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Leukodytrophy in Children: 12 Cases

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ABSTRACT

Introduction: Leukodystrophies are a rare geneLc disease characterized by damage of the myelin sheath. They represent a large number of diseases that are heterogeneous by their clinical and physiopathological aspects.

Material and Methods: We report 12 cases of leukodystrophies collected at the Neuropediatric Unit of Abderrahim Harouchi Mother and Child Hospital CHU Ibn Rochd, Casablanca, Morocco. **Results:** The average age of diagnosis was 2 years and 9 months, with a predominance of females (sex raLo:0.33). Consanguinity was found in 5 cases. The onset symptomatology was dominated by psychomotor regression, found in 8 paLents, and seizures in 4 paLents. Motor signs were in the foreground: pyramidal syndrome in 5 cases, hypotonia in 4 cases, tetraparesis in 1 case, dysarthria in 1 case. The lumbar puncture, carried out in 4 paLents, revealed hyperproteinorachy in 3 cases, glycorachy and cytological study were normal. We noLced a decreased level of Aryllsulfatase A in 6 cases. Imaging was performed in all paLents and showed diffuse white ma]er demyelinaLon. MRI allowed us to classify our cases and showed 7 cases of metachromaLc leukodystrophy, 1 case of cavitary leukodystrophy, 1 case of Refsum disease, 1 case of Canavan disease, 1 case of Cockaynes syndrome and 1 case of adrenoleukodystrophy. The electroneuromyogram showed a decrease in nerve conducLon velociLes in 2 cases. Molecular study was performed in one paLent finding a hyccin mutaLon.

Conclusion: The diagnosis of leukodystrophies is o_en difficult because of their clinical heterogeneity. The partnership of clinicians with geneLcists may be the key point to improve diagnosis and therapeuLc management.

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INTRODUCTION

Leukodystrophies (LD) are defined as geneLc, primary diseases affecLng the white ma]er (WM) of the central nervous system (CNS) and someLmes also the peripheral nervous system (PNS).

The concept of LD gradually emerged from the study of diffuse cerebral sclerosis (HEUBNER 1887). They are characterized by disturbances in myelin formaLon (4), leading to the producLon of abnormal myelin responsible for demyelinaLon. Onset varies from birth to adulthood but is most common in children (3). The clinical presentaLon includes neurological signs associated with progressive demyelinaLon. Diagnosis of the disease has significantly benefited from advances in magneLc resonance imaging (MRI) and molecular biology. MRI can suggest the diagnosis in individuals with a suggesLve neurological presentaLon. The advancements in molecular biology now enable the detecLon of mutaLons responsible for the disease.

MATERIALS AND METHODS

We conducted a descripLve retrospecLve study of 12 cases of LD collected over a 4-year period (January 2019 - January 2023) in the Neuropediatric Unit, Abderrahim Harouchi Mother-Child Hospital of Casablanca University Hospital.

RESULTS

In our series, the mean age at diagnosis of these paLents was 2 years and 9 months, ranging from 6 months to 7

years. The majority were girls (75%). In their medical history, consanguinity was noted in 5 cases, and a similar symptomatology in the family in 3 cases. Early symptoms were dominated by psychomotor regression in 8 paLents and convulsions in 4. Motor signs included pyramidal syndrome in 5 cases, hypotonia in 4, tetraparesis, and dysarthria in 1 (Figure 1).

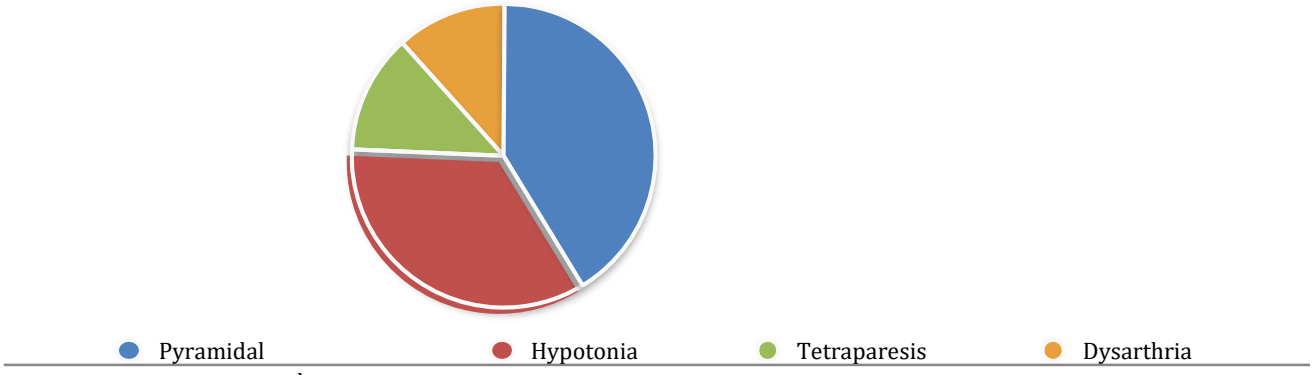

Figure 1: Clinical findings

Paraclinical findings:

Lumbar puncture, performed in 4 paLents, revealed hyperproteinorachia in 3 cases. Glycorrhachia and cytological studies were normal. Arylsulfatase A assay was performed in 6 cases, showing decreased levels in all 6. MRI was conducted in all paLents, revealing diffuse demyelinaLng white ma]er and white ma]er hypersignal in T2 sequences (Figure 2 - 3). This examinaLon was also used to determine the nature of the leukodystrophy, revealing: 7 cases of metachromaLc LD, 1 case of cavitary LD, 1 case of Refsum disease, 1 case of Canavan disease, 1 case of Cockayne syndrome, and 1 case of adrenoleukodystrophy (confirmed by a high C24/C22 raLo).

Electroneuromyograms showed reduced nerve conducLon velociLes in 2 cases. Molecular studies in one paLent revealed a hyccin mutaLon. Management primarily relies on symptomaLc treatment, including rehabilitaLon, re-educaLon, and comfort care prescribed for all paLents. AnLconvulsant therapy was iniLated in the four paLents who developed convulsions, two of whom were on dual therapy. Clinical signs stabilized in nine paLents, while three were lost to follow-up.

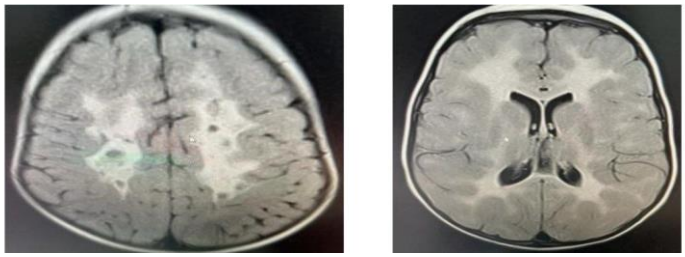

Figure 2: Cerebral MRI, Supra and infratentorial white matter signal change related to the metachromatic leukodystrophy

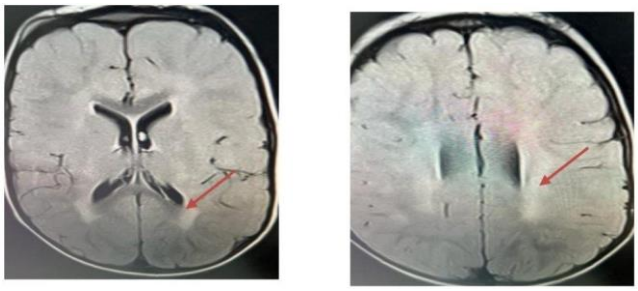

Figure 3: Cerebral MRI, High signal area in the supratentorial periventricular white matter related to the metachromatic leukodystrophy

DISCUSSION

LDs are a group of geneLc, progressive, metabolic diseases that can affect the enLre nervous system. Each type of leukodystrophy is caused by a specific geneLc abnormality leading to abnormal development or

destrucLon of the white ma]er (myelin sheath), responsible for demyelinaLon.

LDs can be classified into different categories:

- LDs of the peroxisomal disease group:
- Adrenoleukodystrophy(ALD) / Adrenomyeloneuropathy (AMN).
- Adult Refsum disease.
- Zellweger spectrum diseases / Neonatal adrenoleukodystrophy / InfanLle Refsum disease.
- LD of the lysosomal disease group: - MetachromaLc leukodystrophy (MDL)
- Krabbe disease.
- LD of the cavitary type:
- Alexander's disease/Canavan's disease/CACH syndrome/Megalencephalic leukodystrophy with subcorLcal cysts (or MLC).
- HypomyelinaLng LD:

Pelizaeus-Merzbacher disease (or PMD) / Pelizaeus-Merzbacher-like disease - SpasLc paraplegia 2 / HypomyelinaLon and congenital cataract (or HCC).

Unclassified or undetermined LD.

LDs are rare diseases, and their overall incidence is difficult to assess due to the challenges in diagnosis. A study conducted in Germany by the pediatric department of the University of Hamburg in 1997 (5) reported that the general incidence of LD is esLmated at 2.0/100,000 births. In our context, the incidence cannot be specified due to the lack of epidemiological studies.

Consanguinity plays a significant role. In our series, three paLents came from consanguineous marriages, with two presenLng similar family histories. Compared with the literature, in an Indian series of metachromaLc leukodystrophy (MDL), 70% of paLents were from consanguineous marriages, with four similar family histories. In other series, consanguinity was present in all paLents.

(7-8)

Symptomatology in LD typically appears a_er a free interval, with the onset of psychomotor regression. Motor impairment is common, leading to delayed achievement of motor milestones or motor regression (10). Hypotonia may manifest as peripheral neuropathy in the early stages but can transiLon to spasLcity later. CogniLve impairment is prevalent, and seizures may occur early or later in the disease course.(11)

Peripheral neuropathy with diminished deep tendon reflexes may be an early sign, posing a diagnosLc challenge and potenLally being mistaken for other condiLons such as Guillain-Barré syndrome (11). The diagnosLc pathway for LD involves a comprehensive assessment of history, psychomotor development, clinical examinaLon, and paraclinical examinaLons, including MRI and geneLc studies.

Cerebral MRI is a sensiLve diagnosLc tool for detecLng white ma]er abnormaliLes. Different MRI sequences provide valuable informaLon, and recent studies suggest systemaLc analysis of white ma]er signal abnormaliLes in different sequences could aid diagnosis.(12)

In this sense, one classificaLon proposes to divide LDs into two subtypes according to the results of cerebral MRI [13] :

HypomyelinaLng LDs, in which a slight hyperintensity of the cerebral white ma]er is evident on the MRI T-sequence, and the T1-sequence shows no exclusive pa]ern of intensity in terms of intensity, and is generally isolated from the cerebral cortex.

DemyelinaLng LD, in which significant T2 hyperintensity and significant T1 hypointensity can be detected.

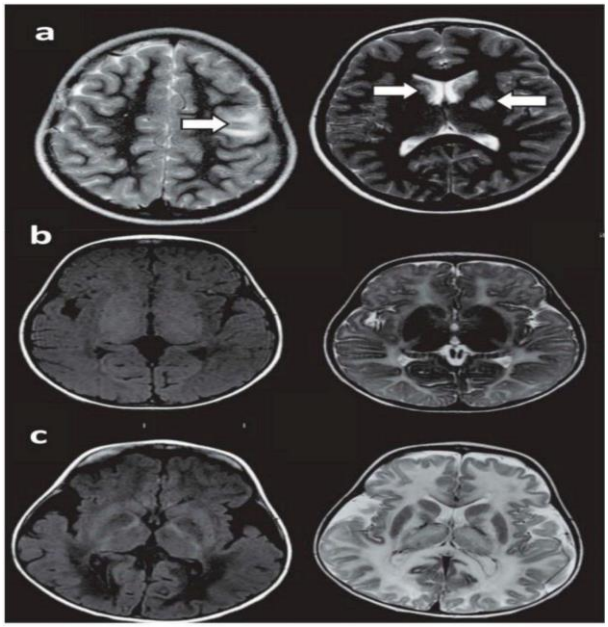

Figure 4 cerebral MRI

(a) Demyelinating leukodystrophy T2-weighted sequences showed asymmetric multifocal white matter damage (white arrows).

(b) hypomyelinating leukodystrophy) was identified. Aconfluent, mild T1-weighted hyposignal (left image) and a mild T2-weighted hypersignal (right image) were detected.

c) Demyelinating leukodystrophy was diagnosed. A prominent confluent T1-weighted hyposignal (left image) and a prominent T2-weighted hypersignal (right image).

MagneLc resonance spectroscopy (MRS) can disLnguish between various white ma]er abnormaliLes, with specific pa]erns associated with certain LDs(14-15). Advances in geneLc study and high-throughput sequencing technologies have revoluLonized the molecular diagnosis ofinherited white ma]er disorders.(16) Several mutaLons are described in LD (Table 1)

Table 1 : Types of leukodytrophia with the geneLc mutaLon

LD	Trasmission	Gene
Pelizaeus-Merzbacher	X linked	PLP1 gene
LD with GJA12	Autosomal recessive	Gja12/GJC2 gene
LD with hyccine	Autosomal recessive	FAM126A gene
LD with Hsp60	Autosomal recessive	HSPD1 gene
LD with MCT8	Recessive X linked	SCL16A2 gene
18q syndrome	Sporadic	18q- Deletion
LD with SOX10	Autosomal dominant	SOX10 gene
H-ABC syndrome	Sporadic	
LD with metaphysary chondrodysplasia	X linked	Locus Xq 25-q27
4H syndrome	Autosomal recessive	PoIIIA & PoIIIB

Morocco's populaLon is highly inbred, increasing the risk of autosomal recessive LD.

LD in its autosomal recessive forms. The use of geneLc studies remains difficult due to the cost and accessibility of molecular biology techniques. Comprehensive assessment of clinical findings, brain magneLc resonance imaging and geneLc studies play a key role in the early diagnosis of people with LD.

No cure is available for most hereditary white ma]er disorders, but prevenLve and symptomaLc prevenLve and symptomaLc care can increase quality of life and extend the lifespan of children with LD

This treatment is based on rehabilitaLon and re-educaLon in the face of major symptoms: swallowing disorders, spasLcity and joint deformiLes, which improve gross and fine motor skills as well as cogniLve funcLons in affected individuals [13]. NutriLonal support is also essenLal for LD children, but can be difficult due to the inability to feed and swallowing difficulLes. Follow-up by nutriLonists and speech therapists can help improve these paLents' quality of life.

Bone marrow transplantaLon, when performed early in the course of the disease, before signs of neurological deterioraLon appear, can stabilize or reverse demyelinaLng brain lesions by replacing damaged microglial cells with healthy ones [11]. In some people with MDL, this therapy can halt central nervous system damage (with electrophysiological evidence), prevent mental deterioraLon and improve IQ [17]. However, cohort studies have shown that in paLents with the juvenile form of MDL, demyelinaLon conLnues to progress a_er bone marrow transplantaLon in 31% of cases. This phenomenon could be a]ributed to late iniLaLon of treatment [18].

Gene therapy using autologous CD34+ cells, which are enriched from paLents' bone marrow or mobilized peripheral blood and transduced with a lenLviral vector that inserts one or more copies of the human ARSA gene, so that the geneLcally modified cells become capable of expressing the funcLonal ARSA enzyme (LIBMELDY). It is a therapeuLc opLon only for asymptomaLc children with no clinical manifestaLons of the disease, in terms of motor, cogniLve and/or behavioral impairment, suffering from the late infanLle or early juvenile form of MDL. In other children within the scope of LIBMELDY's markeLng authorizaLon, corresponding to symptomaLc children with early clinical manifestaLons of the disease, suffering from the early juvenile form of MDL, even if they have retained the ability to walk independently and before the onset of cogniLve decline. The HAS Transparency Commission considers that LIBMELDY has no place in the therapeuLc strategy [19].

CONCLUSION

LDs are rare geneLc diseases with complex diagnosLc challenges. CollaboraLon between clinicians and medical

geneLcists is crucial for accurate diagnosis. Although no cure exists, symptomaLc care and intervenLons such as rehabilitaLon, nutriLonal support, and bone marrow transplantaLon can improve the quality of life and extend lifespan in affected individuals. Gene therapy remains a promising area of research, but its clinical applicaLon requires further evaluaLon.

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