

Endogenous pellagra and cerebellar ataxia without aminoaciduria. Hartnup disease?^{*}

Pelagra endógena e ataxia cerebelar sem aminoacidúria. Doença de Hartnup?^{}*

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Abstract: A seven-year-old boy with history of convulsion, cutaneous hyperpigmentation in sun-exposed areas and recurrent episodes of cerebellar ataxia is presented. Once established the clinical diagnosis of Hartnup disease, treatment with nicotinamide was started, with improvement. Laboratorial results did not confirm aminoaciduria nor other identified metabolic changes. In Hartnup disease, defective renal and intestinal transport of neutral amino acids occurs, resulting in reduction of tryptophan to produce to nicotinamide. Symptomatic cases present with intermittent episodes of cerebellar ataxia, pellagra-like skin rash and mental disturbances. Urinary chromatographic amino acid pattern confirms diagnosis; however, cases compatible with Hartnup disease, but without aminoaciduria, have been reported.

Keywords: Aminoaciduria, renal; Hartnup disease; Pellagra

Resumo: Menino, 7 anos, com história de convulsão, hiperpigmentação cutânea em áreas de exposição solar e episódios recorrentes de ataxia cerebelar. Estabelecido diagnóstico clínico de doença de Hartnup, foi tratado com nicotinamida, com melhora. Análises não confirmaram aminoacidúria ou outras alterações metabólicas. Na doença de Hartnup ocorre defeito no transporte renal e intestinal de aminoácidos neutros, reduzindo triptofano disponível para produção de niacina. Cursa com ataxia cerebelar intermitente, erupções cutâneas pelagroides e distúrbios mentais. Aminoacidúria em cromatografia urinária confirma diagnóstico, porém são descritos casos compatíveis com doença de Hartnup sem aminoacidúria.

Palavras-chave: Aminoacidúria renal; Doença de Hartnup; Pelagra

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INTRODUCTION

Hartnup disease is a rare recessive autosomic genetic condition, which affects mainly children between five and 15 years of age,¹ described by Baron and colaborators² in 1956. Its physiopathology is related to a defect in renal proximal tubule and jejunal bowel transport of neutral aminoacids, the genesis of its clinical manifestations being attributed to a fall in niacin (vitamin B3) levels, caused by a decrease in the absorption of its precursor, tryptophan.^{1,3}

Multiple clinical presentations may be recognized, ranging from completely asymptomatic subjects, or a more frequent presentation identified by pellagra-like photosensitive dermatitis associated to intermittent cerebellar ataxia and neuropsychiatric symptoms,^{3,4} to, in some cases, the development of more severe presentations with progressive neurodegenerative lesions^{2,4} and death. Exposure to sunlight, fever, use of sulphonamides, emotional stress, infections and irregular or inappropriate diet are all factors described as likely triggers of symptoms and signs.^{1,3,5-7}

Diagnosis of Hartnup disease is established by the identification of hyperaminoaciduria in urine chromatography. Absence of hyperaminoaciduria in patients with clinical picture of Hartnup disease, nevertheless, has been described by some authors.^{5,7,9} Tratement is based on oral administration of nicotina-mide (40 to 250mg/day).

CASE REPORT

White, seven-year-old boy, coming from a rural area, single child of non-cosanguineous healthy parents, was seen in an emergency room, in July 2003, when the mother reported an episode of generalized seizure of sudden onset in his home, one hour before. She denied recent or remote history of head trauma, central nervous system infections, similar seizures or any other associated diseases, nor use of any medictaion.

Mother reported that in two ocasions (June 2001 and July 2002) the child developed non-pruritic erythematic-desquamative cutaneous lesions, initially wine-colored, later evolving to reddish desquamative areas, always restricted to areas of sunlight exposure, associated with important gait alterations (staggering gait), which lasted for two or three weeks, with spontaneous resolution of both the lesions and gait, having received the diagnosis of pellagra.

Upon hospital admission, was noteworthy the dry aspect of the skin, which was erythematic, with areas of superficial desquamation located in face, nape, neck, back of the forearms, hands (Figure 1A), legs and feet (Figure 1B). He denied alterations of intestinal habit. Neurologically, he was conscious, auto and alo-oriented, had global hyperreflexy of

deep tendons, had no signs of meningeal irritation, presented ataxic gait (enlarged base and rigid joints), which evolved to inability to deambulate. Normal eye fundus examination. Other systems with no alterations. Anthropometric evalutaion: weight of 25 kg (p75) and 118 cm of stature (p25).

Upon hospitalization, laboratorial exams of blood count, uranalysis and 24 hour urine, blood glucose electrolytes and proteins (total and fractions), hepatic and renal function tests, cephalorachidian fluid analysis (including bacterioscopy, and assessment for the presence of fungi, toxoplasmosis and VDRL), thorax and skull x-ray, were carried out, all with normal results. Computerized tomography and magnetic resonance of the head revealed no anomalies. Resting and hyperventilation-activated electroencephalogram (EEG) revealed diffuse disorganization in the tracing. His bone age was calculated to be seven years, according to Pyle criteria for male patients.

Plane and bi-dimensional aminoacid paper chromatography did not reveal elevation in urinary aminoacid excretion. Seric aminoacid levels were within normal standards. Urinary indican was not detected, nor was any other alteration in screening tests for innate errors of metabolism. There is no report in the family of any similar case, nor of disorders that suggest any especific metabolic disease.

The patient remained in the hospital for 11 days, using polyvitamin B complex (80 mg/day of nicotinamide). With progressive improvement in both the cutaneous and neurologic picture beginning on the fourth day of hospitalization, he was discharged with normal gait and almost complete resolution



FIGURE 1: Patient upon admission in the hospital, presenting erythematic-desquamative cutaneous lesions in areas of sun exposure; (A) face, neck and dorsal surface of upper limbs; (B) lower limbs

Reported after written consent of patient/legal guardian



FIGURE 2: Aspects of lesions in face and neck before beginning of treatment (A) and on the ninth day of nicotinamide administration (B)

of the pellagra-like dermatitis (Figure 2, A and B). In the three following months, he returned to the Pediatrics outpatient clinic, with no symptoms and still in use of polyvitamin B complex (nicotinamide 20mg/day).

DISCUSSION

Clinical manifestations of pellagra-like dermatitis – characterized by erythematous-desquamative lesions in areas of sun exposure – associated to the simultaneous appearing of intermittent cerebellar ataxia, up to the point of inability to deambulate, fit perfectly the present patient to the clinical diagnosis of Hartnup disease in its classical presentation. Moreover, secondary findings, such as emotional lability, global hyperreflexy of deep tendons, seizure and diffuse EEG alterations, have been cited by other authors as possible findings in patients with Hartnup disease.^{3,5,6,9}

The intermittent character of the clinical alterations, with periods of exacerbation, mainly in June-July period, identical to what has been reported by Da Gloria and collaborators,⁹ is due, very likely, according to the mother's report, to a significant exposure to sunlight in this period, which is the same a school vacations, besides the fact that seasons are little defined in the region.

Goulon and collaborators⁵ subdivide cases of pellagra into exogenous and endogenous. Exogenous pellagra is associated to B3 hypovitaminosis, induced mainly by tryptophan-poor diet, and is not associated to an increase in renal excretion of aminoacids, unlike endogenous pellagra, whose main example is Hartnup disease, where the fall in niacin levels are

the result of a defect in renal and intestinal tryptophan absorption.

Vitamin deficiency pellagra should be considered the main differential diagnosis, which is excluded, however, by the lack of typical gastrointestinal disorders of the syndrome (mainly diarrhea) and by difference between neuropsychiatric manifestations presented by the patient and the characteristic dementia of exogenous pellagra. Moreover, daily ingestion of cow milk (rich in tryptophan), seasonality of clinical alterations and inexistence of similar signs and symptoms of other children living in the same rural area as the patient are also factors that add up to exclude the diagnosis of nutritional pellagra. Other possible etiologies for endogenous pellagra, besides Hartnup disease, are prolonged use of isoniazide or 6-mercaptopurine and carcinoid tumors, none of those being observed in the present patient.⁵

Thus, given the clinical presentation of the patient and the efficacy of proposed treatment, responsible for remission of both the cutaneous lesions and neurological alterations, we suggest the diagnosis of endogenous pellagra. However, similarly to cases described by Goulon and collaborators⁵ (France), Da Gloria and collaborators⁹ (Brazil), Borrie and Lewis⁷ and Tada and collaborators⁸ (Japan), also in the present case hyperaminoaciduria, typical of Hartnup disease, was not evidenced by plane and bidimensional aminoacid paper chromatography.

A possible and already considered explanation for the lack of aminoaciduria in patients with clinical picture of Hartnup disease could be an alteration in tryptophan metabolism, which in turn would affect a disturbance in its transformation into cirunenin as a result of a defect in the enzyme tryptophan pyrrolase.⁸ Or, still, as in the case described by Borrie and Lewis,⁷ dichotomy between clinical and laboratory findings could be due to a possible heterozygotic genotype of the evaluated patient.

However, as in the cases reported by Goulon and collaborators⁵ and Da Gloria and collaborators,⁹ distinguishing whether niacin deficiency was a result of alteration in the metabolism or renal/intestinal transportation of tryptophan was not possible. Da Gloria and collaborators⁹ have questioned whether the presence of signs and symptoms of Hartnup disease without association with any metabolic dysfunction identified up to the present, or with increased urine levels of aminoacids could even be a new entity, which, as believe the authors, should be the target for further investigation, given the singularity and similarity between the presently described case and the others already cited. □

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