral treatment with thiamine at the dose of 250 mg per day was initiated. Two weeks after thiamine treatment alone, reticulocytes rose to 3.5% (154000/mm3) and white blood cells to 7800 (35.2% neutrophils). This patient had also received iron therapy because of the iron deficiency associated to thiamine responsive megaloblastic anemia. After two months of the combined treatment a complete resolution of anemia was observed. Insulinotherapy was successfully stopped at one month after beginning treatment with thiamine. The serum lactate level was also normalized (1.35 mmol/l) and hepatomegalia and splenomegalia disappeared with thiamine therapy.

At the follow up, the thiamine therapy was interrupted and the diabetes reappeared. The resumption of the treatment with thiamine led to the normalization of the blood glucose levels within few days. At three years of follow up, this patient didn't need any insulinotherapy and glucose levels in plasma were normal. Audiometry failed to demonstrate any amelioration and on the electrocardiogram, P waves were absent.

DISCUSSION

Thiamine responsive megaloblastic anemia is an autosomal recessive disorder caused by a mutation in the thiamine transporter gene SLC19A2 (TRMA; OMIM 249270). The gene for thiamine responsive megaloblastic anemia is located to chromosome 1q23.3 [4]. The SLC19A2 thiamine transporter belongs to a family of three solute carriers, two of which mediate the transport of thiamine, a cation at physiological pH [6]. Thiamine uptake is thought to take place via two pathways: active transport by a saturable, high-affinity carrier; and passive uptake by a low-affinity carrier. Once taken up by cells, thiamine is converted into its active form, thiamine pyrophosphate, which is required for the proper functioning of four enzymes: the pentose phosphate shunt enzyme transketolase, and three multi-enzyme complexes involved in oxidative decarboxylation (pyruvate dehydrogenase, ·-ketoglutarate dehydrogenase and branched-chain acid dehydrogenase). Barrett et al have demonstrated reduced ·-ketoglutarate dehydrogenase activity in the myocytes of patients with thiamine responsive megaloblastic anemia, which increases with exogenous thiamine [7]. Stagg et al documented the absence of the high-affinity thiamine transporter on fibroblasts of thiamine responsive megaloblastic anemia patients, and demonstrated that a low thiamine concentration may cause cell death by apoptosis [8].

Megaloblastic anemia is the main haematological manifestations. Thrombocytopenia has been less commonly reported and leucopenia is rare in thiamine responsive megaloblastic anemia patients probably due to different needs

of the hematopoietic progenitor cells to the intracellular thiamine [9]. Some patients exhibited severe pancytopenia with bone marrow dysplasic changes [4]. The combination of megaloblastic finding and ringed sideroblasts at bone marrow characterizes thiamine responsive megaloblastic anemia. It is suggestive of a myelodysplasic state and has lead authors to term this condition "thiamine responsive myelodysplasia" [4]. Our patient had megaloblastic anemia on bone marrow study; however on the automatic scanning of blood cells, it was noted hypochromic microcytic anemia due probably to an additional iron deficiency. These can misdiagnose the entity which is characterized by macrocytic anemia. The association of anemia even microcytic, diabetes mellitus and deafness should suggest thiamine responsive megaloblastic anemia and make manuel differential blood cells to search macrocytes. All the haematological anomalies found in our patient resolved after thiamine therapy. Hepatomegalia and splenomegalia are unusual features of thiamine responsive megaloblastic anemia. Our patient had hepatomegalia and splenomegalia which disappeared with thiamine therapy. His two sisters, who presented probably the same disease and died, had also splenomegalia.

The diabetes in thiamine responsive megaloblastic anemia is generally a non type I. the patients do not present acanthosis nigricans or obesity suggesting insulin resistance, and are negative for antibodies to islet cells and glutamic acid decarboxylase [9]. Diabetic ketoacidosis is rare and diabetes mellitus is diagnosed in the most cases coincidentally. However, our patient presented diabetic ketoacidosis. The response to thiamine therapy in 17 patients reported in the litterature showed no improvement of glycemic control in eight of them, partial response with reducing temporally the insulin dose in five patients, and an improvement of the diabetes in four patients for a variable period [10]. Bappal et al reported an improvement of the diabetes in two siblings with thiamine responsive megaloblastic anemia on five years follow up [11]. Ricketts et al studied 13 patients from seven families and had follow-up data for a median of nine years. All patients presented with non-immune, insulin-deficient diabetes mellitus, sensorineural deafness and a variable anemia in the first five years of life. The diabetes mellitus responded to oral thiamine hydrochloride 25 mg per day, but during puberty thiamine supplements became ineffective, and almost all patients required insulin therapy [12]. Our patient had a non type I diabetes which completely responded to 250 mg of thiamine per day. We did not try smaller doses which may have been equally effective.

With regard to the cardiac defects, the rate of observed cardiac malformations and myocardial dysfunction in thiamine responsive megaloblastic anemia patients is much higher than that in the population at large. Cardiac anomalies include cardiac rhythm disturbance and congenital structural anomalies [13]. The analysis of the electrocardiogram of this patient revealed absent P waves during what appears to be a normal sinus rhythm. The lack of P waves should be attributed to the metabolic disturbances associated with thiamine deficiency in thiamine responsive megaloblastic anemia syndrome. Our patient had also mitral insufficiency; to the best of our knowledge this anomaly has never been reported.

Optic nerve atrophy and retinal dystrophy have been reported in a small number of patients with thiamine responsive megaloblastic anemia. Human retinal pigment epithelial cells play a pivotal role in supplying thiamine to the highly metabolically active retina. Subramanian et al demonstrated the existence of a specialized and regulated uptake process for thiamine in a cellular model of human retinal pigment epithelia that involves the human thiamine transporter-1 (hTHTR-1) and the human thiamine transporter-2 (hTHTR-2) [14]. Nystagmus is an uncommon feature in thiamine responsive megaloblastic anemia. Our patient presented retinitis pigmentosa, nystagmus, seizure and development delay; these features are more common in respiratory chain deficiency.

Ischemic stroke are exceedingly rare in thiamine responsive megaloblastic anemia and only three cases were reported. In the case reported by villa et al the woman had been treated with estro-progestins for one year before thrombotic event and the authors suggested that her stroke may be related to the use of oral contraceptive pills [10]. In the case reported by Ho et al, the authors presumed that the stroke may result from diabetes, dehydration and hypercoagulable state [15]. In the case of Scharfe et al [16], the girl had parietal cortical lesion without clinical correlate. She had severe deficiency of pyruvate deshydrogenase which are expected but also unreported severe complex I of the respiratory chain deficiency. Morphological and ultrastructural examination of skeletal muscle didn't show definite mitochondrial abnormalities and the frequent mitochondrial DNA (mtDNA) mutations associated mitochondrial encephalomyelopathies were excluded. This case is the closest to our case. The diagnosis of thiamine responsive megaloblastic anemia in our patient was based on clinical features, the response to thiamine therapy and the absence of the m.3243A>G mutation located in MTTL1 gene (OMIM 590050) encoding for transfer RNA leucine (tRNALeu(UUR)) and associated with Maternally Inherited Diabetes and Deafness and Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes syndrome (17,18). It was difficult for us to differentiate between thiamine responsive megaloblastic anemia and respiratory chain deficiency because the main symptoms of thiamine responsive megaloblastic anemia, sideroblastic anaemia, diabetes, and deafness, as well as many of the additional symptoms described here, are more frequently found in diseases with respiratory chain deficiency. Our patient had also increased lactate levels and the lactate/pyruvate ratio before treatment, and lactate levels were normalized after thiamine therapy. These findings sign the importance of thiamine to the activity of the respiratory chain and the cerebral lesion found in our patient may represent a metabolic decompensation of the energy dependant cortex, as it is seen in Mitochondrial myopathy, Encephalopathy, Lactic Acidosis and Stroke-like episodes syndrome [19]. Respiratory chain activities should be determined in this patient and in others thiamine responsive megaloblastic anemia patients and correlations between genotype, biochemistry, and phenotype should be established.

Figure 1 : Axial Spin Echo T1 Magnetic Resonance Imaging showing a right prerolandic lesion of the periventricular white matter with hypointense signal

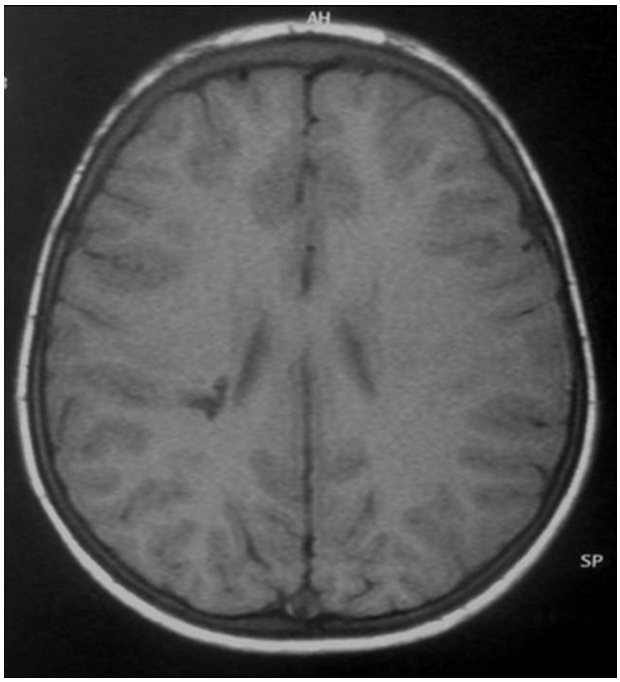


Figure 2 : Axial Spin Echo T2 Magnetic Resonance Imaging showing a lesion with hyperintense signal

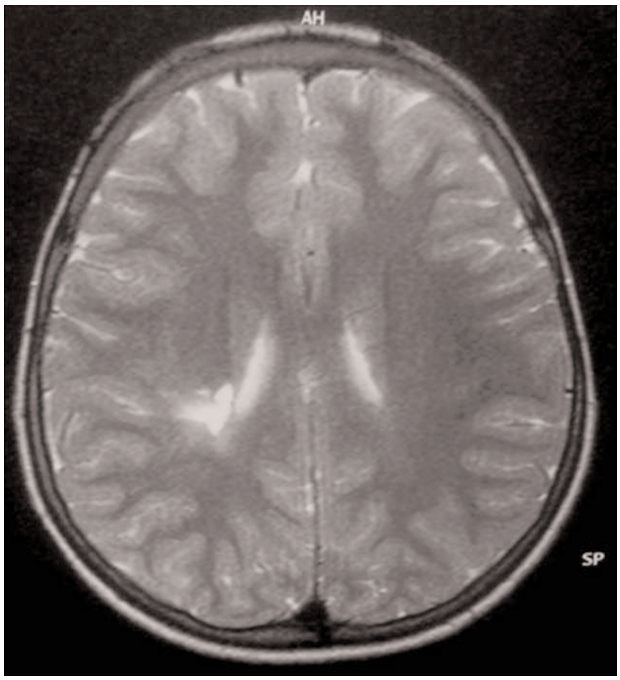


Figure 3 : Axial Inversion Recovery T2 magnetic resonance imaging showing lesion with hypointense signal surrounded by hyperintense signal

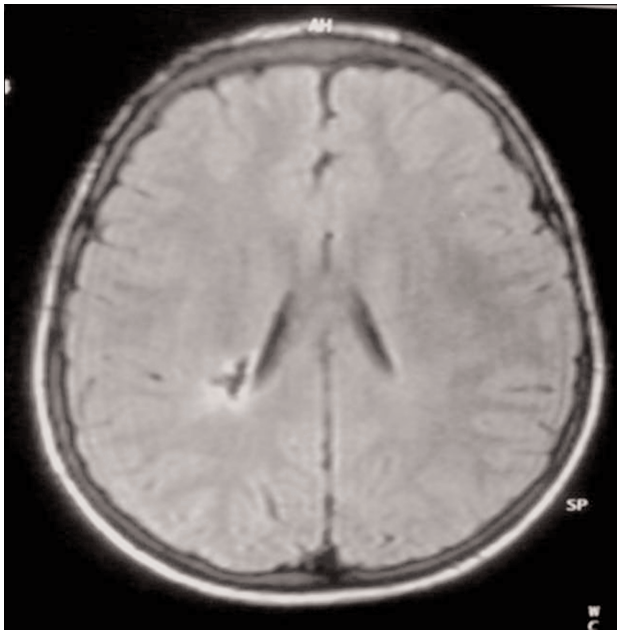
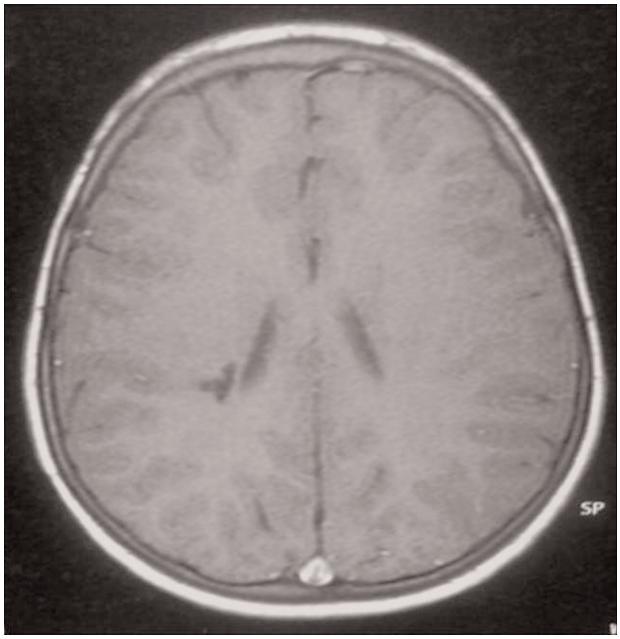


Figure 4 : Axial T1 post contrast magnetic resonance imaging showing hypointense signal lesion without enhancement.



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