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METACHROMATIC LEUKODYSTROPHY: ABOUT 04 CASES AND REVIEW OF THE LITERATURE

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Abstract:-
Metachromatic leukodystrophy (MDL) is a hereditary lysosomal inheritance disorder with autosomal recessive transmission. It is due to the deficiency of the enzyme arylsulphatase A or it's activating protein soposin B. It can occur at any age, but the infant form is the most frequent. The diagnosis is based mainly on data from brain magnetic resonance imaging and the arylsulfatase a dosage. We report a serie of 04 cases collected in the pediatric department at Rabat's children's hospital, allowing us to know the clinical and paraclinical characteristics of the disease, as well as the current situation in the field of therapeutic.

Keywords: *Metachromatic leukodystrophy - arylsulphatase a – demyelinisation*

INTRODUCTION:

Metachromatic leukodystrophy is an autosomal recessive hereditary disease that affects the central and peripheral nervous system. It is a rare disease that is part of lysosomal diseases as well as leukodystrophies[1]. It is due to a deficiency of Arylsulfatase a (ASA) or, in rare cases, to a deficiency of an enzyme activating protein called SAP-B (sphingolopid activating protein B) or saposin B [1]. This deficiency is responsible for an accumulation of sulphatides in various cells, particularly in the white matter of the central and peripheral nervous system. It leds to progressive demyelinisation responsible of neurological symptoms who occurs at different ages and hence that classifies the disease in 3 forms: Infant (1 to 2 years), juvenile (3 to 16 years) and adult.The infantile form is the most frequent [2-3]. We report 4 clinical observations of infantil metachromatic leukodystrophy.

Observations:

Case 1: It is a 22-month-old male infant, born from a second-degree consanguineous marriage, unique to his family, without a particular pathological history, admitted for motor regression. His psychomotor development was normal up to the age of 18 months, when the mother discovered walking disorders beginning with easy falling and then regression of walking (walking with support). The clinical examination found a weight, a size and a cranial perimeter compatible with the age, difficult autonomous march with a pyramidal syndrome (ROT alive and babinski positive).The patient had no cognitive retardation. Moreover, there was no dysmorphism or visceromegaly, the rest of the clinical examination was normal. The paraclinical examination revealed at the electromyogram (EMG) a slowing of the motor and sensitive conduction velocities with elongation of the motor distal latencies and the latencies of the F waves to the 4 limbs which are the signs of a demyelinating sensorymovy polyneuropathy. Cerebral MRI demonstrated diffuse central demyelination. The clinical profile and the radiological signs strongly evoked metachromatic leukodystrophy. Arylsulfatase A was assayed at 1 nM / h / mg (normal: 10 to 20 nM / h / mg) and confirmed the diagnosis. The initial management was based on functional rehabilitation and Genetic counseling. The evolution was marked by a regression on the psychomotor level: the child showed a severe polyhandicap and a deterioration of the cognitive functions.

Case 2: It is a 3-year-old and half male, born of a non-consanguineous marriage, elder sibling of two, without medical history, hospitalized for motor regression. The history of his illness started at the age of 2 years old by walking disorder: walking with support, sitting and bedridden, followed by the installation of balance disorders and a nystagmus, without convulsion or myoclonus. Clinical examination found a correct cranial perimeter for age, neurological examination showed pyramidal spasticity, live ROTs a positive babinski and a rotatory nystagmus; the rest was normal. Cerebral CT showed an appearance suggestive of leukodystrophy. The cerebral MRI showed the presence of a hyposignal T1, hypersignal T2 and T2 bilateral and symmetrical flair of the white peri-ventricular substance at the frontoparieto-occipital level. "Tigroid" and "combed" Of the substance in T2 (figure 1, 2). This is in favor of metachromatic leukodystrophy. The dosage of arylsulfatase A has been shown to be 1 Nm / h / mg. The diagnosis was metacromatic leukodystrophy due to arylsulfatase A deficiency. The evolution was marked by polyhandicap with severe malnutrition, epileptic seizures and repeated bronchopneumopathies. It is undergoing symptomatic treatment based on: functional rehabilitation, treatment of epileptic seizures and treatment of complications.

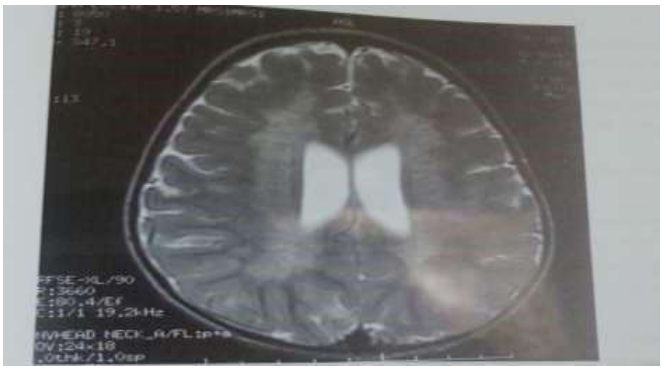

Figure 1: Cerebral MRI in axial section T2: Hypersignal bilateral and symmetrical white substance; with a tigroid and combed aspect indicating an alternation of the normal white substance and the white substance demyelinated

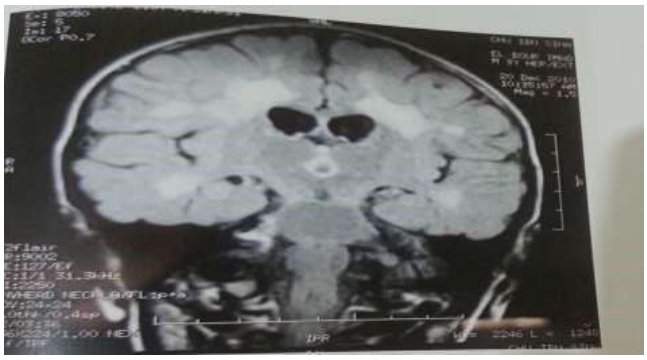

Figure 2: Cerebral MRI in coronal section FLAIR: hypersignal of the white substance of oval and semi-oval centers as well as temporal, bilateral with discrete reactional ventricular dilatation

Case 3: A 2-year-old male, born to first-degree consanguineous parents, 3rd of 3 siblings, no similar case in the family, who presented at the age of 18 months a psychomotor regression: starting with o walking disturbances, leading to incapacity of walking, of sitting and the rapid installation of axial hypotonia with speech regression and deglution disorders. Clinical examination found axial hypotonia, pyramidal spasticity with vivid ROT; there was no dysmorphic or visceromegaly. The rest of the examination was normal. Cerebral MRI demonstrated diffuse central demyelination (figure 3). The dosage of arylsulfatase A showed a level at 0 Nm / h / mg.The initial management was based on the functional rehabilitation of the patient. The evolution was marked by the worsening of the psychomotor regression and the degradation of his neurological state with occurrence of visual disorders. An ophthalmological opinion was in favor of a bilateral papillary pre-atrophy with reduction of all the ocular reflexes. The child was lost to follow-up.

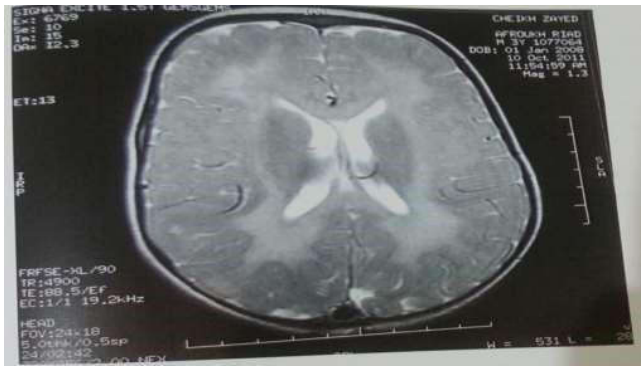

Figure 3: Cerebral MRI in axial section T2: hypersignal T2 of bilateral and symmetrical white hemispheric substance. It affects the frontal and occipital regions and extends to the knee and splenium of the corpus callosum as well as to the two external capsules

Case 4: It is a 3-year-old male, born of a first-degree consanguineous marriage, unique to his family, hospitalized for psychomotor regression observed since the age of 2 years, by Regression of the step of progressive agravation with swallowing disorders that have settled later. The clinical examination found a pyramidal syndrome and axial hypotonia. The EMG has objectified the absence of paroxysmal abnormalities or suffering signs. Cerebral MRI showed diffuse cerebral demyelination (figure 4). The diagnosis of metachromatic leukodystrophy was discussed and the arylsulfatase a assay was performed showing a level at 0 Nm / h / mg. The management was based on functional rehabilitation, as well as genetic counseling of parents.

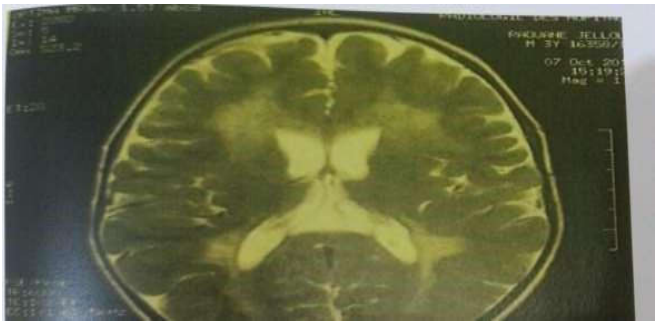

Figure 4: Cerebral MRI in axial section T2: signal anomaly in the range of the periventricular white substance in hypersignal T2 symmetric with predominance frontal and occipital

Discussion:

MDL is a rare metabolic diseases related to abnormalities of a lipid constituent of myelin, sulfogalactosylketamide. They result from an ASA deficiency, which hydrolyzes the sulphate binding with galactose present in sulfatide and other sulfated glycolipids. This enzyme requires, in order to hydrolyze the natural substrate, a sphingolipid activator protein (SAP-1) [1]. The ASA deficiency is the most common with an overall prevalence between 1/40 000 and 1/160 000. The ASA deficiency was fond in all our patients. However, due to pseudodeficiencies, it is necessary to demonstrate the sulfatide overload to confirm the pathological nature of the disease. [2-3]. MDL can appear at different ages of life. There are three clinical forms depending on the age of onset; the infantile, juvenile and adult form [1]. We described 4 infantile forms; this form is the most frequently encountered in the literature. It is also the most serious and rapidly evolving. It usually occurs between ten and 25 months of life. Psychomotor development is normal in the first year. The motor regression is generally done in stages, successively reaching the standing position, the sitting position and holding the head. Initially, three clinical forms can be seen: flaccid paralysis with hypotonia and abolition of osteotendinous reflexes, combination of Pyramidal signs with abolition of osteotendinous reflexes, which is the most frequent, and spastic paraplegia with vivid reflexes. At an advanced stage, pseudobulbar signs, stiffness of decerebration and / or postures of decortication with tonic spasms are observed, enhanced by stimulations. Epileptic seizures are exceptional and intellectual functions remain long preserved. This form is very serious, death occurrs between three and seven years [1]. During the MDL, accumulation of sulphatides occurs not only in the central nervous system, but also in other tissues, including the peripheral nervous system, or the occurrence of peripheral neurological signs [4,5]. The association of these signs with pyramidal involvement is very evocative of the diagnosis. The investigations are based on imagery and biology. The EMG is an indispensable examination. It shows a decrease in nerve conduction in all varieties caused by demyelination. It may be the only sign of peripheral neurogenic involvement if it is masked by pyramidal or beeing asymptomatic. For our study, and for socio-economic reasons, the EMG was performed only in one of our patients showing signs of demyelinating sensory-motor polyneuropathy.

Cerebral imaging is essential and critical for the diagnosis of MDL. The combination of clinical signs with MRI abnormalities is often characteristic. It reveals abnormalities of the white matter of the central nervous system [6]. The involvement is symmetrical marked by hypersignal plaques in T2 (figure 5). The presence of streaks in hyposignal, radial dispositions, visible within the beaches in hypersignal, is very evocative of a lysosomal disease, in particular LDM. This aspect is called tigroid aspect or leopard skin, can also be observed in other lysosomal diseases (Figure 6).

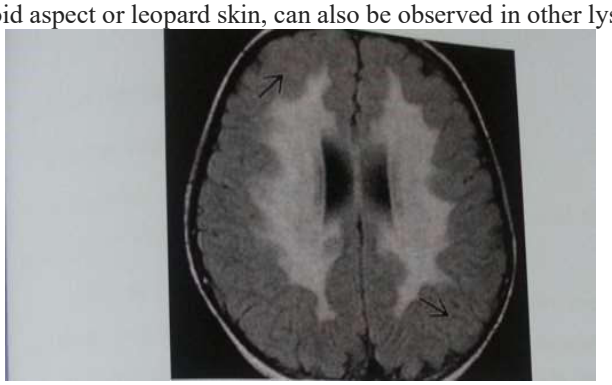

Figure 5: MRI cerebral axial cut showing a hypersignal in incidence T2 FLAIR with butterfly appearance and diffuse involvement of the predominantly posterior periventricular white substance

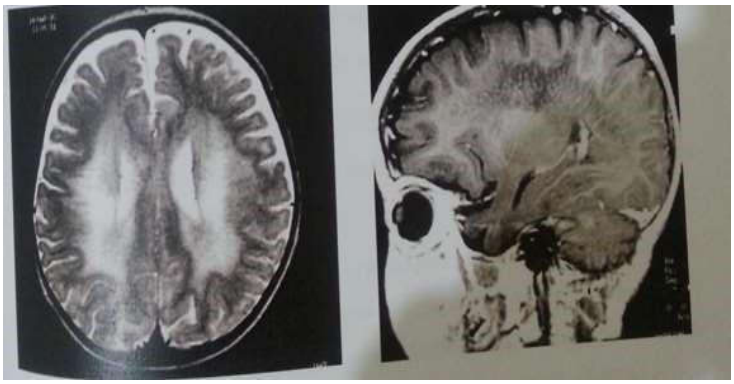

Figure 6: Tigroid aspect of white substance

Confirmatory diagnosis is based on evidence of enzymatic deficiency in ARSA; this deficiency could be demonstrated in subjects with MDL in serum, urine, fibroblast culture, lymphocytes as well as bone marrow cells. However, in routine practice, the assay is performed in serum, leukocytes and / or fibroblast culture [7]. We performed the ARSA dosage in serum. The biopsy of the peripheral nerve is performed on the sural nerve for a pathological study in order to show the accumulation of lipids in the myelin of the nerve. It is helpfull in atypic cases... Prenatal diagnosis is possible through choriocentesis and amniocentesis. Currently, the identification of the fetal genotype and the prediction

of the disease have become easier, with the use of molecular techniques. There is currently no curative treatment. The management of the MDL is mainly based on symptomatic treatment and psychological management. Otherwise; in individuals with infantile or juvenile form of asymptomatic disease, bone marrow transplantation may be considered to stabilize neurocognitive functions but without guarantee of efficacy [8]. Enzymatic replacement therapy and gene therapy are under study [9, 10, and 11]. Preventive treatment requires genetic counseling and possibly prenatal diagnosis.

Conclusion:

MDL is a rare, inherited, autosomal recessive sphingolipidosis. It is a real health problem in Morocco. While several therapeutic projects with a curative aim are taken abroad, the treatment is essentially symptomatic in Morocco; It is expensive because it requires the intervention of different specialists. Genetic counseling and prenatal diagnosis are essential to help avoid the disease.

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