الجمهورية الجزائرية الديمقراطية الشعبية

People's Democratic Republic of Algeria
République Algérienne Démocratique et Populaire

وزارة التعليم العالي والبحث العلمي

Ministery of Higher Education and Scientific Research
Ministère de l'Enseignement supérieur et de la Recherche Scientifique

Brothers Mentouri University
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Nature and Life Science Faculty
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جامعة الاخوة منتوري قسنطينة 1
كلية علوم الطبيعة والحياة
قسم بيولوجيا الحيوان

Graduation Genetic Science Master's degree
Diploma Thesis

Field: Nature and Life Science
Sector: Biological Sciences
Speciality: Molecular Genetics

Order N°:
Serie N°:

Title :

Genetic diagnosis of patients with Progressive Myoclonic Epilepsy

Presented by: BEHLOUL SoundousMalek **13 /06/2024**

Evaluation Jury :

President:	Sedrati Khadidja.	(MCA- University Constantine 01 Frères Mentouri).
Supervisors :	Mecheri Yasser	(DR – CHU Constantine).
	Boulefkhad Assia	(Pr – CHU Constantine).
Reviewer :	Semmame Ouarda	(MCA - University Constantine 01 Frères Mentouri).

Academic Year
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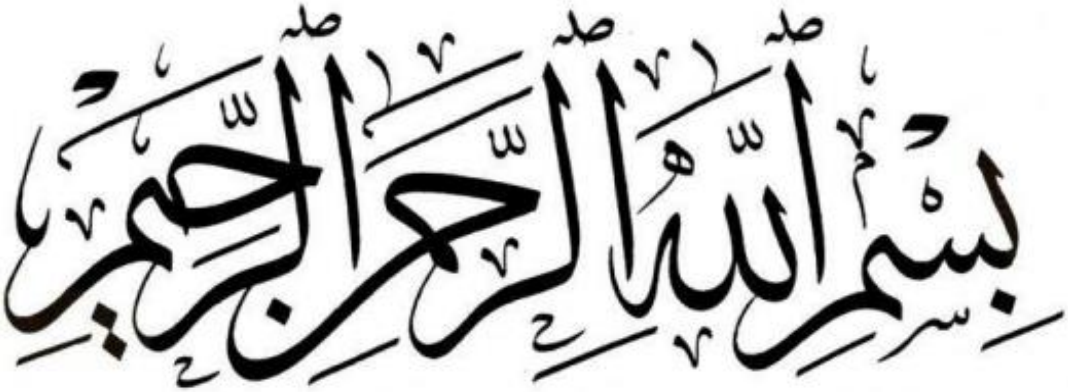
بسم الله الرحمن الرحيم

Aknowledgement

First and foremost, I would like to praise **Allah** the Almighty, the Most Gracious, and the Most Merciful for His blessing during my studies and thesis.

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Dedication

For My Dear grandparents

For My Dear Parents

For my Lovely Sisters and Brothers

For all my family members and friends

Who Helped me, supported me, believed on me and pried for me!

Abbreviations

°C: Degree celsius

A: Absorption

ACMG-AMP: American College of Medical Genetics and Genomics and the Association for Molecular Pathology

AD: Autosomal dominant

AR: Autosomal recessive

ASAH1: N-acylsphingosine amidohydrolase 1

ATN1: Atrophin 1

ATP: Adenosine triphosphate

BAFME: Benign adult familial myoclonic epilepsy

CERS1: Ceramide synthase 1

CLN: neuronal ceroid lipofuscinosis

CNS: Central nervous system

CSTB: Cystatin B

DBD: DNA-binding domain

DLinDMA: 1,2-dilinoleyloxy-N,N-dimethyl-3-aminopropane

DRPLA: Dentatorubral-Pallidoluysian Atrophy

EDTA: Ethylenediamine tetraacetic acid

EEG: Electroencephalogram

EMG: Electromyogram

EPM1: Epilepsy, Progressive Myoclonus 1

EPM2A: Epilepsy, Progressive Myoclonus 2

EPM2B: Epilepsy, progressive myoclonic 2B

F1: Family N°1

FD: Farber disease

FLAIR: Fluid-attenuated inversion recovery

GBA: Glucosylceramidase beta

GD: Gaucher disease

GOSR2: Golgi SNAP Receptor Complex Member 2

GTCSs: Generalised tonic-clonic seizures

Hz: Hertz

IPS: intermittent photic stimulation

JME: juvenile myoclonic epilepsy

KCNC1: Potassium voltage-gated channel subfamily C member 1

KCTD7: Potassium Channel Tetramerization Domain Containing 7

KV3.1: Potassium voltage channel 3.1

LBD: Carboxy-terminal ligand-binding domain

LD: Lafora disease

LIMP-2: lysosomal integral membrane protein type 2

LMNB2: Lamin B2

MEAK: Myoclonus epilepsy and ataxia due to potassium channel mutation

MERRF: Myoclonus Epilepsy and Ragged-Red Fibers

Min: Minute

Ml: Millilitre

Mmol: Millimole

MRCA: Most recent common ancestor

MRI: Magnetic resonance imaging

MTTK: Mitochondrially Encoded TRNA-Lys (AAA/G)

N°: Number

NAA: N-acetylaspartate

NaCl: Sodium chloride

NEU1: Neuraminidase 1

NGS: Next generation sequencing

NGS: Next-generation sequencing

NHLRC1: NHL Repeat Containing E3 Ubiquitin Protein Ligase 1

Nm: Nanometer

NSPME: North Sea PME

OD: Optical Density

OMIM: Online Mendelian Inheritance in Man

ONS: Organisation nationale des statistics (national statistics organisation)

PCR: Polymerase chain reaction

PH: Potential of hydrogen

PMEs: Progressive Myoclonus Epilepsies

POLG: DNA polymerase gamma

PRDM8: PR domain zinc finger protein 8

R: Ratio

REM: Rapid eyes movement

RFLPs: Restriction Fragment Length Polymorphisms

RORB: Retinoic acid-related orphan receptor B

RP-PCR: repeat primed PCR

RPM: Revolutions per minute

SANDO: Sensory Ataxic Neuropathy, Dysarthria, and Ophthalmoparesis

SARA: Assessment and Rating of Ataxia score

SCAE: Spinocerebellar ataxia with epilepsy

SCARB2: Scavenger Receptor Class B Member 2

SDS: Sodium Dodecyl Sulfate

SEMA6B: Semaphorin 6B

SLC7A6OS: Solute Carrier Family 7 Member 6 Opposite Strand

SMA-PME: spinal muscular atrophy with progressive myoclonic epilepsy

SNARE: Soluble NSF attachment protein receptor

SNPs: Single nucleotide polymorphism

SSLPs: Simple Sequence Length Polymorphisms

TE: Tris-EDTA

tRNA: Transfer Ribonucleic acid

ULD: Unverricht and Lundborg disease

UV: Ultraviolet light

VCF: Variant Call Format

VS: versus

WES: Whole exome sequencing

WGS: Whole genome sequencing

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INTRODUCTION

Progressive myoclonus epilepsies (PMEs) are a rare, complex and heterogeneous group of neurological genetic disorders **(Zimmern & Minassian, 2024)**. They are mainly autosomal recessive (AR) **(Franceschetti et al., 2014)** and characterised by progressive cognitive decline, cerebellar ataxia, generalised epileptic seizures, and myoclonus that constitute the constant hallmarks distinctive from other mimicking disorders **(Berkovic et al., 1986; Zupanc & Legros, 2004)**.

We can identify twelve main PME subgroups with distinctive features, genetics, pathophysiological pathways, age of appearance, severity, progression and treatment response **(Kälviäinen, 2015)**.

PMEs can also be divided into two big groups; typical and atypical PMEs (or PME-like disorders). Atypical PMEs in contrast to the typical ones either don't express PME's hallmark characteristics only in some phenotypic variants or express some additional atypical features **(Knupp & Wirrell, 2014)**.

Typical PMEs include:

- EPM1 (epilepsy, progressive myoclonus 1) or Unverricht and Lundborg Disease (ULD).
- EPM2 (epilepsy, progressive myoclonus 2) or Lafora Disease (LD).
- Batten disease (neuronal ceroid lipofuscinosis: CLN).
- acid ceramidase deficiency.
- Sialidosis.
- Myoclonus Epilepsy and Ragged-Red Fibers (MERRF).
- Type 3 Neuronopathic Gaucher Disease.
- Dentatorubral-Pallido-luysian Atrophy (DRPLA).
- Myoclonus-renal Failure Syndrome.
- Progressive Myoclonus Epilepsy-Ataxia Syndrome (EPM5).
- North Sea Progressive Myoclonus Epilepsy.
- Myoclonus Epilepsy and Ataxia due to pathogenic variants in the potassium channel.
- Others. **(Zimmern & Minassian, 2024)**

Whereas the not exhaustive list of atypical PMEs includes:

- Huntington disease: myoclonic variant **(Thakor et al., 2021)**.
- Wilson disease **(Sachan et al., 2017; Verma et al., 2016).**
- Example of epilepsy linked to *RORB* mutations **(Rudolf et al., 2016).**
- Young-onset Alzheimer's dementia **(Mahale et al., 2023).**
- Cerebrotendinous Xanthomatosis **(Desai et al., 2021)**.

- Mitochondrial recessive ataxia syndrome (includes SANDO (Sensory Ataxic Neuropathy, Dysarthria, And Ophthalmoparesis) and spinocerebellar ataxia with epilepsy (SCAE) formerly designated caused by mutations in the *POLG* gene **(Yi Shiau Ng, 2017).**

Study aims and objectives:

- In this study we will provide a clinical, epidemiological and genetic description of the main PME groups focusing on the most frequent ones like Uverchrit-Lundburg disease (ULD), Lafora disease (LD), Neuronal ceroid lipofuscinosis (CLN)
- We aim also to describe some of the more frequent and more recently identified mimics like *RORB* mutations, Wilson disease and Huntington's disease.
- An important objective is to provide an analysis of the most frequent PMEs encountered in the Algerian population.

BIBLIOGRAPHIC PART

I. General review of Progressive Myoclonic Epilepsies:

1. History

1.1. History of the disorder discovery

- In 1891, **Heinrich Unverricht** described two Estonian families with Myoclonus and called them "*familiäre Myoklonie*"**(Unverricht, 1891)**.
- In 1903, **Herman Lundborg** gave the name of "progressive myoclonus epilepsy" to a particular type of neurological disorder associating epilepsy and myoclonus observed in many Swedish consanguineous families **(Lundborg, 1903)**.
- In 1911, **Lafora** found abnormal brain inclusions in a patient with a "myoclonic epilepsy"**(Lafora, 1911)**.
- In 1921, **Hunt** described "Ramsay Hunt syndrome" which included Friedreich's ataxia, myoclonus and epilepsy **(Hunt, 1921)**.
- In 1968, **Van Bogaert** tried to establish a clear definition of PMEs based on clinical and pathological features but without outcome **(L. Van Bogaert, 1968)**.
- In 1973, **Diebold** identified a new concept belonging to PMEs called "hereditary myoclonus-epilepsy-dementia nuclear syndromes"**(Diebold, 1973)**.
- In 1989 and before the genetics era, was the establishment of the first world recognised PMEs consensus by "**Marseille Consensus Groupe 1990**": in which affections were divided into:

- Identified biochemical mechanisms affections: MERRF and sialidosis.
- Known pathological marker affections: Lafora's disease, CLN.
- Affections without any marker also known as "degenerative" types: ULD and DRPLA **(Genton et al., 1990)**.

1.2. History of gene discovery

Before the genetics era, classic biochemical methods were used to identify genes responsible for sialidosis **(Genton et al., 2016)**. Other genes responsible for different PMEs were discovered one after the other starting from 1989 with the development of chromosomal mapping using genetic mapping and physical mapping **(Rommens et al., 1989)**. Genetic mapping also known as linkage mapping include Restriction Fragment Length Polymorphisms (RFLPs), Simple Sequence Length Polymorphisms (SSLPs) by minisatellites and microsatellites mapping and Single Nucleotide Polymorphisms (SNPs)**(Altshuler et al., 2008; Brown, 2002)**.

More recently, PMEs gene discovery was facilitated by next-generation sequencing (NGS) techniques **(Canafoglia, Franceschetti, Gambardella, Striano, Giallonardo, Tinuper, Di**

Bonaventura, Michelucci, Ferlazzo, Granata, Magaudda, Licchetta, Filla, La Neve, Riguzzi, Cantisani, Fanella, Castellotti, et al., 2021; Han & Lee, 2019) including (whole-exome sequencing (WES) and whole-genome sequencing (WGS))**(Qin, 2019).**

Table 01 resumes the PMEs responsible genes, chronological discovery and genetics techniques used.

Table 01: PMEs responsible genes, chronological discovery and genetic techniques

Disease	Gene	Year	Genetic techniques
Infantile CLN **(Vesa et al., 1995)**	*CLN1* (1p32)	1995	Chromosomal mapping
CLN **(« Isolation of a Novel Gene Underlying Batten Disease, CLN3. The International Batten Disease Consortium », 1995)**	*CLN3* (16p12.1)	1995	Chromosomal mapping
ULD **(Lafrenière et al., 1997; Pennacchio et al., 1996)**	*Cystatin B* (21q22.3)	1996-1997	Northern Blot
Late infantile CLN **(Sleat et al., 1997)**	**CLN2** (11p15.4)	1997	Homozygosity and linkage mapping
Lafora's Disease	- Tyrosine phosphatase gene (6q24.3) - *6q EPM2* gene (6q23-q25) - *NHLRC1*(6p22.3)	-1998 **(Minassian et al., 1998)** -1999 **(Serratosa et al., 1999)** -2003 **(Chan, Young, et al., 2003)**	linkage analysis and homozygosity mapping
Myoclonus renal failure syndrome **(Berkovic et al., 2008)**	*SCARB2/Limp2* (4q13-21)	2008	Single nucleotide polymorphism (SNPs)

2.Epidemiology

- Individually, each PME is considered to be infrequent **(Orsini et al., 2019)**, however taken together, the group constitutes one of the most frequent Neurogenetics disorders **(Zimmern & Minassian, 2024)**. The most common PMEs are ULD, LD and CLN **(Kälviäinen, 2015)**.
- PMEs are found worldwide with some exceptions and prevalence variations **(Zupanc & Legros, 2004)**.
- High prevalence regions are those where consanguineous marriage rate is high **(Cameron et al., 2023; Jain, 2011).**

3.Genetics

3.1.Transmission type

Most PMEs are transmitted in an AR manner **(Delgado-Escueta et al., 2001; Franceschetti et al., 2014)** , biallelic pathogenic variants -either homozygous or compound heterozygous- are required to induce the disorders. Like other AR diseases, consanguineous marriage between healthy carriers have a 25% risk to transmit the disease to the descendants **(Gulani & Weiler, 2024)**. PMEs therefore are more frequently observed in regions and cultures favouring consanguinity or where allele carriers number is high **(Cameron et al., 2023).** MERRF being a mitochondrial disease is maternally transmitted **(Matsuoka et al., 1991; Rosing et al., 1985)** and EPM11 linked to *SEMA6B* mutations are transmitted in an autosomal dominant (AD) manner **(Hamanaka et al., 2020)**.

3.2.Mutation types

Most disorders are caused by deleterious pathogenic single nucleotide variants or small deletions, ULD is the exception being caused by a repeat expansion **(Cameron et al., 2023).**

Variants classification, following American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) recommendation **(Richards et al., 2015)** allows to identify pathogenic variants: clearly documented in the literature, likely pathogenic variants that have high pathogeny scores and likelihood, and variants with unknown significance that need further validation by functional or segregation studies.

3.3.Founder effects :

Some examples of founder effect in PMEs were reported in LD by **(Solís, 2000)** in four cases issued from two families from Costa Rica having common ancestors where no cases were reported before or at that time. Many cases from unrelated families were reported in Palestine sharing the same homozygous haplotype **(Gomez-Abad et al., 2007)**. Another study by **(Moulard et al., 2003)**

included 14 ULD patients from Reunion Island showed a founder effect (same haplotype expansion) with probably 12 generations until the most recent common ancestor (MRCA). Same results were found in Serbia with four unrelated ULD patients who shared a MRCA from about 110 generations ago and were related with some Baltic and north african patients **(Kecmanović et al., 2014)**. Founder effect was revealed too in CLN by **(Sharp et al., 2003)**.

3.4. New mutations: The fifty mutations identified in PMEs genes are not exhaustive **(Cameron et al., 2023)**, new discoveries are made thanks to investigations and genetics testing developpement:in 2014, many new mutations were discovered in *EPM2A* gene of LD **(Jara-Prado et al., 2014)** than in 2022 **(Nordli et al., 2022)**. In 2023, new *SEMA6B* mutations were reported by **(Castellotti et al., 2023)** responsible for PME.

4. Pathophysiology

Even though each disease of the PMEs group has its specific pathophysiology **(Zimmern & Minassian, 2024)**, some common etiopathogenic points were found: neuroinflammation is common in at least 03 PMEs (ULD, LD and CLN) **(Sanz & Serratosa, 2020)**.

Mice models brain tissue analysis showed the activation of some genes responsible for phagocytosis **(Sanz & Serratosa, 2020)**, inflammatory and immune response **(Joensuu et al., 2014)**. Also, it was noted increased levels of glial proteins, cyto-chemokines (also in serum) **(Okuneva et al., 2016)** and immunoglobulin receptors that accumulate over time with mice ageing and symptoms worsening **(Lahuerta et al., 2020)**.

Electrophysiological dysfunction was explained by the excessive cortical excitability caused probably by abnormal post-excitatory inhibition and brainstem reticular formation repression **(Coşkun et al., 2015)**.

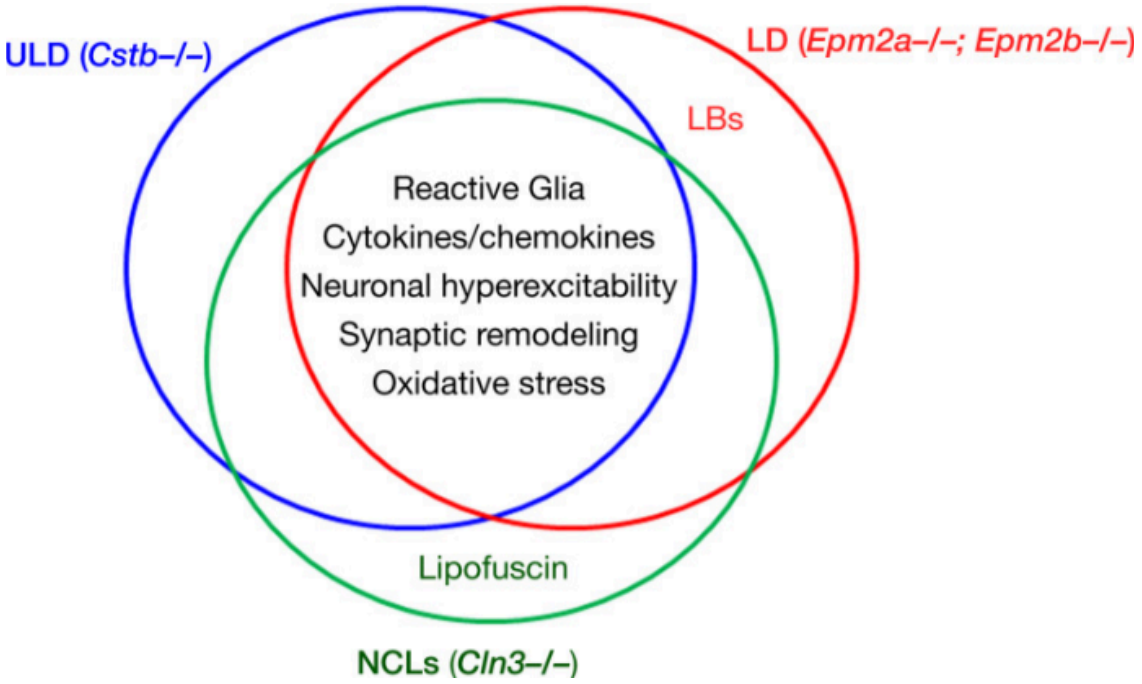

Figure 01: Common physiopathological points between ULD, LD and CLN **(Sanz & Serratosa, 2020)**

5.Diagnosis

- **Clinical signs:** childhood or adulthood onset, symptoms include myoclonus, epilepsy (focal ou generalised), cerebellar ataxia and cognitive decline. In addition, some affections associate visual impairment, psychiatric symptoms and sleep disorders…**(Zimmern & Minassian, 2024).**
- **EEG findings:** The EEG is initially normal, when the disease is clinically manifesting, abnormalities depend on seizure type (polyspikes, polyspikes and waves, spikes and waves) **(Holmes, 2020; Panzica et al., 2003)**, with normal or abnormal background activity **(Sinha et al., 2007)**.
- **Brain Magnetic resonance imaging (MRI):** Often normal **(Franceschetti & Canafoglia, 2016)**. Non-specific brain **(Manninen et al., 2013)**, cerebellum or brainstem **(Ito et al., 2008)** lesions can be observed in late stages **(Uyama et al., 1995).**
- **Genetic testing:** Is necessary to confirm the diagnosis by identifying the causal gene which will allow to provide a precise genetic counselling and prognosis. Whole exome sequencing (WES) and gene panels are considered to be the gold standard in clinical practice **(Canafoglia, Franceschetti, Gambardella, Striano, Giallonardo, Tinuper, Di Bonaventura, Michelucci, Ferlazzo, Granata, Magaudda, Licchetta, Filla, La Neve, Riguzzi, Cantisani, Fanella, CASTELLOTTI, et al., 2021)**.

6.Evolution and prognosis

- Progression is the rule **(Zimmern & Minassian, 2024)**, some disorders have severe courses and lead to important disability and early death **(Sanz & Serratosa, 2020)**. Other disorders are considered more benign and can stabilise overtime **(Leppik, 2003)**.
- Usually onset of the disease occurs in childhood or adolescence, and depending on the course of the disease, death will occur after 5-10 years in most severe disorders like LD and CLN **(Turnbull et al., 2012)**. Other disorders like ULD have a more benign course and could have a normal life expectancy **(Kälviäinen et al., 2008)**.
- Motor disability is linked to cerebellar ataxia and the severity of myoclonic jerks that may become very frequent and erratic inducing falls and limiting walking capacity causing patients in more advanced stages to become wheelchair-bound **(Michelucci et al., 2016)**.
- Cognitive decline is a major cause of disability and dependency and contributes to early death risk **(Kälviäinen, 2015)**.

7.Treatment

- Anti-epileptic drugs are necessary to control seizures and reduce myoclonus, usually generalised seizures are easier to control and myoclonus is treatment-resistant **(Holmes, 2020; Sanz & Serratosa, 2020)**.
- Anti-inflammatory medications could help reduce neuroinflammation and have shown a decrease in symptoms severity **(Minassian et al., 2016)** but further studies are needed.
- New therapies development is ongoing, this include: gene replacement therapy, gene modification therapies, enzyme replacement therapy **(Johnson et al., 2019)**, deep brain stimulation **(Sobstyl et al., 2023)**.
- Treatment offerings are limited, physical therapy is an important pillar of care combined with a healthy lifestyle and adapted diet that can improve overall outcome **(Uthman & Reichl, 2002)**.

II. Typical PMEs

1. Introduction and classification:

As mentioned previously, typical PMEs share, constantly, PMEs characteristics with additional specific features for each one of them.

This is a non-exclusive list of disorders considered as typical PMEs reviewed by **(de Siqueira, 2010; Ramachandran et al., 2009)** :

- EPM1 (epilepsy, progressive myoclonus 1) or Unverricht and Lundborg Disease (ULD) (OMIM #254800, AR), caused by mutations in the *CSTB* gene **(A. E. Lehesjoki et al., 1991, 1992)**.
- EPM1B (OMIM #612437, AR), caused by mutations in the *PRICKLE1* gene **(Berkovic et al., 2005; El-Shanti et al., 2006)**.
- EPM2A or Lafora Disease-1 (LD) (OMIM #254780, AR), caused by mutations in the *EPM2A* gene **(A. E. Lehesjoki et al., 1992; Sainz et al., 1997)**.
- EPM2B or Lafora disease-2 (OMIM #620681, AR), caused by mutations in the *NHLRC1* gene **(Chan, Bulman, et al., 2003; Chan, Young, et al., 2003)**.
- EPM3 or CLN14 (OMIM #611726, AR), caused by mutations in the *KCTD7* gene **(P. Van Bogaert et al., 2007)**.
- EPM4 or Myoclonus-renal Failure Syndrome (OMIM #254900, AR), caused by mutation in the *SCARB2* gene **(Balreira et al., 2008; Berkovic et al., 2008)**.
- EPM6 or North Sea PME (NSPME) (OMIM #614018, AR), caused by mutations in the *GOSR2* gene **(Corbett et al., 2011)**.
- EPM7 or Myoclonus epilepsy and ataxia due to potassium channel mutation (MEAK) (OMIM #616187, AD), caused by mutations in the *KCNC1* gene **(Muona et al., 2015)**.
- EPM8 (OMIM #616230, AR), caused by mutations in the *CERS1* gene **(Ferlazzo et al., 2009; Vanni et al., 2014)**.
- EPM9 (OMIM #616540, AR), caused by mutations in the *LMNB2* gene **(Damiano et al., 2015)**.
- EPM10 (OMIM #616640, AR), caused by mutations in the *PRDM8* gene **(Turnbull et al., 2012)**.
- EPM11 (OMIM #618876, AD), caused by mutations in the *SEMA6B* gene **(Hamanaka et al., 2020)**.
- EPM12 (OMIM #619191, AR), caused by mutations in the *SLC7A6OS* gene **(Mazzola et al., 2021)**.
- Batten disease (Neuronal Ceroid Lipofuscinosis: CLN).

- Sialidosis (cherry-red spot myoclonus). (OMIM #256550, AR) caused by mutations in the *NEU1* gene **(Harada et al., 1987)**.
- Myoclonus Epilepsy and Ragged-Red Fibres (MERRF) (OMIM #545000, maternal) caused by mutations in the *MTTK* gene **(Rosing et al., 1985; Shoffner et al., 1990)**.
- Type 3 Neuronopathic Gaucher Disease (OMIM # 231000) caused by mutations in the *GBA* gene **(Herrlin & Hillborg, 1962)**.
- Dentatorubral-Pallidoluysian Atrophy (DRPLA) (OMIM #125370, AD) caused by mutations in the *ATN1* gene **(Kuwano et al., 1996; Nagafuchi et al., 1994)**.

In our study we will talk more specifically about three of the most frequent typical PMEs: ULD, LD and CLN and go more briefly over other PME types.

2.Unverricht and Lundborg Disease (ULD) OMIM #254800

2.1.Introduction and Definition

The most common **(Zupanc & Legros, 2004)**, less severe and purest PME type **(Genton, 2006)**. Also known as EMP1A or Baltic Myoclonus **(Eldridge et al., 1983)** because it was first described in Estonia and Sweden **(Lundborg, 1903; Unverricht, 1891)**.

2.2.Epidemiology

- Age of onset: late childhood and adolescence **(Bureau et al., 2013)**.
- Sex ratio: 1 **(Hosny et al., 2021)**.
- Unknown worldwide frequency.
- Some regions have high prevalence: Finland (2 per 100,000) **(Sipilä et al., 2020)**, Mediterranean region **(A.-E. Lehesjoki & Gardiner, 2012)**, Reunion Island and regions with high consanguinity **(Orsini et al., 2019)**.

2.3.Genetics

ULD is inherited in an autosomal recessive manner **(Noad & Lance, 1960)** and is caused by biallelic pathogenic variants in the *CSTB* gene located in the 21q22.3 region **(A. E. Lehesjoki et al., 1991, 1992)**. The gene is 2,500 bp in length **(Pennacchio et al., 1996)** and contains 3 small exons **(Pennacchio & Myers, 1996)** encoding the "cystatin B" protein of 98-amino acids **(Pennacchio et al., 1996)**.

The most common genetic anomaly is an unstable minisatellite tandem repeats dodecamer expansion (CCCCGCCCCGCG) in the 5-prime untranslated gene region **(Lalioti et al., 1997)**.

The condition is phenotypically expressed if expended alleles of more than17 repeats are present on both alleles. The normal allele has 2-3 repeats and having 12-17 repeats is considered an asymptomatic permutation that may expand in the next generation and cause ULD phenotype **(Berkovic et al., 2005; Lehesjoki & Gardiner, 2012)**.

Rarely compound heterozygous mutations between point or indel mutations in one allele and either an expanded allele or a point mutation in the other allele can cause ULD with atypical features; gender-specific expressivity, rare seizures and sporadic myoclonus in females compared to a more severe phenotype, refractory epilepsy and severe myoclonus in men **(Canafoglia et al., 2012).**

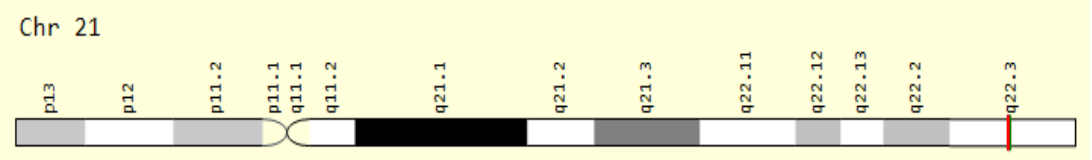

Figure 02: *CSTB* gene location ***(GeneCards - Human Genes | Gene Database | Gene Search*, 2024).**

2.4. Pathophysiology

- Cystatin B is a non glycosylated small protein of 98 amino acids **(Pennacchio et al., 1996)**, expressed in neurons and glial cells. It is considered to be an endogenous neuroprotector and a protease inhibitor **(Joensuu et al., 2008)** as it inhibits cathepsins (B, H, L and S) which are intracellular proteases with antigen and apoptosis action. It also inhibits apoptosis in cerebellar cells.
- The lack of Cystatin B causes hyperexcitability and neuronal dysfunction **(Orsini et al., 2019)** responsible for seizures, cerebellar ataxia and leads to neurodegeneration.
- Glial and microglial activation are also noted followed by secondary gliosis and neuronal loss **(Kuriko et al., 2002)**.
- Oxidative stress plays an important role as in all other PMEs **(Hurd et al., 1996)**, N-acetylcysteine and other antioxidant therapies, may ameliorate ULD symptoms.

2.5. Clinical symptomatology

Was recently resumed by **(Cameron et al., 2023; Zimmern & Minassian, 2024)** and consists on:

- **Myoclonus:** Both positive and negative myoclonic jerks are present. Myoclonus constitutes the first and major symptom and often manifests as diffuse myoclonic jerks at awakening. It is typically distal and triggered by movement -especially passive joint mobilisation- sensory

stimulation (auditory and light stimuli), surprise, and stress. With progression, it could become violent, intense or progress to GTCSs.

- **Epileptic seizures:**
  - **Generalised tonic-clonic seizures (GTCSs):** They may be the first noticeable sign. and usually occur at awakening or during sleep. Their frequency decreases overtime.
  - **Other seizure types may occur less frequently like** absence seizures and atonic seizures.
- **Cerebellar ataxia, impaired walking and disability upon standing:** worsened by seizure and especially myoclonus. they are ameliorated by seizure control.
- **Cognitive decline:** affecting attention, short-term memory, executive functions and psychomotor speed.
- **Psychiatric symptoms** like emotional lability and depression **(Carmassi et al., 2017; Sipilä & Kälviäinen, 2022)**.

2.6.**EEG:**

- Background activity: can be normal **(Magaudda et al., 2006)** or moderately slowed **(A. E. Lehesjoki & Koskiniemi, 1999)**.
- Generalised fast high amplitude spike or polyspike and wave discharges at 3–5 Hz frequency occur either spontaneously **(Ferlazzo et al., 2007)** or with intermittent photic stimulation (IPS) **(Genton, 2006)**.
- Focal EEG abnormalities: seen from the central to the posterior regions, more evident during the rapid eyes movement (REM) sleep, on the vertex with central fast spikes **(Franceschetti et al., 1993)**.
- EEG abnormalities decrease after approximately 15 years of evolution **(Ferlazzo et al., 2007; Magaudda et al., 2006)**.
- Photosensitivity is constant in ULD and tends to disappear with an average of ~30% after 15 years of evolution **(Ferlazzo et al., 2007; Magaudda et al., 2006).**

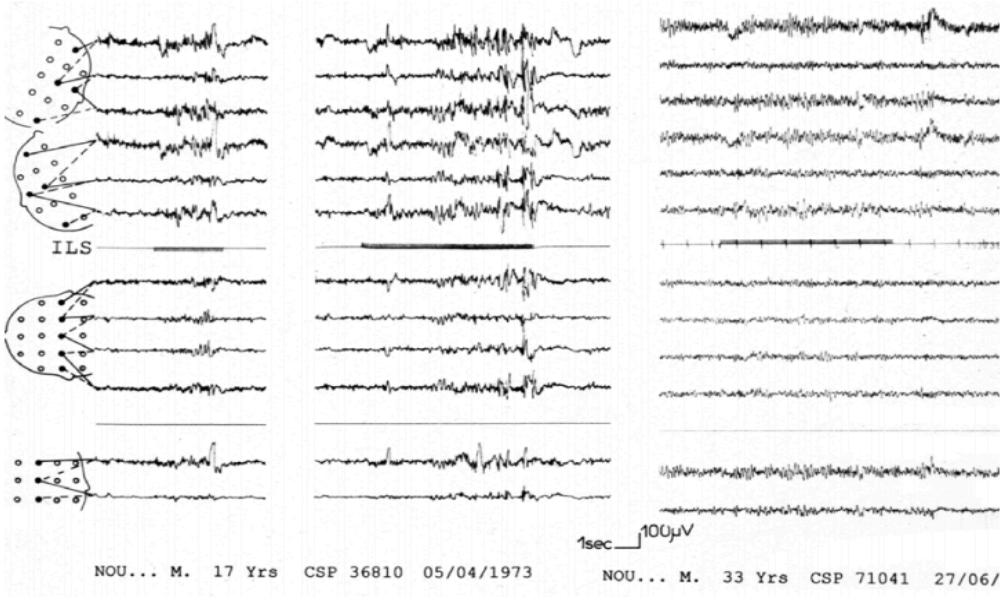

Figure 03: EEG evolution in patients with ULD between the age of 17 to 33 showing photosensibility and GTCS disappearance. **(Genton, 2006)**

2.7.**MRI:**

- Non-specific brain atrophy can be seen with progression **(Mascalchi et al., 2002)**. Spectroscopy metabolic changes in lactate, N-acetyl-aspartate, and choline in basal ganglia, thalamic nuclei, insula, and occipital areas **(Hyppönen et al., 2023)** associated with psychomotor and executive functions degradation.
- Fluorodeoxyglucose positron emission tomography shows hypometabolism in the posterior brainstem, thalami, frontal and parietal lobes **(Muccioli et al., 2022)**.

2.8.Diagnosis

- Based on history, clinical examination and EEG.
- Genetic testing confirms the diagnosis using Southern blot or repeat primed PCR showing increased number of dodecamer repeats in the promoter region of the cystatin B gene **(Krysa et al., 2012, p. 8)**.
- Skin biopsy can be useful and shows vacuoles bounded on the membrane of the sweat glands of the armpit region **(Zupanc & Legros, 2004)** **.**

2.9.Evolution and prognosis

- EMP1 has a good prognosis compared to other PMEs, however a severe progression rate had been reported **(Kälviäinen, 2015)**.
- Cognitive decline is not so profound and progresses slowly **(Laura Canafoglia, 2017)**.
- Seizures and myoclonus increase overtime, GTCS are usually controlled by appropriate anti-epileptic drugs and in some cases spontaneously **(Ferlazzo et al., 2007)**. However myoclonus is usually resistant to treatment and could become a major disabling factor **(Kälviäinen et al., 2008).**

2.10.Treatment

In order to control myoclonus and seizures, it is recommended to use : Valproic acid, associated or not to piracetam, topiramate, levetiracetam or clonazepam (to decrease myoclonus frequency and severity) **(Zimmern & Minassian, 2024).**

3.Lafora Disease (LD) OMIM #254780

3.1.Introduction and Definition

Lafora disease was the second PME identified in 1911 by "Gonzalo Lafora" **(Lafora, 1911)**, it is a rare fatal autosomal recessive **(Minassian et al., 1998)** neurodegenerative disease due to a glycogen storage disorder **(Gentry et al., 2018)**. It is characterised by the presence of pathognomonic Lafora bodies **(Busard et al., 1987; Schwarz & Yanoff, 1965)**.

3.2.Epidemiology

- Age of onset: late childhood and adolescence between the age of 8–19 years **(Monaghan & Delanty, 2010)**. Late onset forms also exist **(Baykan et al., 2005).**
- Sex ratio: 1 **(Gentry et al., 2018)**.
- Prevalence: 1-4/1000000 **(Brenner et al., 2019; Pondrelli et al., 2021)**.
- Distribution: world wide with high prevalence in the Mediterranean region, North Africa, Middle East, South India and Pakistan **(Ferrari Aggradi et al., 2023; Orsini et al., 2019).**

3.3.Genetics

- Lafora disease-1 or EPM2A (OMIM #254780, AR) is the most frequent and caused by biallelic pathogenic variants in the *EPM2A* gene located in 6q24.3 **(Serratosa et al., 1995)**. The gene has 110,719 pb and 15 exons.

- Lafora disease-2 or EPM2B (OMIM #620681, AR) is caused by mutations in the *NHLRC1* gene located in the 6p22.3 region **(Gómez-Abad et al., 2005)**.
- The most frequent pathogenic variants are splice site, missense, nonsense and small intragenic deletions and insertions **(Orsini et al., 2019).**

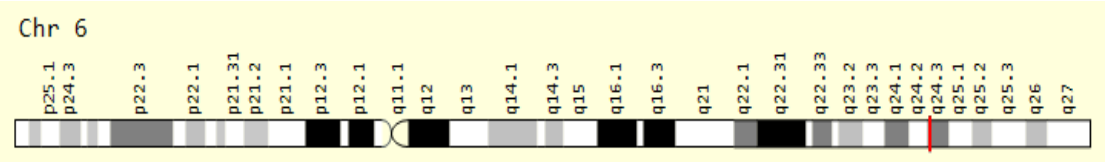

Figure 04: *EMB2A* gene ***(EMP2A related genes - GeneCards Search Results*, 2024)**

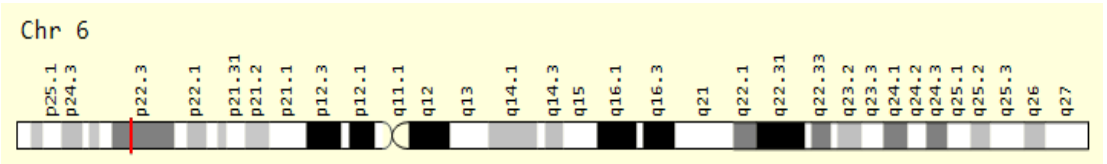

Figure 05: *NHLRC1* gene ***(EMP2A related genes - GeneCards Search Results*, 2024)**

3.4.Pathophysiology

The glucan phosphatase Laforin and E3-ubiquitin ligase malin **(Mitra et al., 2023)** are proteins encoded respectively by the *EPM2A* and *EPM2B genes* which bind together to form the Laforin-Malin complex that negatively regulates the synthesis of glycogen and controle glycogenolysis **(Singh et al., 2012)**. Laforin and Malin contribute equally to the pathogenesis of the disease **(Orsini et al., 2019)**, as their complex alterations cause abnormal shaped glycogen accumulation in the endoplasmic reticulum named "Lafora bodies" formed of fibrillary polysaccharides (insoluble glycogen derived molecules) **(Andrade et al., 2003; Yokoi et al., 1968)**. Lafora bodies are present in the brain and in many other tissues (hepatocytes, myocytes and cardiomyocytes, eccrine duct and sweat glands apocrine myoepithelial cells) **(Turnbull et al., 2016)** and are responsible for central nervous system (CNS) inflammation, neurodegeneration and seizures **(Chan, Young, et al., 2003; Ferrari Aggradi et al., 2023).** Laforin and Malin contribute equally to the pathogenesis of the disease **(Orsini et al., 2019)**.

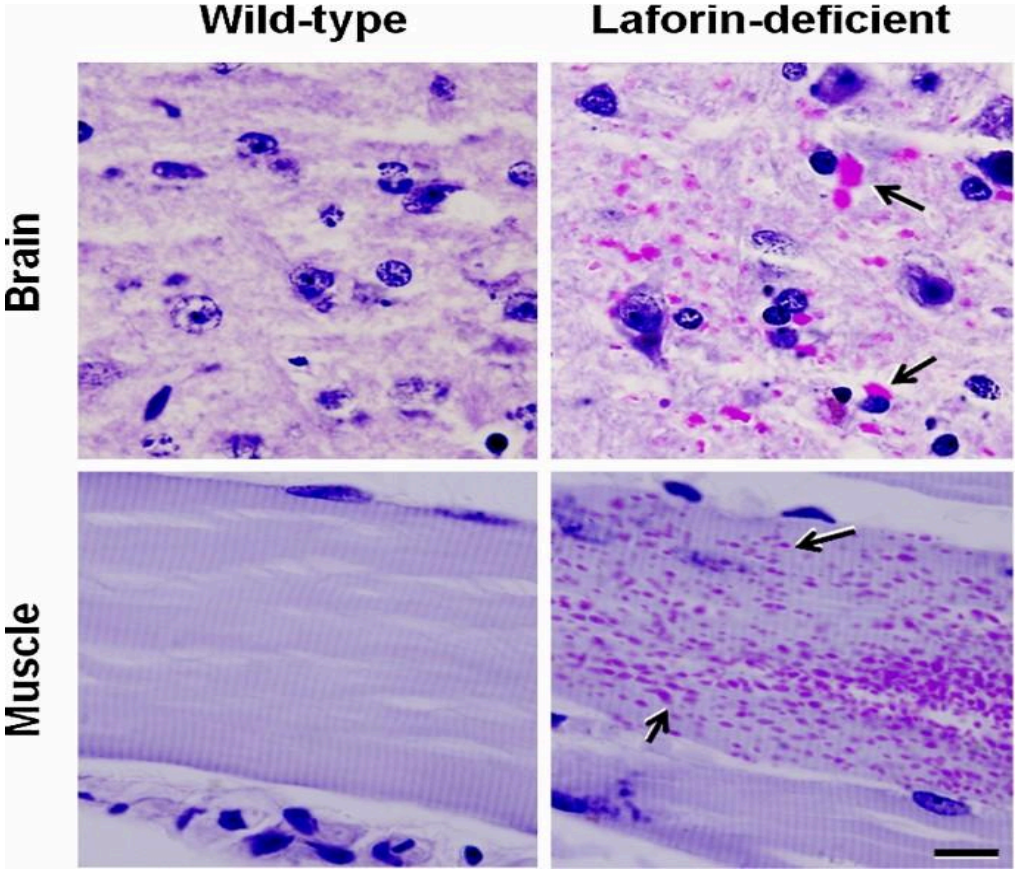

Figure 06: Microscopic image of Lafora bodies in brain and muscle biopsy **(Parihar et al., 2018)**

3.5.Clinical symptomatology

Resumed by **(Ferrari Aggradi et al., 2023; Orsini et al., 2019; Turnbull et al., 2016)** **:**

- Myoclonus: myoclonic jerks becoming continuous, generalised and uncontrolled **(Norio & Koskiniemi, 1979)**.
- Focal and generalised seizures **(Schwarz & Yanoff, 1965)**: GTC, absence, drop attacks crisis and Occipital seizures which are the earliest sign (transient blindness, visual hallucinations, photo myoclonic seizure…) leading to refractory status epilepticus.
- Non epileptic visual hallucinations and headache **(andrade, 2005)**.
- Cerebellar ataxia, Motor decline and respiratory failure.
- Scholar difficulties and cognitive decline progressing to dementia **(Schwarz & Yanoff, 1965)**.
- Depression, behavioural change and psychosis **(Norio & Koskiniemi, 1979)**.
- Death after 5-10 years of evolution **(Schwarz & Yanoff, 1965)**.

3.6.EEG

Different EEG aspects were found by **(Canafoglia et al., 2004) :**

- In the initial phase of the disease: EEG could be normal or showing reduced background activity. Some isolated or generalised sudden epileptic spike-wave discharges may occur.
- With evolution: Background rhythm becomes deeply altered and is associated with frequent recurrent epileptic discharges including: Occipital focal spikes that are considered the disease hallmark, diffuse fast polyspikes and spike-waves, massive positive and negative myoclonic discharges increased by low frequency IPS and predominant in the occipital region.

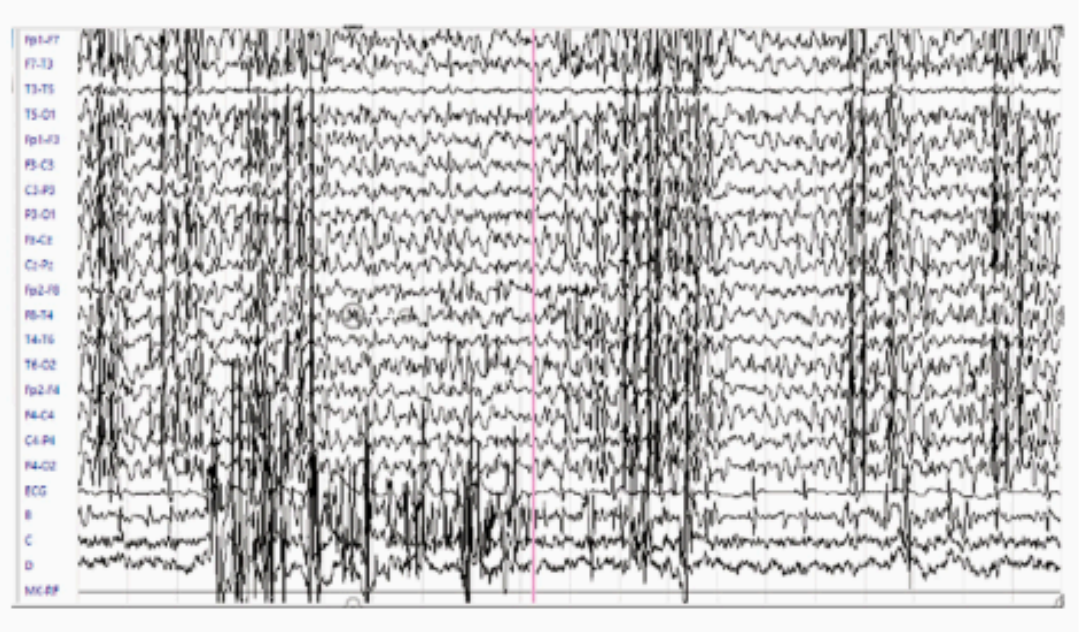

Figure 07: Electroencephalogram (EEG) in a patient with Lafora disease showing bilateral diffuse epileptic discharges. **(Ferrari Aggradi et al., 2023)**

3.7.MRI finding:

- Brain MRI is usually normal in early stages **(Ferrari Aggradi et al., 2023)**. However, posterior hypometabolism was reported in some cases **(Melanie Jennesson, 2010)**.
- In advanced stages, widespread brain degeneration **(Ferrari Aggradi et al., 2023)**, mild brain or cerebellum atrophy **(Turnbull et al., 2016)** and N-acetylaspartate (NAA)/creatine ratio decrease in cerebellum, basal ganglia and cerebral cortex **(Villanueva et al., 2006)** were observed.

3.8.Diagnosis:

Is based on clinical phenotype, evolution, age of onset, family history and EEG findings. Of particular usefulness is the presence of visual hallucinations and Lafora bodies in skin biopsies .

Genetic testing confirms the diagnosis by showing biallelic deleterious pathogenic variants in either *EPM2A* or *NHLRC1* genes **(Ferrari Aggradi et al., 2023; Orsini et al., 2019)**.

3.9.Evolution and prognosis

Observed with the first description of the pathology **(Norio & Koskiniemi, 1979; Schwarz & Yanoff, 1965)** till now **(Ferrari Aggradi et al., 2023)** **:**

- Clinical symptomatology and EEG worsens with evolution.
- Cognitive decline begins early in the disease.
- Death occurs in 5 to10 years from onset as a result of massive seizures or aspiration pneumonitis.
- However symptoms severity vary from one person to another even in the same family members.

It should be noted that EPM2B linked to the *NHLRC1* gene is less severe and manifests later than EMP2A **(Seda Salar, 2012)**.

3.10.Treatment

- There is no curative treatment yet.
- Anti-epileptic drugs are used to reduce seizures.
- Some experimental methods had demonstrate their efficiency in mice:
  - DLinDMA liposomes: ionizable cationic lipids.
  - Malin restoration causes reduced neuroinflammation.
  - Targeting “glycogen synthase” by different methods reduced glycogen production and so Lafora Bodies formation and disease progression.
  - Complementary Ketogenic diet minimises glycogen assembly.
  - Metformin, an anti-diabetes drug, may reduce the accumulation of polyglucosan accumulation, seizure frequency, neuronal loss and astrogliosis reactivity.
  - Propranolol, a beta-blocker, has been shown to module inflammation. **(Ferrari Aggradi et al., 2023)**

4.Neuronal Ceroid Lipofuscinoses (CLN)

4.1.Introduction and Definition:

Neuronal Ceroid Lipofuscinoses or Batten disease were first described in 1826 by Otto Christian Stengel as a progressive dementia and blindness then by Frederick Batten in 1903 and became

known as “amaurotic familial idiocy” **(Brean, 2004)**. The term CLN emerged starting from 1969 after the cytopathological description **(Zeman & Dyken, 1969)**.

CLN is a genetically determined group of phenotypically diverse and severe disorders, including 14 sub-types **(Mink et al., 2013)** from CLN1 to 14 numerically coded following the discovery of the mutated gene. CLN usually present in childhood and have in common similar clinical features, a neurodegenerative origin consisting of lysosomal storage disorder and “ceroid lipofuscin” intracellular accumulation **(Jalanko & Braulke, 2009)**.

It should be noted that sometimes the term “Batten Disease” is used to refer to paediatric forms and “Kufs disease” to indicate adult onset ones **(Arsov et al., 2011)**.

CLN6 is an AR affection **(Gao et al., 2002)**, caused by mutation in *CLN6* gene located on chromosome 15q23 **(Haines et al., 1998; Sharp et al., 1997)**, divided into two forms: CLN6A (OMIM#601780) and CLN6B (OMIM #204300) according to their age of onset.

4.2.Epidemiology:

CLN group is the most common inherited neurodegenerative disorder in children worldwide **(Santavuori, 1988)**. CLN1, CLN2, and CLN3 are the most frequent and were previously known as Infantile, Late-Infantile, and Juvenile CLNs **(Konrad, 2022)**.

- Age of onset: from birth to adulthood **(Zimmern & Minassian, 2024)**.
- Sex ratio: no significant studies in humans.
- Prevalence: 1 in 100,000 live births **(Santavuori, 1988)**.
- Distribution: worldwide with high prevalence in western countries **(Haltia & Goebel, 2013)**.

CLN6A is the variant late infantile (2-4 even 8 years old) form **(Teixeira et al., 2003)** whereas CLN6B, rarer, constitutes the adult form **(Arsov et al., 2011)**.

4.3.Genetics:

- All CLNs are inherited in an AR manner except in adult-onset CLN-4 which is inherited dominantly **(Boehme et al., 1971)**.
- The most frequent mutation types identified are: missens, nonsens, small deletions; insertions and duplications, splice defects **(Weimer et al., 2002)**.
- Genetic diagnosis uses either commercial gene panels or next generation sequencing coupled with direct sanger sequencing in the case of atypical clinical presentation or novel mutations **(Kmoch et al., 2013)**.

- The *CLN6* gene is located on chromosome 15q23 with a length of 22.7 kb and seven exons, encoding a non-glycosylated polytopic endoplasmic reticulum membrane protein, CLN6, composed of 311 amino acids **(Gao et al., 2002; Wheeler et al., 2002)**.

4.4.Pathophysiology:

- The disease is caused by deficiency in lysosomes-linked proteins that will induce the accumulation of an autofluorescent lipopigment called "ceroid lipofuscin" in lysosomes **(Seehafer & Pearce, 2006)** responsible for the increased apoptosis and altered autophagy causing cortical, subcortical, hippocampal, cerebellar, brainstem and spinal cord neuron's destruction and retinal atrophy coupled with glial and microglial activation **(Kollmann et al., 2013)**. However, the exact mechanism causing neurodegeneration is still poorly understood.
- A lipopigment morphotype-genotype correlation specific for each disorder within the CLN group was described **(Johnson et al., 2019)**.
- The deficient proteins have specific intracellular localisation and functions and were divided by **(Mole & Cotman, 2015; Schulz et al., 2013)** into the following subgroups:
  - Lysosomal enzymes: CLN1, CLN2, CLN10, CLN13.
  - Soluble lysosomal protein: CLN5.
  - Transmembrane proteins: CLN3, CLN6, CLN7, CLN8, CLN12
  - Secretory pathway protein: CLN11.
  - Cytoplasmic/membrane associated proteins: CLN4, CLN14.
  - ATPase: CLN12.
  - Potassium channel: CLN14.
- CLN6 pathology reveals frequently the combinations of curvilinear and fingerprint profiles **(Berkovic, 2019)**.

4.5.Clinical symptomatology:

It was resumed in reviews made by **(Bennett & Rakheja, 2013; Johnson et al., 2019; Zimmern & Minassian, 2024)** and includes:

- Signs frequency and their appearance order vary depending on CLN subtype and the causal pathogenic variant.
- Epilepsie could appear as the first symptom or follow the visual and cognitive impairment.
- Myoclonus is infrequent but worsens progressively with GTCSs.
- Early blindness is a distinctive feature coupled with quick and deep cognitive decline leading to dementia. CLN are considered to be the most common cause of child dementia.

- Ataxia and motor regression till quadriplegia.

4.6.EEG:

- Presence of photo-paroxysmal response to low-frequency IPS witness of cortical hyperexcitability **(Trivisano et al., 2022)**.
- Reduced background activity and absent sleep spindles **(Nijssen et al., 2009; Pirkko et al., 2008)**.
- In some types we can find: diffuse or focal epileptic discharges, especially in temporal and occipital regions **(Trivisano et al., 2022)**.

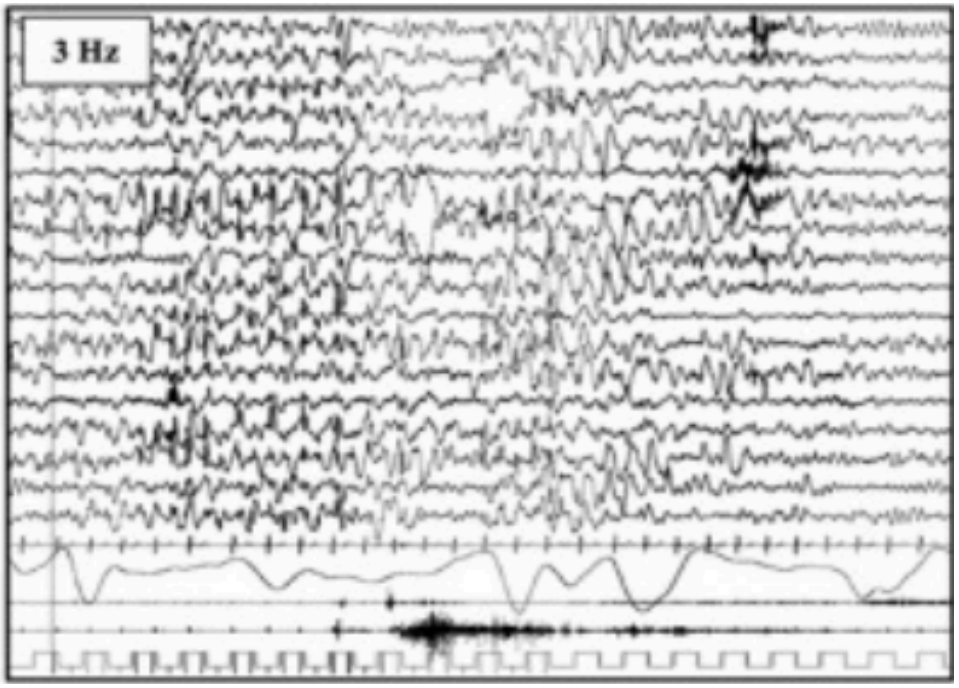

Figure 08: Photoparoxysmal response at the lower frequency of intermittent photic stimulation, at 1, 2, and 3 Hz **(Trivisano et al., 2022)**

4.7.MRI:

Non-specific anomalies described by **(Crain et al., 2020; Johnson et al., 2019)**:

- Brain and cerebellum atrophy in advanced stages.
- T2 and FLAIR sequences can show thalami and basal ganglia hypointensities and white matter hyperintensities.
- Spectroscopy may show: Reduced NAA pic and elevated mobile lipids.

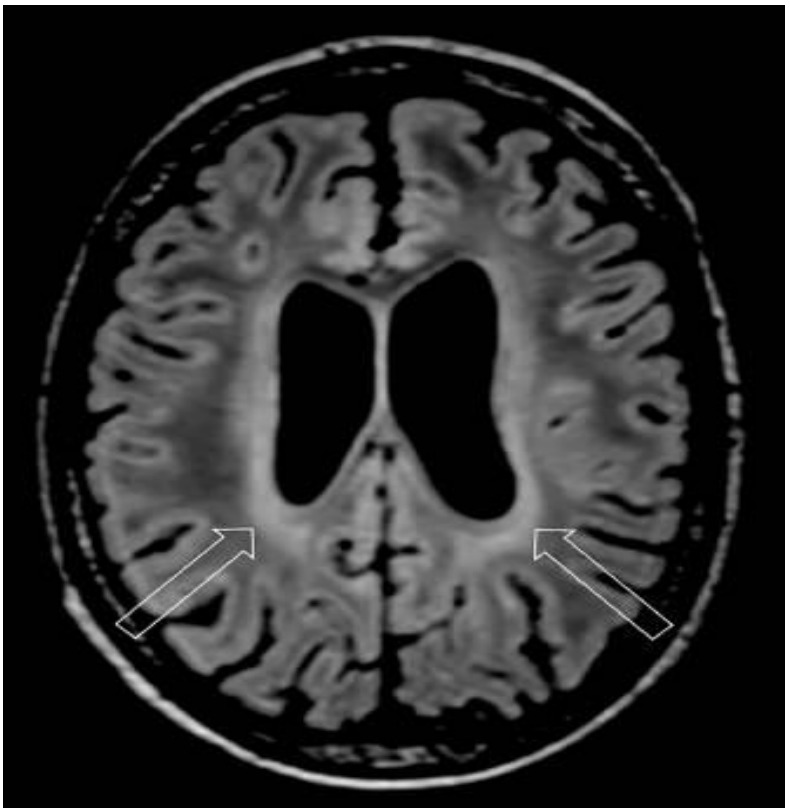

Figure 09: Axial T2 MRI sequence shows brain atrophy and periventricular gliosis (arrows) **(Crain et al., 2020)**

4.8.Diagnosis:

- Clinical severity and early visual loss and dementia allow us to suspect the diagnosis.
- Visual evoked potentials allow us to test visual function **(Vanhanen et al., 1997)**.
- Electroretinogram is very useful to screen for retinal neurodegeneration and can be used routinely to provide diagnosis in limited resources setting when coupled with skin biopsy results **(Konrad, 2022).**
- The diagnosis can be confirmed by biochemical enzyme activity essay on skin biopsies and genetic testing using whole exome sequencing **(Kmoch et al., 2013)**.

4.9.Evolution and prognosis

After a phenotypically normal period, symptoms appear and progressively worsen causing early death **(Johnson et al., 2019; Schulz et al., 2013; Zimmern & Minassian, 2024).**

4.10. Treatment:

Early diagnosis is recommended for optimal therapeutic results. Antiepileptic drugs such as Valproate and lamotrigine can be useful to reduce seizures **(Reddy & Brahmbhatt, 2022)**. No disease modifying therapy is yet available but many studies are being conducted testing potential treatment approaches **(Johnson et al., 2019)** including:

- Enzyme replacement therapies.
- Viral-mediated gene therapies using Adeno-associated virus.
- Stem cells therapies.
- Small molecule therapies:
  - Pharmacological chaperones and readthrough technologies.
  - Autophagy modulators and substrate reduction therapies.
  - Immune modulators and neuroprotective compounds.
  - Combinatorial treatments.

5. Oher PMEs

5.1. PRICKLE1-gene-related PME with ataxia or EPM1B OMIM #612437

- Previously known as PME-ataxia syndrome or PME5.
- EPM1B is an AR disease, variant of ULD, first described by **(Berkovic et al., 2005)** caused by the mutation of planar cell polarity protein 1 (PRICKLE1) gene located on chromosome 12q12 encoding cell polarity pathway proteins **(Gibbs et al., 2016; Yang et al., 2013)**.
- It is characterised by the presence of marked ataxia PME hallmarks associated with systemic signs **(El-Shanti et al., 2006)**, upward gaze palsy and neuropathy **(Straussberg et al., 2005)**.

5.2. Sialidosis OMIM #256550

- Sialidosis or cherry-red spot myoclonus syndrome is an AR metabolic disorder caused by mutations in NEU1 gene located in chromosome 6p21.3 **(Harada et al., 1987; Oohira et al., 1985)** encoding for lysosomal neuraminidase (sialidase) which is a multienzyme complex **(Bonten et al., 1996)** associated with neuronal and endothelial cells vacuolations and the accumulation of lipofuscin like pigment in neurologic and extraneurologic organs **(Allegranza et al., 1989)**.
- We describe two types : I (normomorphic) and II (dysmorphic) **(Lowden & O'Brien, 1979)** having the same gene mutation, distinguished clinically by their severity and age of onset and biologically by the enzyme activity **(Franceschetti & Canafoglia, 2016)**. Sialidosis type I is less severe **(Igdoura, 2010)** and characterised by residual enzyme activity, more frequent in Italy while sialidosis type II is more frequent in Japan **(Lowden & O'Brien, 1979)**.

- Clinical symptomatology involves second decade PMEs hallmarks for sialidosis type I **(Palmeri et al., 2000)**, associated with dysmorphic disorders, hepatomegaly **(Lowden & O'Brien, 1979)**, mental retardation, hearing loss **(d'Azzo et al., 2015)**, vision impairment **(Caciotti et al., 2009)** secondary to corneal opacity and macular destruction by the accumulation of the storage material in ganglionic cells called "cherry-red spot"**(Rapin et al., 1978)** for sialidosis type II in which the onset is congenital or infantile **(Daich Varela et al., 2021)**.
- Brain MRI is normal in early stages of the disease, showing non specific lesions such as atrophy during progression **(Palmeri et al., 2000; Sekijima et al., 2013)**.
- EEG-EMG analysis shows electric abnormalities **(Panzica et al., 2003)**.
- Laboratory analysis reveals augmented urinary sialic acid excretion **(Rapin et al., 1978)** and enzymological deficiency.Genetic analysis confirms the diagnosis **(Franceschetti & Canafoglia, 2016)**.
- Treatment is based on antiepileptic drugs and enzyme replacement therapy in neuropathic patients **(Ortolano et al., 2014)**.

5.3.Myoclonus Epilepsy and Ragged-Red Fibres (MERRF) OMIM #545000

- MERRF is a rare multisystemic mitochondrial syndrome **(Cameron et al., 2023)** caused by the mutation of more than one of mitochondrial genes, more frequently tRNA lysine MTTK (80%), encoding for mitochondrial respiratory chain polypeptides **(Enriquez et al., 1995)**.
- It more often begins in childhood and englobes in association with PME characteristics, myopathy, peripheral neuropathy, cardiomyopathy, endocrinopathies, hearing and vision impairment, dementia, exercise intolerance, cutaneous lipomas and it affects mostly high metabolic organs **(Mancuso et al., 2013)**.
- Brain MRI series made by **(Ito et al., 2008)** showed surprisingly superior cerebellar peduncles and cerebellar atrophy in all patients (and 2 patients brainstem atrophy), which could be considered as an imaging hallmark for MERRF.
- EEG and EMG show abnormalities **(Lorenzoni et al., 2014)** and laboratory analysis reveal blood and cerebrospinal fluid increasing lactic acid levels **(Cohen, 2013)**.
- Skin biopsy reveals ragged red fibers and genetics confirm the diagnosis **(Velez-Bartolomei et al., 1993)**.
- Treatment is based on symptomatic care including antiepileptic drugs **(Finsterer & Zarrouk-Mahjoub, 2017)**, some therapeutic agents such as coenzyme Q10, vitaminic supplementation and L-carnitine,and complication management **(Hameed & Tadi, 2024)**.

5.4.Dentatorubral-pallidoluysian atrophy (DRPLA) OMIM #125370

- DRPLA is a rare AD neurodegenerative inherited affection caused by unstable trinucleotide (CAG) expansion repeat in the ATN1 gene located on chromosome 12p13.31 **(Koide et al., 1994)** encodes atrophin-1 **(Wood et al., 1998)** involved in nuclear signalisation. Repeats number varies between 7-23 in normal individuals and more than that in affected ones **(Nagafuchi et al., 1994)**.
- It is more frequent in Asia, especially in Japan **(Rocha Cabrero & De Jesus, 2024)**.
- Age on onset is correlated with clinical phenotypes that vary from asymptomatic to severe ones **(Vinton et al., 2005)** and include PME hallmarks **(Tomoda et al., 1991)** with dementia **(Lindsay & Storey, 2017)**, choreoathetotic movements **(Naito & Oyanagi, 1982)**, dystonia **(Hatano et al., 2003)**, psychiatric troubles and extrapyramidal symptoms **(Adachi et al., 2001)**. Death may occurs 10 to 20 years after the onset in severe forms **(Farmer et al., 1989)**.
- Brain MRI could show non specific lesions like cerebellum and brainstem atrophy and white matter demyelination **(Shimojo et al., 2001; Sugiyama et al., 2018; Sunami et al., 2011)**.
- EEG shows abnormalities according to the clinical seizure types **(Egawa et al., 2008)**.
- DRPLA patients autopsy showed spinal cord atrophy, neuronal apoptosis and in the dentatorubral and pallidoluysian astrocytosis **(Rocha Cabrero & De Jesus, 2024)**.
- Diagnosis is confirmed by genetic analysis using PCR and whole genome sequencing **(Dunn et al., 2018; Jiang et al., 2014)**.
- Treatment is still symptomatic aiming to control seizures and myoclonus, dystonia and ataxia and other complications **(Rocha Cabrero & De Jesus, 2024)**.

5.5.Gaucher disease type III (GD3) OMIM #231000

- Gaucher disease is the most frequent lysosomal storage disorder **(Ferreira & Gahl, 2017)** englobes three subtypes (GD1 OMIM #230800 GD2 OMIM #230900 and GD3 OMIM #231000) due to a mutation in the same gene, differing in their ages of onset and clinical symptomatology and severity **(Hughes & Pastores, 1993; Stone et al., 2024)**.
- GD3 is an AR disease caused by homozygous **(Dahl et al., 1990)** or compound heterozygous **(Koprivica et al., 2000)** mutation in GBA gene located on chromosome 1q22 and encodes for acid beta-glucosidase (glucocerebrosidase) **(Brady et al., 1965)**. It represents the subacute neuronopathic form, characterised by a later age of onset and slower progression with survival rate till the third decade **(Hughes & Pastores, 1993)**.
- GD3 is divided into two subtypes **(Patterson et al., 1993)**: IIIA includes myoclonus and dementia, and type IIIB with isolated horizontal supranuclear gaze palsy and severe systemic

manifestation. GDIIIC OMIM #231005 is a rare variant of GD3, individualised by its association with cardiovascular calcifications **(Bohlega et al., 2000)**.

- Clinical symptomatology includes PME **(Park et al., 2003)**, supranuclear gaze palsy, cognitive impairment, hepato-scplenomegaly, cytopenia **(Hughes & Pastores, 1993)**, oculomotor troubles **(Nagappa et al., 2015)**, ophthalmologic lesions **(Hopf et al., 2019)**, pulmonary **(Burrow et al., 2015)** and systemic affections and skeletal manifestations **(Wenstrup et al., 2002)** .
- EEG reveals a slow Background activity and/or Epileptiform discharges **(Poffenberger et al., 2020)**. Evoked potentials could be disturbed **(Oguri et al., 2020)**.
- Diagnosis is made in proband by measuring the glucocerebrosidase activity in peripheral blood leucocytes or other nucleated cells **(Boer et al., 2020)** or identifying gene mutation using next generation sequencing **(Daykin et al., 2021)**.
- Many therapies were experienced: bone marrow transplantation **(Svennerholm et al., 1991)**, enzyme infusion therapy using glucosylceramidase **(Erikson et al., 1995)**, enzyme replacement therapy **(Rice et al., 1996)**, combination of enzyme infusion and replacement therapy with macrophage-target **(Vellodi et al., 2001)** and finally the substrate reduction therapy inhibiting glucosylceramide synthase **(Schiffmann et al., 2008)** noting their more efficiency upon systemic symptoms compared with neurological ones. Antiepileptic drugs and symptomatic care are still required **(Pawlinski et al., 2018)**.

5.6.Myoclonus-renal Failure Syndrome or EMP4 OMIM #254900

- Myoclonus-renal Failure Syndrome is an AR degenerative condition caused by mutation in the SCARB2 gene located on chromosome 4q21.1 encoding for a lysosomal hydrolase transporter called lysosomal integral membrane protein type 2 (LIMP-2), leading to the accumulation of LIMP-2 in the endoplasmic reticulum and decreases lysosomal activity **(Gonzalez et al., 2014)**.
- It is characterised by late age of onset (at about 20 years old) **(L. Dibbens et al., 2016)** and the presence of severe ataxic progressive myoclonic epilepsy without cognitive decline **(A et al., 2004)**, inconstant renal failure **(L. M. Dibbens et al., 2009)**, treatment resistance, and severe prognosis till death **(Berkovic et al., 1986)**.
- EEG shows generalised epileptiform abnormalities and background slowing activity in advanced level of the disease associated with myoclonus, best identified by EEG-EMG couple **(Rubboli et al., 2011)**.
- Diagnosis is based on clinical features,proteinuria and confirmed by genetic analysis using whole exome sequencing **(Atasu et al., 2022)**.
- Symptomatic care is the role using antiepileptic drugs, dialysis and renal transplantation **(LoPiccolo et al., 2022)**.

5.7. EPM6 or North Sea PME (NSPME) OMIM #614018

- North sea PME, prevalent in north Europe, is an extremely rare AR disease caused by mutation in the Golgi SNAP receptor 2 (GOSR2) gene located on chromosome 17q21.32 **(Corbett et al., 2011)** encoding for soluble NSF attachment protein receptor (SNARE) on the cis-Golgi membrane responsible for the fusion of endoplasmic reticulum vesicles with the cis-Golgi membrane **(Stenbeck, 1998)**, however the the effects of these mutation are limited to the central nervous system **(Jepson et al., 2019)**.
- Characterised by the presence of PME hallmarkers including respectively the onset of ataxia in the first years of life, myoclonus and seizures in childhood than the gait loss in the second decade. Cognition is usually preserved, however mild memory troubles could be seen in the third decade **(Corbett et al., 2011)**.
- EEG showed focal (especially occipital), multifocal and generalised epileptiform discharges with positive IPS response and background slowing, Polymyographies confirmed the cortical origin of myoclonus in all patients and EMG revealed peripheral neuropathy signs in a cohort study made by **(Polet et al., 2020)**.
- Brain MRI is usually normal but may reveal non specific abnormalities such as cerebellum atrophy **(Polet et al., 2020)**.
- Diagnosis is confirmed by genetic analysis using next generation sequencing **(Boissé Lomax et al., 2013; Corbett et al., 2011)**.
- Treatment is based on antiepileptic drugs. In some cases, the ketogenic diet showed his benefits **(Polet et al., 2020; van Egmond et al., 2017).** Deep brain stimulation could be used in patients with refractory seizures **(Anderson et al., 2016; Polet et al., 2020)**.

5.8. EPM7 or Myoclonus epilepsy and ataxia due to potassium channel mutation (MEAK) OMIM #616187

- MEAK is a rare PME, first described by **(Muona et al., 2015)** as an AD affection caused by mutation in the KCNC1 gene located on chromosome 11p15.1 **(Ried et al., 1993)**, encoding potassium voltage-gated channel subfamily C member 1 (KCNC1) known as KV3.1 largely expressed in CNS excitable cells , inhibitory GABAergic interneurons explaining the occurrence of seizures and in the cerebellum **(Gan & Kaczmarek, 1998; Rudy & McBain, 2001)**.
- The phenotype is quite similar to ULD and englobes; after a normal childhood development; myoclonus and seizures, tremor and ataxia in the first decade of life, progressing to disability and mild cognitive decline **(Barot et al., 2020; Muona et al., 2015; Nascimento & Andrade, 2016)**.

- EEG shows generalised epileptiform activity with inconstant photosensitivity **(Nascimento & Andrade, 2016)**. Abnormalities in sensory evoked potential was reported **(Barot et al., 2020)**.
- Brain MRI is usually normal, cerebellar atrophy was reported in some patients. in some patients **(Muona et al., 2015)** .
- Genetic analysis using next generation sequencing confirms the diagnosis **(Muona et al., 2015)**.
- In addition to symptomatic care, antiepileptic drugs are the only therapy used, waiting for new discoveries **(H. Feng et al., 2024; Gandini & Zamponi, 2024)**. One case was reported of successful deep brain stimulation in patient with PME7 **(Sobstyl et al., 2023)**.

5.9. Acid ceramidase deficiency: Farber disease (FD) OMIM #228000 and spinal muscular atrophy with progressive myoclonic epilepsy (SMA-PME) OMIM #159950

- FD and SMA-PME are rare AR lysosomal storage disorders caused by the mutation of N-acylsphingosine amidohydrolase 1 (ASAH1) gene located on the chromosome 8p22 and encodes a ceramide metabolism enzyme called acid ceramidase **(Li et al., 1999; Zhou et al., 2012)**.Acid ceramidase deficiency mutation is responsible for intralysosomal ceramide accumulation leading to multisystemic disorders **(Alayoubi et al., 2013)**.
- While FD or Farber lipogranulomatosis is the extraneurologic form and includes a common triad for its different phenotypes made of subcutaneous nodules (or lipogranulomas: macrophages with intracellular ceramide), joints affection (arthritis and contractures) and dysphonia, with other systemic disorders such as hepato-splenomegaly… **(Elsea et al., 2020)** with the exception of the FD type 5 called "neurological progressive" type and exhibits CNS manifestations (seizures, myoclonus, cognitive decline) **(Ehlert et al., 2007; Eviatar et al., 1986)** SMA-PME is primarily characterised by the CNS affection (lower motor neuron disease, tremors, myoclonus and seizures, cognitive decline progressing till death at the childhood or adulthood age **(Elsea et al., 2020)**.
- EEG and EMG objectives electric abnormalities and brain MRI is usually normal **(David A Dyment et al., 2018)**.
- Diagnosis is confirmed by genetic analysis or enzyme activity measuring **(Schmoeckel & Hohlfed, 1979)**.
- Symptomatic management is the major treatment (antiepileptic drugs and physical therapy). Gene therapy and enzyme replacement therapy are still future options in progress **(Kleynerman et al., 2023)**.

III. Atypical PMEs

1. Introduction:

Atypical PEMs are a group of neurological affections that may lead in some of their forms to a similar PMEs clinical presentation. We can list:

- Huntington disease: myoclonic variant **(Thakor et al., 2021)**.
- Wilson disease **(Sachan et al., 2017; Verma et al., 2016).**
- Example of epilepsy linked to *RORB* gene mutations **(Rudolf et al., 2016).**
- Young-onset Alzheimer's dementia (Mahale et al., 2023).
- Cerebrotendinous Xanthomatosis (Desai et al., 2021).
- Mitochondrial recessive ataxia syndrome (includes SANDO (Sensory Ataxic Neuropathy, Dysarthria, And Ophthalmoparesis) and spinocerebellar ataxia with epilepsy (SCAE) formerly designated caused by mutations in the *POLG* gene (Yi Shiau Ng, 2017).

Here below we will talk about atypical PME form linked to *RORB* gene mutations.

2. Epilepsy linked to *RORB* mutation

2.1. Retinoic acid-related orphan receptor (ROR)β

Retinoic acid-related orphan receptor (ROR)β also called RORB, coded by the *RORB* gene, is a member of the orphan nuclear receptor family (with RORα or A and RORγ or C) forming with steroid hormone receptors and non-steroid hormone receptors the Nuclear receptors superfamily which play the role of transcription factors **(Cook et al., 2015)**.

The RORB receptor is ubiquitary with high concentration in the brain **(Sumi et al., 2002)**, retina **(André, Gawlas, et al., 1998)**, pineal gland **(Baler et al., 1996)**, bone **(Roforth et al., 2013)**... The binding ligand to the RORB receptor is not yet known, but it plays many important roles including:

- Osteogenic repression **(Roforth et al., 2013)**.
- Circadian rhythm regulation **(Cook et al., 2015; Masana et al., 2007)**.
- Tumour suppression **(S. Feng et al., 2015)**.
- Cell development, organogenesis and differentiation **(Paravicini et al., 1996)**.
- Metabolism management.**(Taneera et al., 2019)**
- Immune regulation **(Cook et al., 2015)**.
- Neuronal cells differentiation.**(Liu et al., 2017)**
- CNS genesis. **(Jabaudon et al., 2012)**
- Retina neurogenesis **(André, Conquet, et al., 1998)**.

- It is also involved in the pathogenesis of epilepsy, intellectual disability and psychiatric disorders. **(Baglietto et al., 2014; McGrath et al., 2009)**

02 RORB isoforms were described in mice: RORβ1 and RORβ2 and only RORβ1 was found in humans **(André, Gawlas, et al., 1998; S. Feng et al., 2015; Jetten, 2009; Masana et al., 2007)**.

RORs family of receptors common structure is made of four functional domains:

- Amino-terminal A/B domain.
- DNA-binding domain (DBD).
- Hinge region.
- Carboxy-terminal ligand-binding domain (LBD).

ROR isoforms differ in their Amino-terminal A/B domain: RORB1 has 2 amino acid while RORB2 has 13 **(S. Feng et al., 2015; Liu et al., 2017)**.

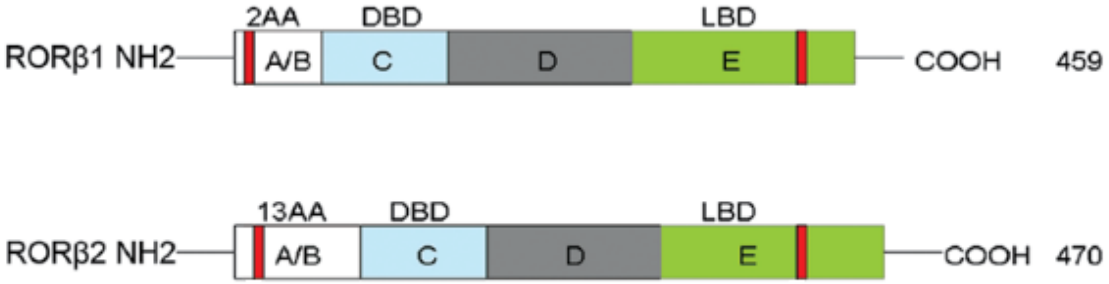

Figure 10: RORβ isoforms structure with 04 functional domains: amino-terminal A/B domain, DNA-binding domain (DBD), a hinge region (D) and carboxy-terminal ligand-binding domain (LBD) **(S. Feng et al., 2015).**

2.2.Epidemiology

Among few studies made on patients with epilepsy secondary to *RORB* mutations, **(Rudolf et al., 2016; Sadleir et al., 2020)** showed the following epidemiologic features:

- Age of onset: First decade.
- Sex ratio: No study found.
- Prevalence: Rare not defined.
- Cases reported in: france and australia

2.3.Pathophysiology

Studies made on mice showed that mutations in one of the two RORB variants could affect different domains and cause multisystemic defects by alteration of homeostatic pathways controlled by

RORB. This include retina photoreceptor abnormalities, interneuronal and synapses dysfunction, epilepsy, intellectual disability… **(Murray et al., 2021)**

Study results published by **(Gokce-Samar et al., 2024)** found that RORB dysfunction leads to length shortened axons compared with normal persons.

2.4.Clinical manifestations

Publications made by **(Gokce-Samar et al., 2024; Liu et al., 2017; Morea et al., 2021; Murray et al., 2021; Rudolf et al., 2016; Sadleir et al., 2020)**, resume non exhaustive clinical manifestations related to *RORB* mutations:

- Seizures : focal and more frequently generalised : absence+++, myoclonic, generalised tonic-clonic, occipital seizure or febrile seizure.
- Behavioural impairment.
- Intellectual disability.
- Autism spectrum disorder.
- Sleep disturbance.
- Retinal defects and vision impairment.
- Ataxia.

2.5.EEG

- Photosensitive seizures **(Morea et al., 2021)**.
- 3 Hz frequency bilateral, synchronous and symmetric spikes, waves and polyspikes discharges **(Rudolf et al., 2016; Sadleir et al., 2020).**

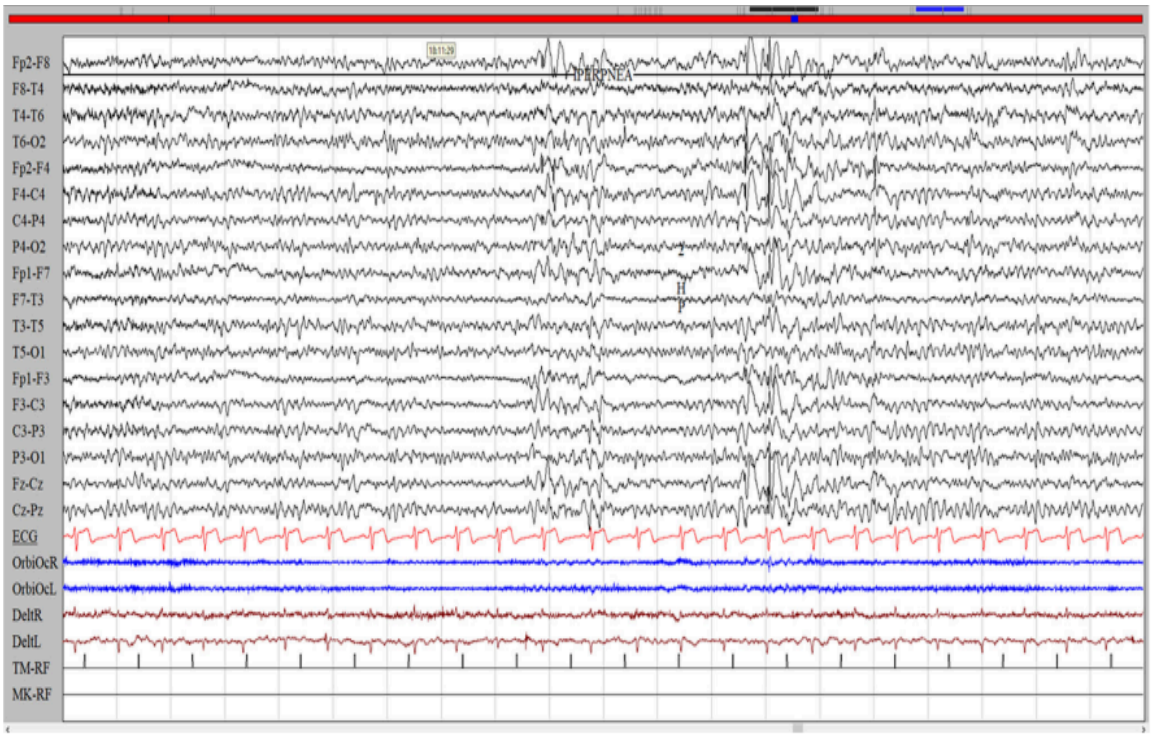

Figure 11: EEG and orbicularis ocular muscles EMG reveal: well organised background activity, discharges of bilateral, synchronous and symmetric spikes and waves **(Morea et al., 2021)**

2.6.Brain imaging

Normal brain imaging was found in patients suffering from Epilepsy with RORB mutations **(Rudolf et al., 2016; Sadleir et al., 2020)**.

2.7.Genetics

Available scientific papers **(Liu et al., 2017; Lungo, 2016; Rudolf et al., 2016; Sadleir et al., 2020)** published about RORB mutation epilepsy reveal that:

- RORB gene is located on chromosome 9q21.13 **(André, Conquet, et al., 1998)**.
- The affection could be sporadic or inherited as autosomal dominant inheritance mode with incomplete penetrance.
- Mutations are detected by WES and WGS .
- Frequent mutations are: (micro)deletion, translocation, nonsense, missense mutations.

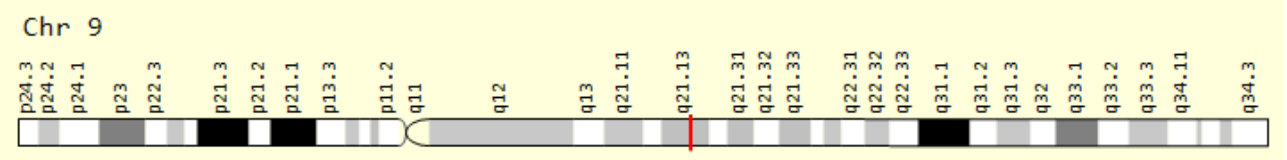

Figure 12: RORB gene (***RORB Gene - GeneCards | RORB Protein | RORB Antibody***, 2024)

2.8.Diagnosis

- Clinical signs and age of onset.
- Family history.
- EEG.
- Confirmed by genetic study **(Rudolf et al., 2016)**.

2.9.Prognosis and evolution

Troubles begin in infancy then progress gradually **(Sadleir et al., 2020).**

2.10.Treatment

- No curative treatment exists.
- Anti-epileptic drugs are used to control seizures and myoclonus **(Sadleir et al., 2020).**

PRACTICAL PART

PATIENTS AND METHODS

1.Study framework:

The study is a transversal retrospective study carried out on patients having PMEs hallmark signs with or without family history of seizure and with or without consanguinity. Patient recruitment was conducted between December 2023 and March 2024 and was conducted in the epilepsy clinic of Dr Benbadis University Hospital receiving patients from all over eastern Algeria.

2.Inclusion and exclusion criteria:

We enrolled patients from both genders and their families (parents and other affected family members) based on the presence of PMEs clinical signs : myoclonus and seizures associated with cognitive impairment, cerebellar ataxia with concordant EEG findings and progression.

We exclude patients who didn't fulfil the clinical criteria, had other confirmed diagnosis explaining their phenotype or symptoms better explained by other diagnosis including acquired causes (infections, traumatism, meningitis, head trauma, cerebral palsy…) or differential myoclonic seizures like juvenile myoclonic epilepsy (JME) and benign familial myoclonic epilepsy (BFME).

Other reasons for exclusion included: lost contact, incomplete data, absent imaging, refusal to participate and sign consent forms.

3.Molecular study

3.1.Patients' phenotype:

We included 14 probands from 11 families, diagnosed clinically as PME's and other affected family members if they exist.

Based on family history, patients were divided into two groups:

- Familial cases: having other affected family members.
- Sporadic cases: without any other affected family members.

Patients were reviewed alongside the student by a Professor of Neurology validating the clinical phenotype and the electrophysiological findings.

We then proceeded to collect relevant demographic data, history, family trees, clinical symptoms, electrophysiological findings, progression and treatments. All patients signed a board approved consent form **(See Appendix)** to approve inclusion in the study and to have anonymous data collected.

3.2.Genetic analysis

Blood samples were collected during medical appointments then sent to DNA extraction, four patients benefited from commercial whole exome sequencing, other patients will be tested when possible.

3.2.1.DNA extraction from whole blood

3.2.1.1.Blood samples

04 to 08 ml of venous blood sample per person was collected to be used for DNA extraction, sterile conditions were strictly observed and vacutainer tubes containing EDTA (Ethylenediamine tetraacetic acid) as an anticoagulant were used.

When DNA extraction wasn't readily available, blood samples were conserved in refrigerators at four degrees celsius for a short period of time.

3.2.1.2.DNA extraction

We used Miller's method **(See Appendix)** to extract DNA from The whole blood sample collected previously, using sodium chloride (NaCl) as an inorganic solvent.

This method consists of four successive steps: leukocytes' preparation, DNA extraction, DNA precipitation and DNA solubilization **(Miller et al., 1988)**.

- **Leukocytes' preparation:** the leukocytes are separated from the blood by red blood cells hypotonic lysis in a Tris-EDTA (TE) 20:5 buffer (containing 20 mmol Tris, 5 mmol EDTA, pH 7.5) for 10 minutes on ice. After washing, the pellet is resuspended in TE 20:5.
- **DNA extraction:** is done by adding a lysis buffer (400 mmol NaCl, 2 mmol EDTA, 10 mmol Tris,pH 8.2), 10% Sodium Dodecyl Sulfate (SDS), 10 mg/ml proteinase K and 4 ml of 4 mol NaCl.
- **DNA precipitation:** using high concentrations of pure and cold ethanol (-80°C and 2.5x sample volume concentration) and TE 10:1.
- **Solubilization:** using TE (10:1) or bidistilled water.

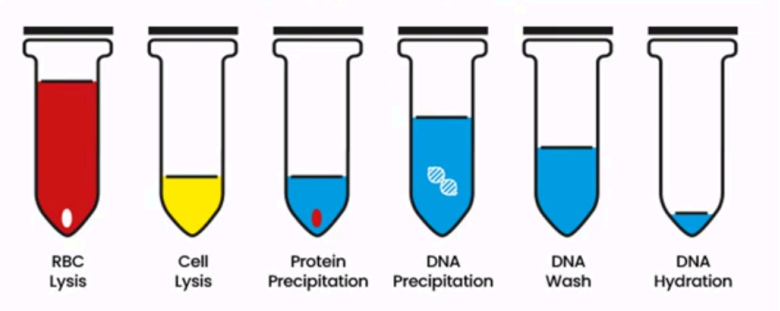

Figure 13: DNA blood extraction Miller's method

3.2.2.Determination of purity and quality of extracted DNA

A Nanodrop spectrophotometer is used to check DNA purity and concentration; replacing the classic UV spectrophotometry technic **(See Appendix)**; by putting 1-2µl of DNA or RNA solution into the sensor pedestal and gently lower the nanodrop arm then the analysis is done automatically using the software.

3.2.3.DNA stability storage

The table below resumes DNA time conservation and the corresponding temperature.

Table 02: DNA stability duration according to the storage temperature **(Matange et al., 2021)**.

Temperature	DNA stability duration
Ambiante	few days
+ 4°C	6 months
-20 °C	1 year
- 80 °C	7 years

3.2.4.Genotyping

In order to genetically analyse our samples, we used the whole exome sequencing method.

Four probands from four families (family 1,2,6 and 7) benefited from commercial whole exome sequencing.

WES is a next-generation sequencing (NGS)-based test in which the protein-coding exonic regions of all of a patient's genes (known as the exome) are tested simultaneously. A gene-agnostic approach was used as the geneticist proceeded to look at variants identified in all the genes without restricting the analysis to only known pathogenic genes. WES is done using short-read NGS technology.

This technology refers to sequencing short strands of DNA with read quality dropping after around 150 bp strand length. Patient genomic DNA is fragmented and exonic DNA is enriched during laboratory processing. Sequencing data are generated only for exonic regions and a small amount of adjacent non-coding DNA (splice sites and moderators mainly). All data is stored and generated in a VCF file (Variant Call Format) containing reads quality and genomic mapping information for all variants. An important step is to proceed to annotation which is based on a bioinformatics algorithm that will process every variant to identify if it is different from the reference human genome

currently in use (Chr38), only variants deviating from the reference are kept. The algorithm then proceeds to fetching all relevant data for each variant including: its type (missense, frameshift, splice site, synonymous, stop-gain, stop-loss), its frequency in known databases for all ancestries, its pathogeny scores from known prediction tools (like splice AI, Polyphene, Sift…), and overall effect of the variant (high, moderate or low). The data now generated is human readable and is analysed through many steps of filtering by the geneticist to generate a list of potentially responsible variants. Phenotypic correlation will then allow the selection of the pathogenic variant if found.

3.2.5. Statistical analysis, data-entry and graphic production:

We have used Microsoft's office 2016 suite of applications: PowerPoint for family trees design and graphs conception, Excel for data entry and statistical analysis.

RESULTS
AND
DISCUSSION

1. Clinical data

1.1.Family N°01 (F1): F1 is a M'zabi family, issued from the same tribe, compounded of at least 27 members divided into 03 generations, with a history of one third degree consanguineous marriage, containing 01 PME affected person.

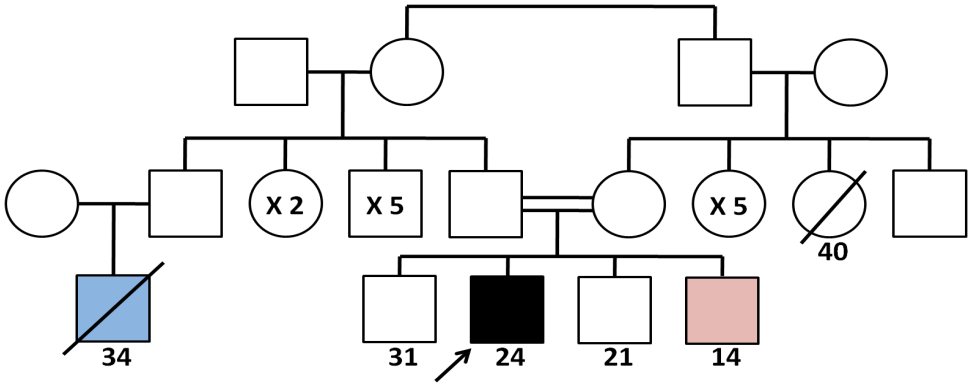

Figure 14: Family N°01 (F1) pedigree. F1.1 is the proband, numbers under figures indicate ages in years, numbers inside figures indicate individual number.

1.1.1.Proband (F1.1): A 24 years old single man born from third degree consanguineous marriage, from Ghardaia, Master's degree student, without previous medical history, had manifested at the age of 11 GTCs, few time after he noticed tremor and execution impairment, at the age of 14 the myoclonus appeared associated with study's difficulty. Clinical exam objectifies mild stato-kinetic cerebellar syndrome associated with myoclonus and insomnia.

Even Though cognitive score evaluation using Montreal Cognitive Assessment (MoCA) **(See Appendix)** was normal, cognitive impairment is noticed, needing to use more efficient tests.

Quality life score showed a mild alteration.

EEG showed epileptic discharges with normal background activity.

Brain MRI revealed generalised atrophy more marked on frontal lobes. The patient receives Leveteracetam as anti-epileptic drug and reports a stationary progression after a slow evolution. We suspected the diagnosis of ULD. WES was negative which is expected since ULD dodecamer expansions cannot be detected by this technique.

1.1.2.Other affected family members: No one has been reported.

1.2.Family N°02 (F2): F2 is a family from Skikda. Composed of at least 18 member divided into 03 generations, with a history of one third degree consanguineous marriage, containing 01 PME affected person.

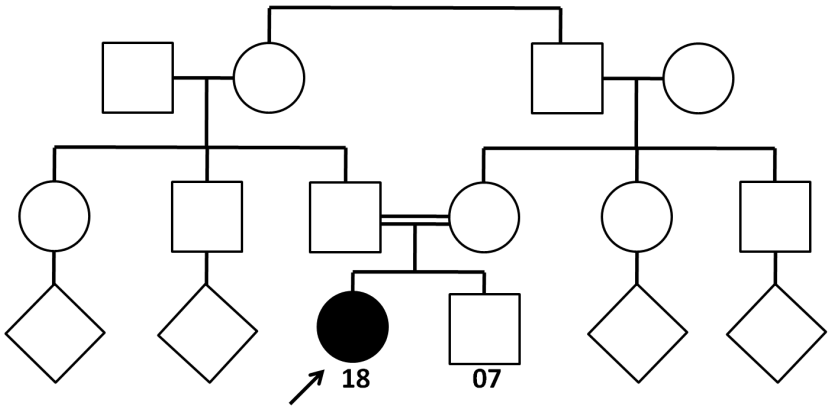

Figure 15: Family N°02 (F2) pedigree. F2.1 is the proband, numbers under figures indicate ages in years, numbers inside figures indicate individual number.

1.2.1.Proband (F2.1): An 18 years old single girl born from third degree consanguineous marriage, from Skikda, without previous medical history, had manifested at the age of 12 occipital seizures (blindness with simple visual hallucinations) then GTCs at 15 years old. At 16 years old parents reported absence seizures and myoclonus with cognitive regression rapidly worsening. Clinical exam objectifies: an altered general status, Anarthria, major cognitive decline, cerebellar ataxia, loss of walking, drooling and dysphagia, myoclonus, myoclonic tremor and insomnia.Quality life scores are deeply altered.

EEG showed diffuse epileptic discharges and slow background activity. Brain MRI was normal. The patient receives Valproate, Levetiracetam and Rivotril as anti-epileptic drugs and the family reports a quick progression of the symptomatology. We suspected the diagnosis of LD which was confirmed by skin biopsy showing the presence of Lafora Bodies and by WES genetic testing showing the presence of a novel missense variant ***EMP2A*:c.659T>A (p.Leu220Gln)**.

1.2.2.Other affected family members: No one had been reported

1.3.Family N°03 (F3): F3 is a family from Mila. Compounded of at least 17 members divided into 03 generations, without consanguineous marriage history, containing 02 PME affected person.

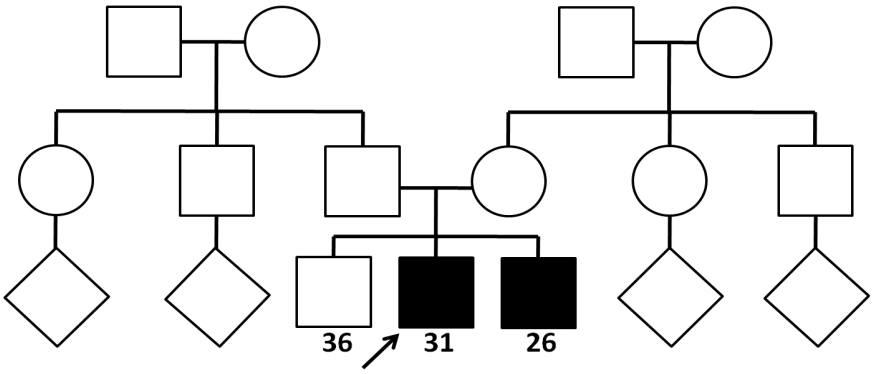

Figure 16: Family N°03 (F3) pedigree. F3.1 is the proband, F3.2 is the other affected member. Numbers under figures indicate ages in years, numbers inside figures indicate individual number.

1.3.1.Proband (F3.1): A 31 years old single man born from non consanguineous marriage, from Mila,without previous medical history, had manifested at the age of 06 years old frequent absence seizures with resolution a complete at 13 years old when myoclonus, GTCs and tremor appeared. At 14 years old he was excluded from the school because of his cognitive impairment. Clinical exam objectifies: cerebellar syndrome made of dysarthria, nystagmus, action and attentional tremor, hypermetria and static ataxia; myoclonic tremor and insomnia. Quality life scores are moderately altered.

EEG showed diffuse epileptic discharges with normal background activity. Brain MRI was normal. The patient receives Valproate, Levetiracetam and Topiramate as anti-epileptic drugs and reports a stationary progression. We suspected the diagnosis of ULD, genetic analysis is in progress.

1.3.2.Other affected family members (F3.2): A brother **(F3.2)** was reported as the only other affected family member with quite similar history and symptomatology, under monotherapy (Valproate), reporting slow disease progression and for whom genetic analysis is in progress.

1.4.Family N°04 (F4): F4 is a family from Skikda. Compounded of at least 17 member divided into 03 generations, without consanguineous marriage history, containing 01 PME affected person.

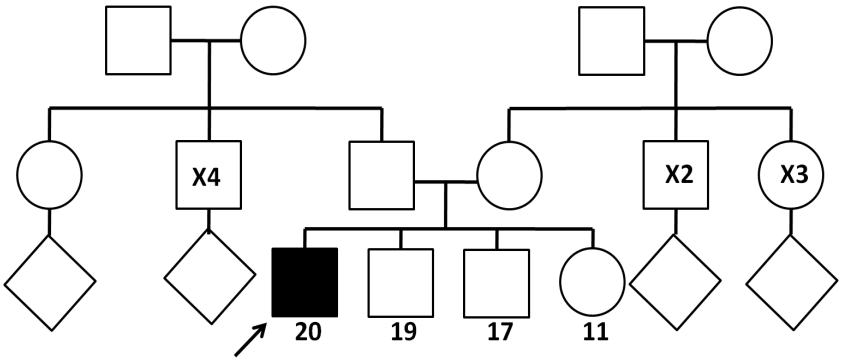

Figure 17: Family N°04 (F4) pedigree. F4.1 is the proband. Numbers under figures indicate ages in years, numbers inside figures indicate individual number.

1.4.1.Proband (F4.1): A 20 years old single man born from non consanguineous marriage, from Skikda,without previous medical history, had manifested at the age of 12 years old progressive myoclonus causing scholar eviction. At 13 years old, GTCs appeared. At 15 Years old he reported tremor and at 18 years old he was unable to walk. Clinical exam objectifies: Cerebellar syndrome made of dysarthria , hypermetria, adiadococinesia, loss of walking and gait balance, myoclonus and myoclonic tremor, without cognitive impairment. Quality life scores are moderately altered.

EEG showed diffuse epileptic discharges with normal background activity. Brain MRI was normal. The patient receives Valproate, Gardenal, Levetiracetam as anti-epileptic drugs and reports a slow progression. We suspected the diagnosis of ULD, genetic analysis is in progress.

1.4.2.Other affected family members: No one had been reported

1.5.Family N°05 (F5): F5 is a family from Biskra, issued from the same tribe, composed of at least 36 member divided into 03 generations, with consanguineous marriage history, containing 03 PME affected person.

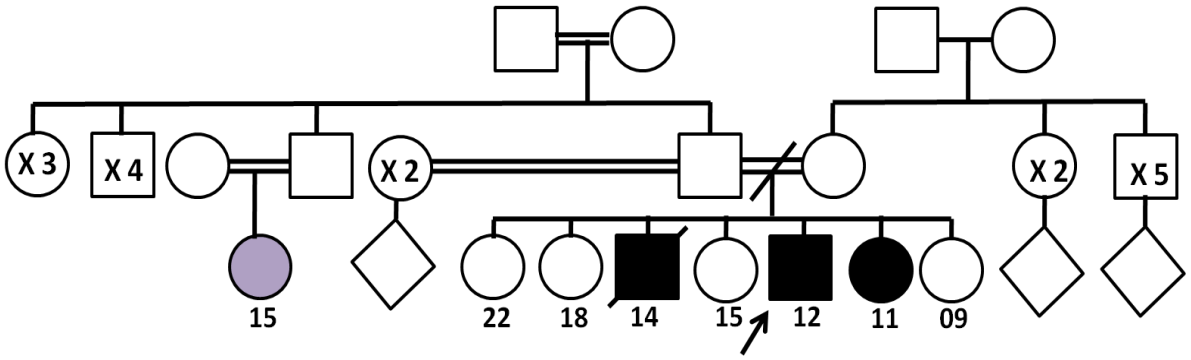

Figure 18: Family N°05 (F5) pedigree. F5.1 is the proband, F5.2-3 are other affected members. Numbers under figures indicate ages in years, numbers inside figures indicate individual number.

1.5.1.Proband (F5.1): A 12 years old boy, born from third degree consanguineous marriage, from Biskra,without previous medical history, had manifested at the age of 08 years old GTCs, visual seizures (animals: dogs), absence seizures and myoclonus associated with rapid cognitive decline and severe behaviour trouble. At 09 years old tremor, dysarthria and gait balance impairment appeared and at 10 years old he lost walking, speech and vision. Clinical exam objectifies: Important motor and cognitive decline, walking and speech and vision loss, severe behaviour troubles. Quality life scores are extremely altered.

EEG showed diffuse epileptic discharges with abnormal and slow background activity. Brain MRI is not available. The patient receives Valproate, Topiramate, Levetiracetam as anti-epileptic drugs. The mother reports a quick progression. We suspected the diagnosis of CLN, genetic analysis is in progress.

1.5.2.Other affected family members (F5.2 and F5.3): The same phenotype was reported in an older brother **(F5.2)** who died after a status epilepticus at the age of 14 years old, 06 years after disease onset. We also confirmed clinically the affection of one little sister **(F5.3)** having the same phenotype without vision loss yet and for whom genetic analysis is in progress.

1.6.Family N°06 (F6): F6 is a family from Constantine, composed of at least 19 member divided into 03 generations, with consanguineous marriage history, containing 05 PME affected person.

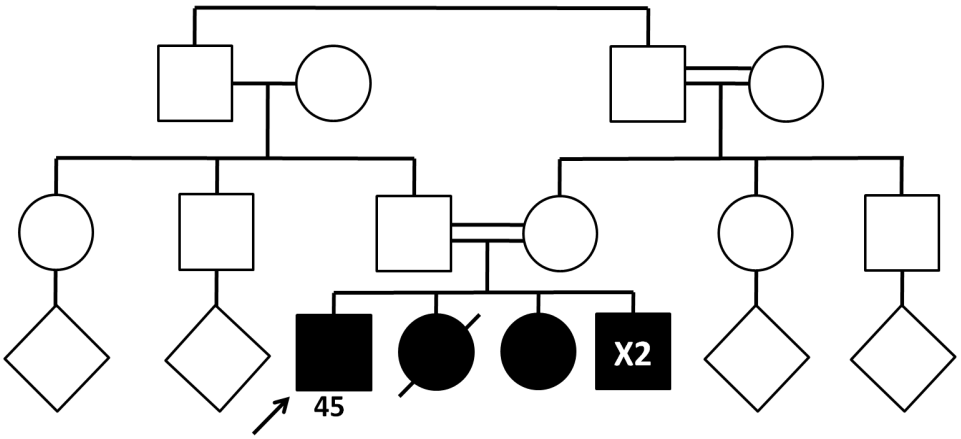

Figure 19: Family N°06 (F6) pedigree. F6.1 is the proband, F6.2-5 are other affected members. Numbers under figures indicate ages in years, numbers inside figures indicate individual number.

1.6.1.Proband (F6.1): A 45 years old single man, born from third degree consanguineous marriage, from Constantine,without previous medical history, had manifested at the age of 10 years old progressively worsening myoclonic jerks associated with GTCs and cognitive decline leading to scholar exclusion, speech and walking loss.

Clinical exam objectifies: severe cerebellar ataxia, important cognitive decline, speech and walking loss, myoclonus and myoclonic tremor.

Quality life scores are extremely altered. EEG showed diffuse epileptic discharges with abnormal and slow background activity.

Brain MRI is not available. The patient receives Gardenal as anti-epileptic drug. The family reports a quick progression.

We suspected the diagnosis of a severe ULD variant. However, genetic analysis revealed a *RORB* known pathogenic splice site variant ***RORB*:c.94-1G>A.**

1.6.2.Other affected family members (F6.2-5): The same phenotype was reported in a dead sister **(F6.2)**, alive sister **(F6.3)** and two alive brothers **(F6.4-5)**.

1.7.Family N°07 (F7): F7 is a family from Constantine, compounded of at least 65 members divided into 04 generations, with consanguineous marriage history, containing 06 PME affected persons.

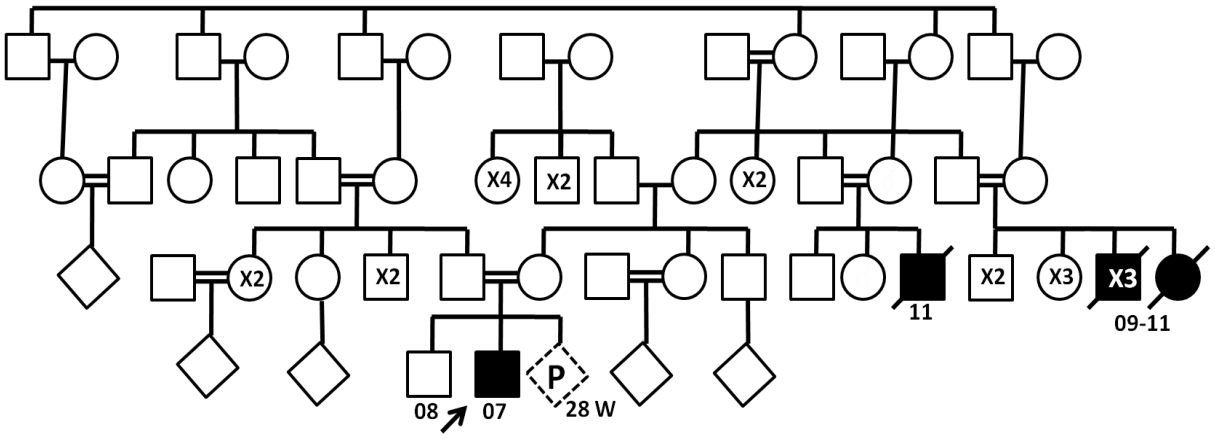

Figure 20: Family N°07 (F7) pedigree. F7.1 is the proband, F7.2-6 are other affected members. Numbers under figures indicate ages in years, numbers inside figures indicate individual number. "P" inside the figure indicates a pregnancy in progress for which the age is calculated in weeks "W".

1.7.1.Proband (F7.1): A 07 years old boy, born from fourth degree consanguineous marriage, from Constantine,who suffered from neonatal anoxia, had manifested at the age of 03 years old dysarthria and hypermetria. Few months later, the mother noticed behaviour troubles and intellectual impairment compared with his brother. At 04 years old myoclonus appeared with insomnia. At 05 years old, balance and vision impairment started. At 06 years old, walking became impossible without aid, sitting was impossible and he totally lost walk, vision and speech. At 07 years old he manifested GTCs and myoclonus tremor. Clinical exam objectifies: Deep mental retardation with speech, walking and vision loss, motor decline , retraction, trophic troubles, general state alteration server ataxia, myoclonic tremor and insomnia.

Quality life scores are extremely altered. EEG showed diffuse epileptic discharges, abnormal and slow background activity with posterior predominance. Brain MRI revealed fronto-parieto-temporal bilateral atrophy, cerebellum atrophy, Dandy walker variant and decreased NAA pic in spectroscopy. The patient receives Valproate, Levetiracetam, Urbanyl, Topiramate, Rivotril as anti-epileptic drug and Melatonin for insomnia. The family reports a quick progression.

We suspected the diagnosis of CLN. Genetic analysis using WES confirmed that the patient is carrying a known pathogenic inframe deletion variant ***CLN6*:c.791CCT[1] (p.Ser265del).**

1.7.2.Other affected family members (F7.2-6): Five dead cousins **(F7.2-6)** were reported having similar phenotypes 6-8 years after disease onset.

1.8.Family N°08 (F8): F8 is a family from Setif, compounded of at least 28 member divided into 03 generations, without consanguineous marriage history, containing a twin PME affected person.

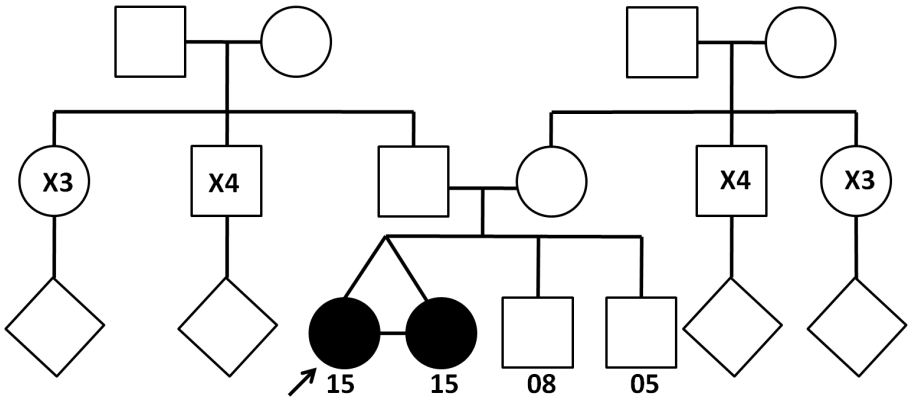

Figure 21: Family N°08 (F8) pedigree. F8.1 is the proband, F7.2 is the affected twin. Numbers under figures indicate ages in years, numbers inside figures indicate individual number.

1.8.1.Proband (F8.1): A 15 years old girl, born from non consanguineous marriage, from Setif, without previous medical history, had manifested at the age of 12 years old tremor of the superior limbs than the inferior ones. 08 months later she presented GTCs. At 14 years old, gait and balance instability appeared and 10 months later, the family reported rapidly worsening myoclonus with important cognitive decline leading to scholar exclusion. Clinical exam objectifies: Cerebellar syndrome with important motor and cognitive decline, walking and speech loss, myoclonus and myoclonic tremor, dysphagia, mastication difficulty and insomnia. Quality life scores are extremely altered.

EEG showed diffuse epileptic discharges, abnormal and slow background activity. Brain MRI revealed periventricular hyperintensity. The patient receives Valproate, Levetiracetam, Topiramate, Clonazepam as anti-epileptic drugs. The family reports a quick progression. We suspected the diagnosis of CLN. Genetic analysis is in progress.

1.8.2.Other affected family members (F8.2): We confirmed clinically the similar affection of her twin **(F8.3)** who took part in the genetic analysis.

1.9.Family N°09 (F9): F9 is a family from Batna, composed of at least 38 member divided into 04 generations, with consanguineous marriage history, containing only one affected individual.

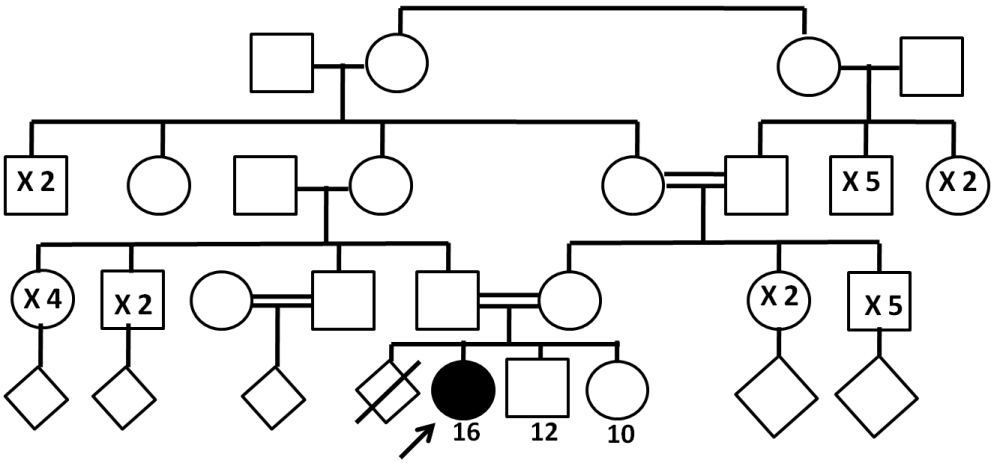

Figure 22: Family N°09 (F9) pedigree. F9.1 is the proband. Numbers under figures indicate ages in years, numbers inside figures indicate individual number.

1.9.1.Proband (F9.1): A 16 years old girl born from third degree consanguineous marriage, from Batna,without previous medical history, had manifested at the age of 05 years old, progressive worsening GTCs and temporal seizures. At 14 years old simple occipital seizures (colours), myoclonus and ataxia appeared. At 17 years old she was excluded from school. Clinical exam objectifies: Cerebellar syndrome made of dysarthria, nystagmus, hypermetria, hypotonia, gait and balance impairment and head tremor, behaviour and attentional troubles, severe cognitive decline myoclonus and myoclonic tremor.

Quality life scores are moderately to severely altered.

EEG showed diffuse epileptic discharges with slow background activity. Brain MRI was normal. The patient receives Valproate and Levetiracetam as anti-epileptic drugs and the family reports a quick progression of the symptomatology. We suspected the diagnosis of CLN. Genetic analysis is in progress.

1.9.2.Other affected family members: No one had been reported.

1.10.Family N°10 (F10): F10 is a family from Skikda, composed of at least 26 member, divided into 04 generations, with consanguineous marriage history, containing 03 PME affected persons.

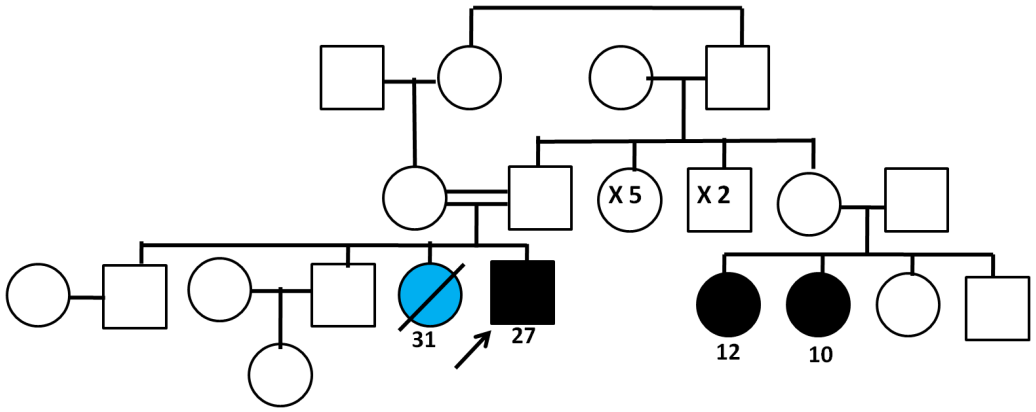

Figure 23: Family N°10 (F10) pedigree. F10.1 is the proband. F10.2-3 are other affected family members. Numbers under figures indicate ages in years, numbers inside figures indicate individual number.

1.10.1.Proband (F10.1): A 27 years old single man, born from third degree consanguineous marriage, from Skikda, with a history of febrile seizures, head trauma at the age of 05 and 09 years old and hypothyroidism, had manifested at the age of 10 years old myoclonus then GTCs and intellectual decline at 14 years old. At the age of 17 years old he noted seizures disappearing for 04 years. At the age of 22 years myoclonus and GTCs reappeared with progression associated with temporal seizure (*déjà vu, déjà vécu*). Clinical exam objectifies mild cerebellar syndrome made of tremor, hypermetria and gait impairment, mild cognitive decline with attentional troubles, partial hearing loss and myoclonus. Quality life score showed a quite mild alteration.

EEG showed epileptic discharges with normal background activity.

Brain MRI was normal. The patient receivesValproate, Levetiracetam and Topiramate as anti-epileptic drugs and reports a slow progression of the disease. We suspected the diagnosis of ULD. Genetic analysis is in progress.

1.10.2.Other affected family members (F10.2-3): Two affected cousins were reported having the same phenotype **(F10.2-3)**.

1.11.Family N°11 (F11): F11 is a family from Mila, composed of at least 58 members, divided into 04 generations, with consanguineous marriage history, containing 07 PME affected persons.

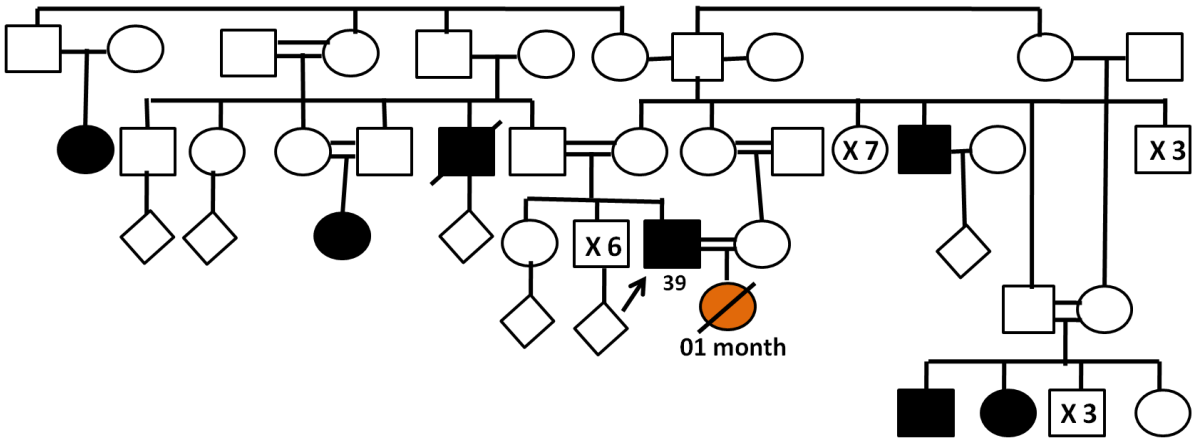

Figure 24: Family N°11 (F11) pedigree. F11.1 is the proband. F10.2-7 are other affected family members. Numbers under figures indicate ages in years, numbers inside figures indicate individual number.

1.11.1.Proband (F11.1): A 39 years old married man and father of a dead girls secondary to a cardiac problem, born from third degree consanguineous marriage, from Mila, with a history of head trauma at the age of 05 years old, had manifested at the age of 14 years old GTCs with cognitive impairment then myoclonus and absence seizures at the age of 34 years old. 03 months ago anterograde amnesia was reported.

Clinical exam objectifies mild cerebellar syndrome made of nystagmus, hypermetria, adiadococinesia, tremor and static ataxia with moderate cognitive impairment and partial vision loss. Quality life score showed a quite mild alteration. EEG showed epileptic discharges with normal background activity. Brain MRI is not available. The patient receivesGardenal, Levetiracetam and Gabatrex as anti-epileptic drugs and reports a slow progression of the disease. We suspected the diagnosis of ULD. Genetic analysis is in progress.

1.11.2.Other affected family members (F11.2-7): One dead uncle **(F11.2)** and five uncle and cousins were reported having the same phenotype **(F11.3-7).**

2. Epidemiology Results

2.1.Frequency

To better calculate frequency in the population we opted to include all reported affected family members even if they were not formerly included and evaluated for the current study described **33** affected persons (**25** alive and **08** dead) issued from **11** families. We calculated the disease prevalence based on 2020 *ONS* (*Organisation National des Statistiques*) demographic data.

The prevalence was about **4/1 million**. We could not compare this prevalence to the global one because of the lack of specific statistics involving all disorders in the literature while we lack a specific diagnosis for most patients. It's important to note that our population isn't representative of the overall population, thus an enlarged study will be more informative.

2.2.Familial and sporadic cases

We noticed that **28.6% (04 subjects)** were sporadic cases whereas **71.4% (10 subjects)** had familial history. All literature reviews and studies reported the predominance of familial cases as affections are mostly AR **(Cameron et al., 2023; Jain, 2011)**.

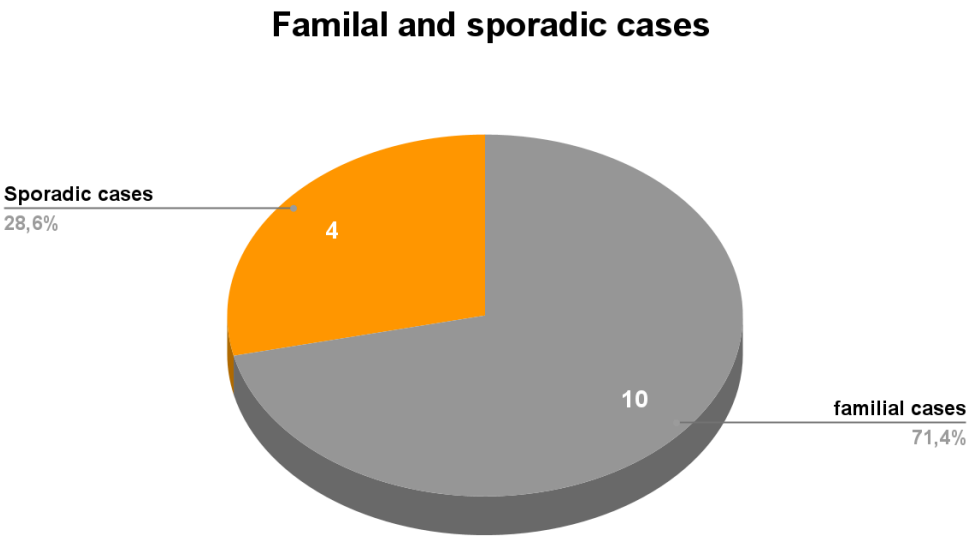

Figure 25: Distribution according to familial or sporadic cases

2.3.Gender

35.70 % (5 Subjects) of our study patients were females while **64.3% (9 subjects)** were males. Sex ratio is **1.8** but no study is available to compare, needing a global one to be more informative

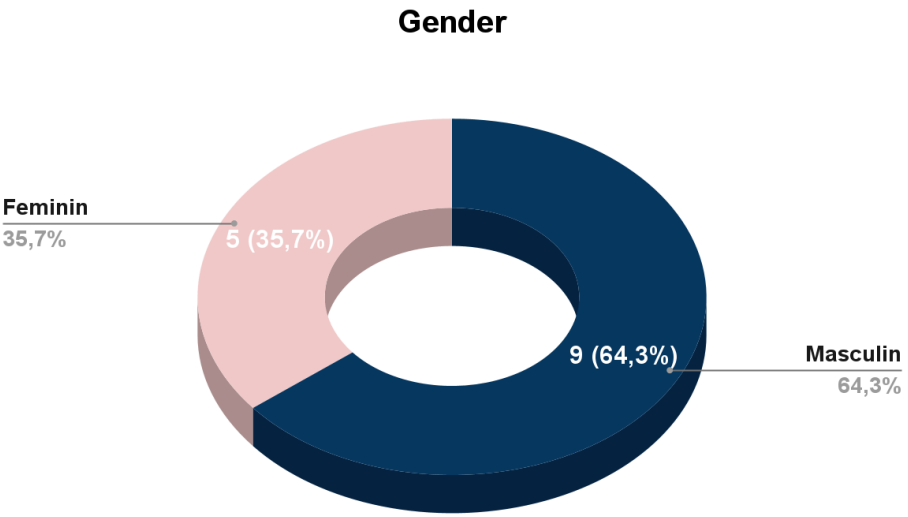

Figure 26: Distribution according to the gender

2.4.Consanguinity

We noticed that **35.70 % (5 Subjects)** of our study sample were born from non consanguineous marriage, while **64.30 % (9 subjects)** were born from consanguineous marriage. This finding is expected since most PMEs are transmitted in an autosomal recessive manner and concord with previous findings **(Cameron et al., 2023; Jain, 2011)**.

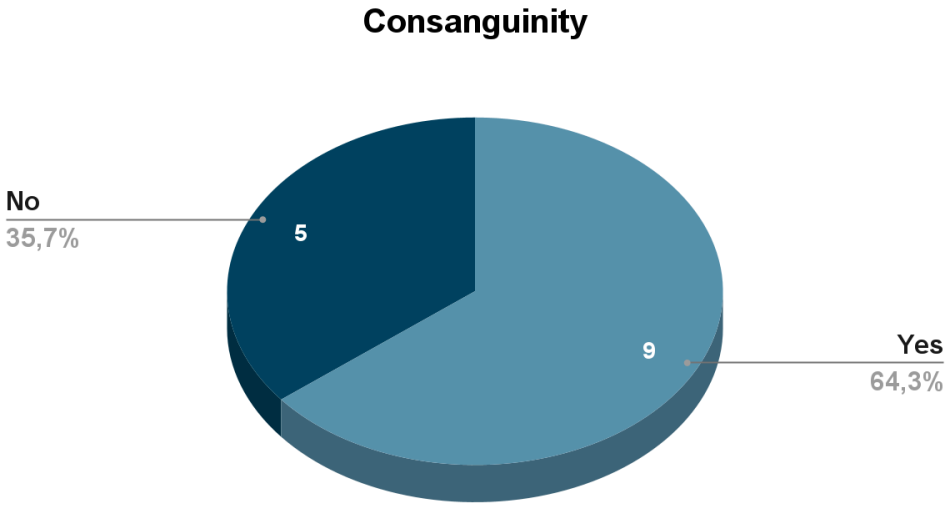

Figure 27: Distribution according to the consanguinity

2.5.City of origin

The majority of patients are from Skikda and Mila, followed by Constantine, Biskra and Setif, and finally Batna and Ghardaia. This can be explained by a bias selection as our recruiting centre is located in the Eastern part of the country. However, no studies upon the rate of consanguineous marriage in eastern Algeria were made permitting to take it as reason for this average difference.

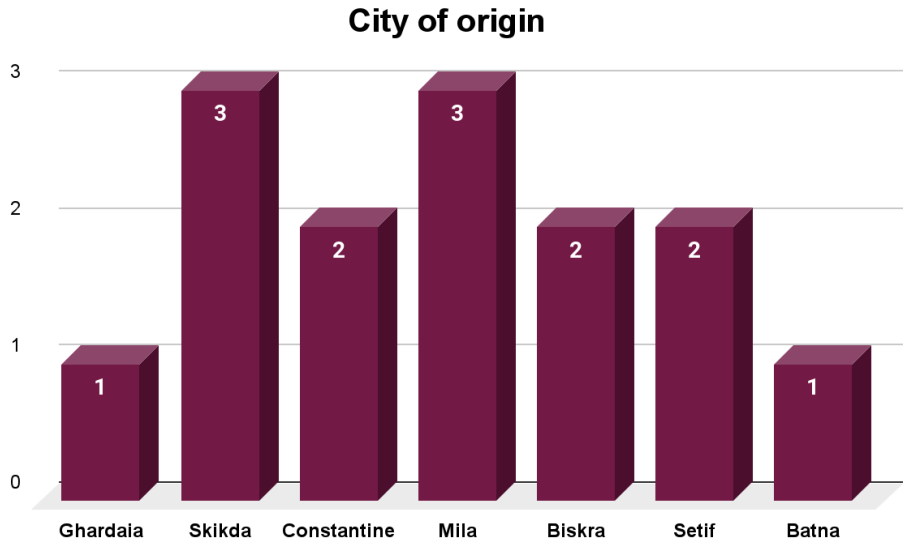

Figure 28: Distribution according to the city of origin

2.6.Ethnicity

All patients reported being Arabs except for one reporting being from Beni M'zab. And that can be explained by the selection area, requiring an enlarged study to take the result in concideration.

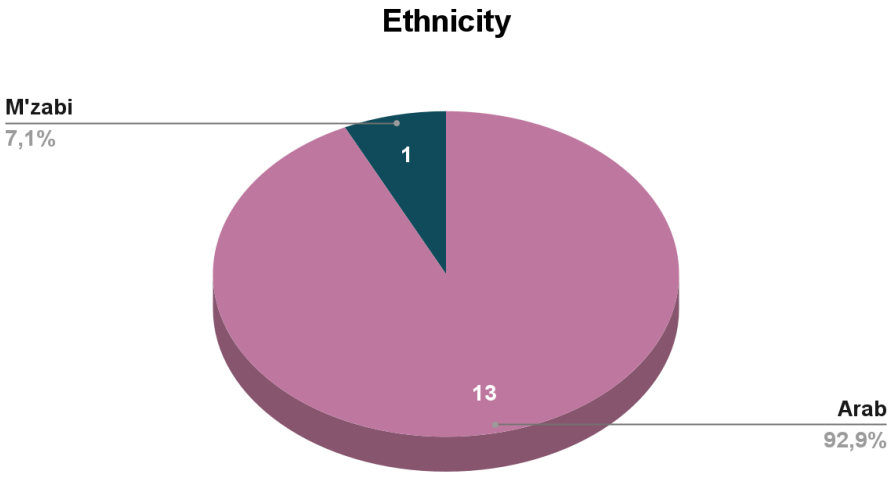

Figure 29: Distribution according to the ethnicity

2.7.Ages

- We included in our study PME patients aged between **7-45 years old**, with a mean age of **21.85 years.**
- Age of onset varies according to the PMEs type. The majority of patients had an age between **5-15 years old** representing **78.57 % (11 subjects)** of all subjects when they first manifested their disease with a mean age of **9.07 years old** which concords with the literature PMEs epidemiology **(Bureau et al., 2013)**.
- Patients have been diagnosed as epileptic soon after the onset. However, PME diagnosis was further suspected. The delay varies between **1 to 16 years** for a mean delay of **5.7 years**, but no study was found to compare.

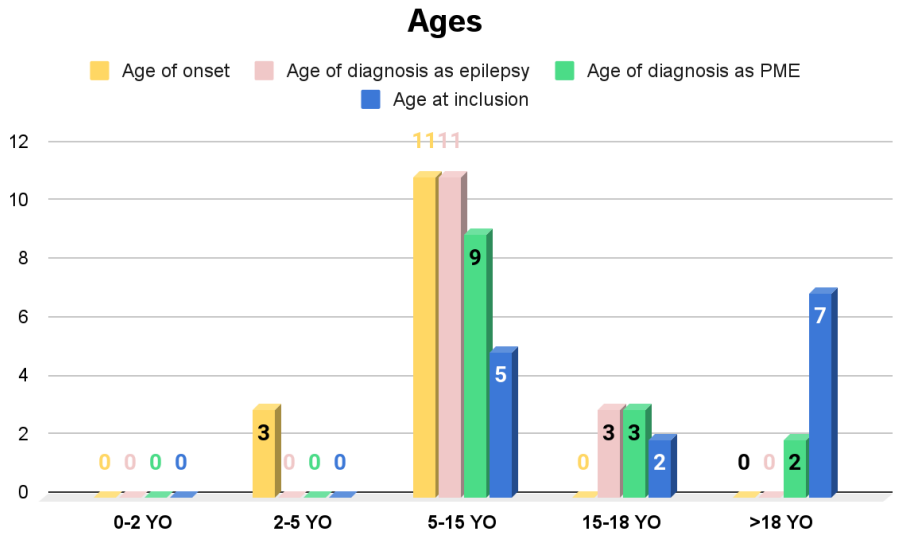

Figure 30: Distribution according to the age of onset, diagnosis and epilepsy, diagnosis as PME and age at inclusion.

2.8.Pregnancy and delivery complications

Neither pregnancy, nor maternal delivery complications were reported, however one patient presented neonatal anoxia while after delivery.

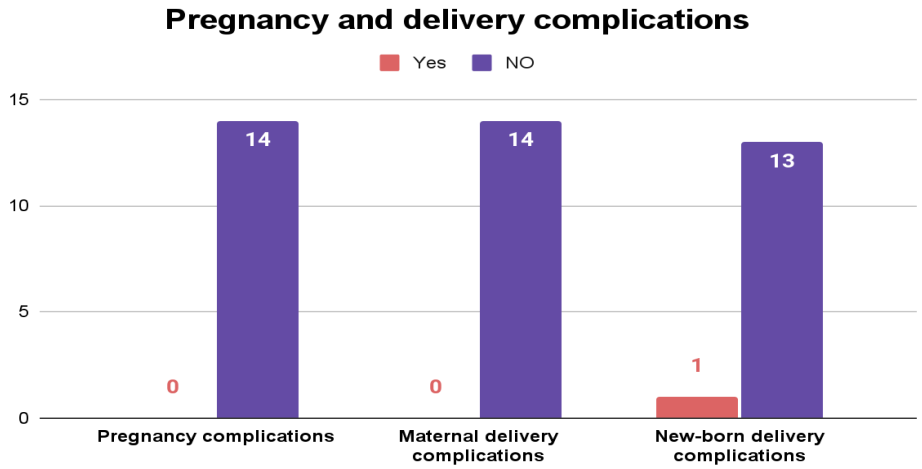

Figure 31: Distribution according to the pregnancy and delivery complications

2.9.Medical history

Head trauma was reported in 02 cases whereas delayed psychomotor development, mental retardation, febrile seizures and hypothyroidism were reported in one case each.

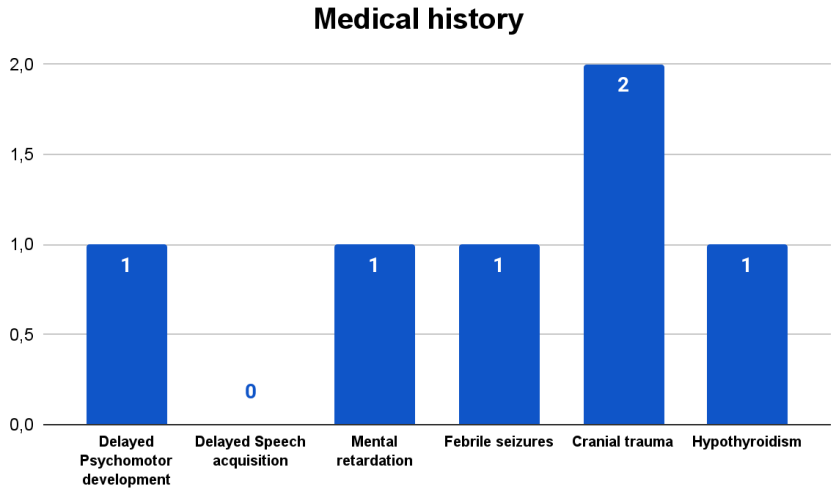

Figure 32: Distribution according to the medical history

2.10.Sign of onset

Onset signs differ from case to case according to the literature **(Zimmern & Minassian, 2024)**. In our study GTCs were the sign of onset in **40%** of cases **(6 subjects)**. **20%** reported either myoclonus **(3 subjects)** or ataxia **(3 subjects)** as the first symptom appearing. Dysarthria, occipital seizures and absence seizures revealed the disease in one case each **(6.7%).**

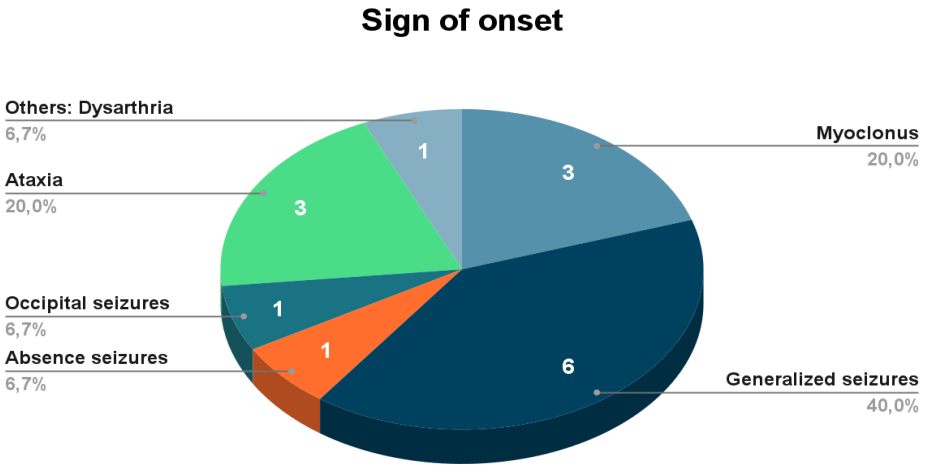

Figure 33: Distribution according to the sign of onset

2.11.Clinical features progression

From a global analysis we conclude that each phenotype has its own clinical symptomatology and progression, with four common points: Myoclonus, Seizures (GTCs+++), Ataxia and Cognitive impairment, corresponding to PMEs group definition **(Cameron et al., 2023)**.

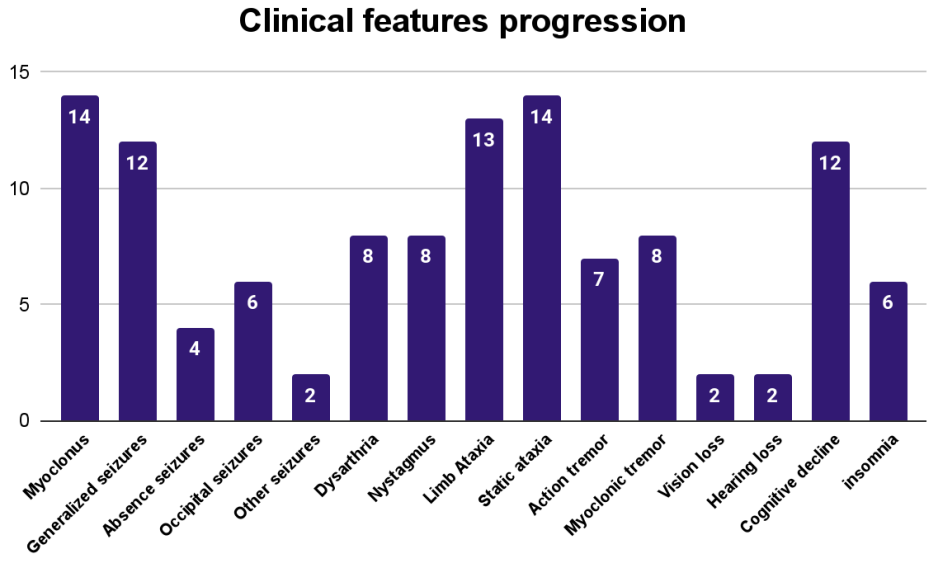

Figure 34: Distribution according to clinical features progression

2.12.Walking

Gait and balance are important signs to evaluate disability and ataxia.

In our study 11 of 14 patients; ie **78.6%**; have walking impairment. **21.4% (3 subjects)** have a mild impairment, **28.6% (4 subjects)** use a wheelchair and **28.6% (4 subjects)** are bedridden.

Previous studies reported that disability is quite constant and is due to myoclonus and/or cerebellar ataxia **(Sanz & Serratosa, 2020)**.

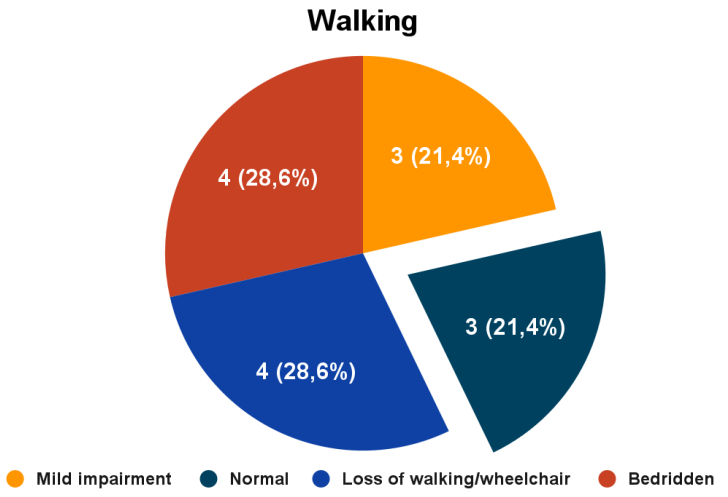

Figure 35: Distribution according to walking quality

2.13.Progression rate

Progression rate is variable for each case and phenotype **(Leppik, 2003)**.

In our study we noticed that the major portion had quick progression **(8 subjects, 57.1%)**, **28.6% (4 subjects)** reported slow progression and **14.3% (2 subjects)** are stationary.

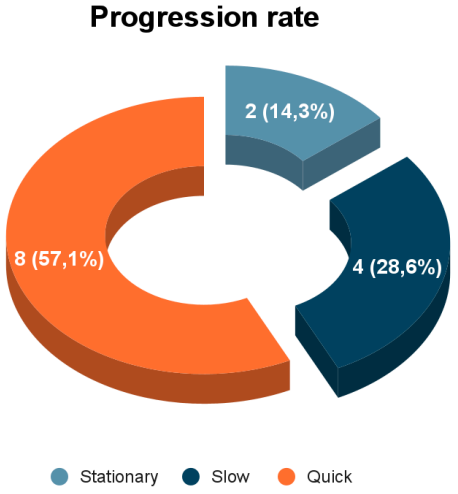

Figure 36: Distribution according to progression rate

2.14.EEG findings

Following previous studies findings, EEG could be normal at early stages which is not our case. It could show abnormal background activity (**8 cases**), focal or general epileptic discharges (**all patients**) which may be activated by ILS (**4 cases**) or HPN (**01 case**) and that was reported respectively by **(Sinha et al., 2007)** and **(Holmes, 2020; Panzica et al., 2003)**.

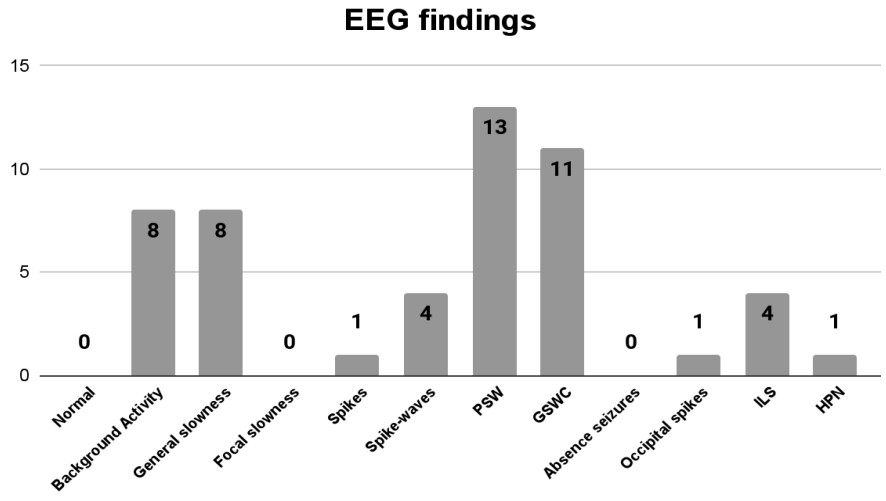

Figure 37: Distribution according to EEG findings

2.15.Complementary exams

- Complementary exams were not available in **25%** of cases.
- **16.7%** of patients had done specific blood analysis.
- **16.7%** of patients had brain CT scan imaging and was normal.
- **75%** of patients had done Brain MRI which was normal in **20.8%**, showed lobar atrophy in **4.2%**, generalised atrophy in **4.2%,** periventricular hyperintensity in **4.2%**, dandy walker variation in **4.2%**. Brain MRI results were described in literature.
- One of them benefited from EMG and was normal.

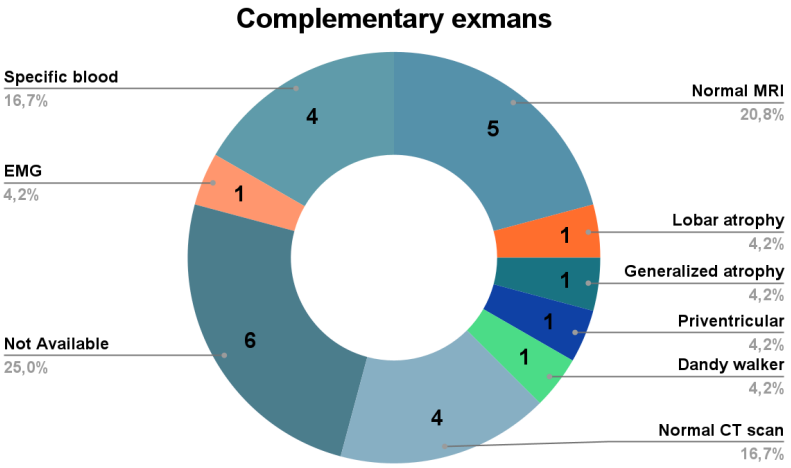

Figure 38: Distribution according to complementary exams and their results

2.16.Genetic testing

All **14** persons recruited had blood extraction but only **04** of them had WES genetic analysis done.

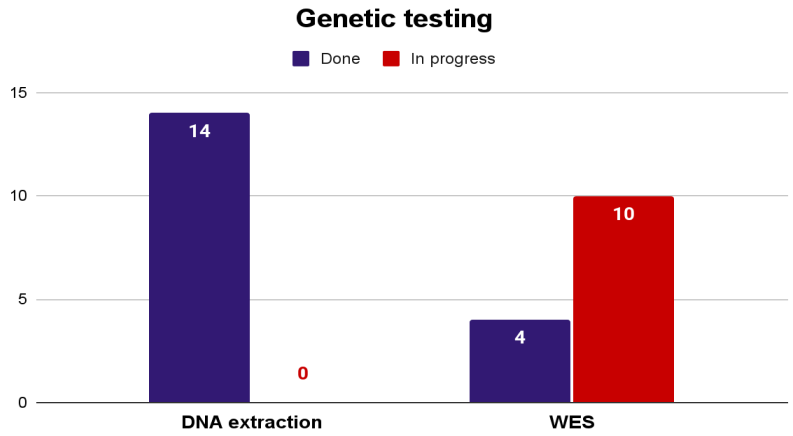

Figure 39: Distribution according to genetic testing progress

2.17.Pathology

We were based on a clinical phenotype approach to indicate pathology analysis. Skin biopsy was made for a patient having LD phenotype and was positive showing Lafora Bodies which is pathognomonic for the disease **(Busard et al., 1987; Schwarz & Yanoff, 1965)**.

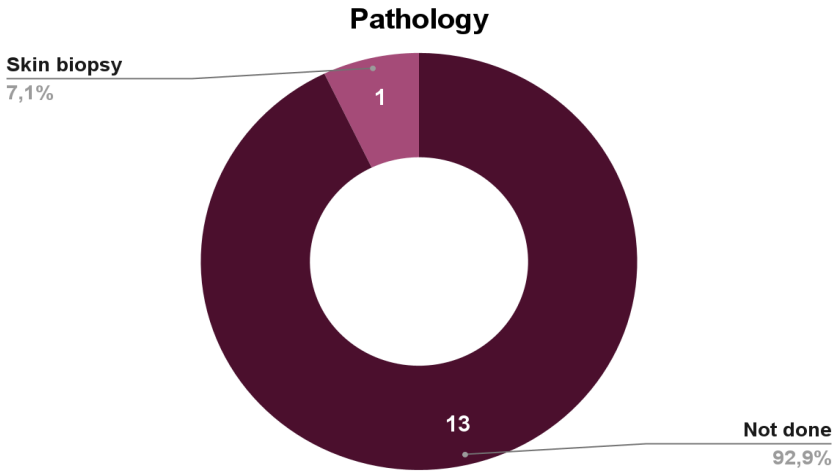

Figure 40: Distribution according to Pathology

2.18.Quality of life

We used SARA and Rankin score **(See Appendix)** to evaluate respectively ataxia and autonomy and to have an appreciation about the quality of life of our patients.

All of them suffer from ataxia impairment and **50% (7 subjects)** of cases had an extremely severe disability due to ataxia, typically reported in the literature **(Michelucci et al., 2016)**.

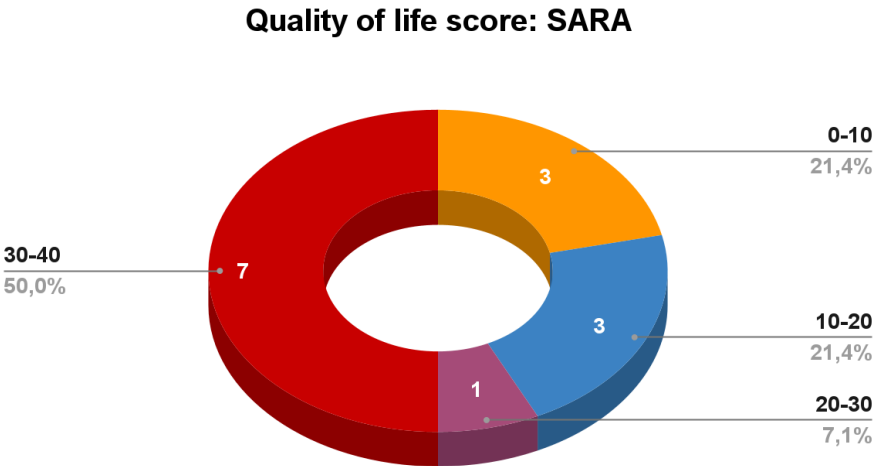

Figure 41: Distribution according to SARA score rates

Autonomy is totally preserved in **21.4%** of cases **(3 subjects)**. **78.6% (9 subjects)** of our population study suffer from mild to severe autonomy loss. **50% (7 subjects)** are totally dependent. This distinction is related to the PME type **(Sanz & Serratosa, 2020)**.

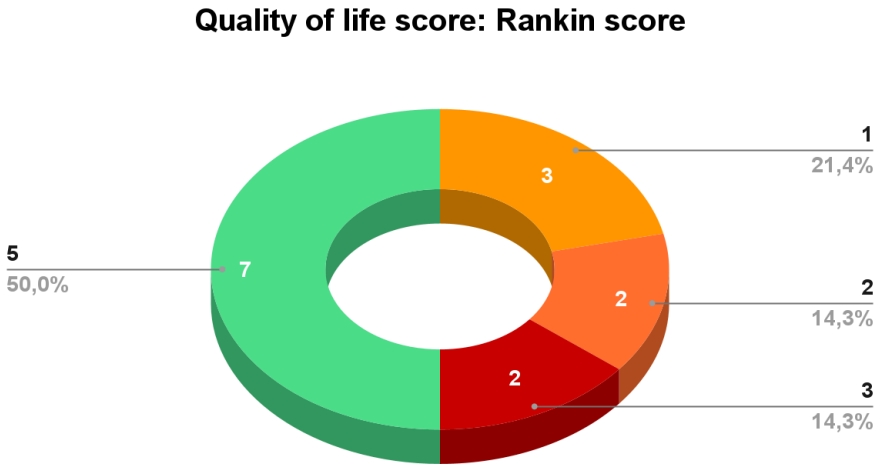

Figure 42: Distribution according to Rankin score rate

2.19.Treatment

All patients were under anti-epileptic drugs to control their seizures and myoclonus.

Most of them use Levetiracetam, Valproate. Topiramate is given for **50%** of them.

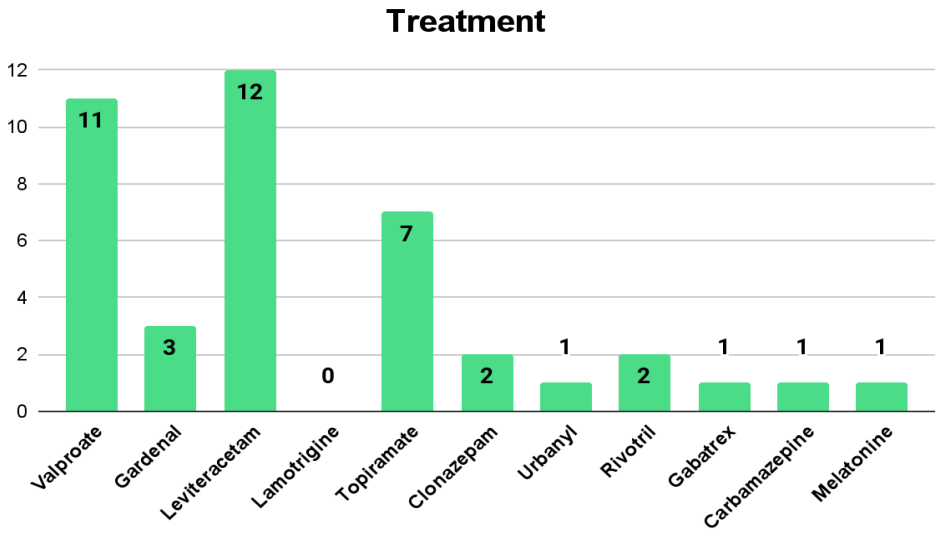

Figure 43: Distribution according to taken treatment

The number of used anti-epileptic drugs illustrate seizures and myoclonus control: **20% (3 subjects)** of patients are controlled under monotherapy, whereas **6.7% (1 subject)** need bitherapy. However a big portion (**73.4% - 10 subjects**) is using 3 or more anti-epileptic drugs.

Treatment response and resistance isn't previsible and most patients loss control upon their seizures and myoclonus while evolution **(Holmes, 2020; Sanz & Serratosa, 2020)**.

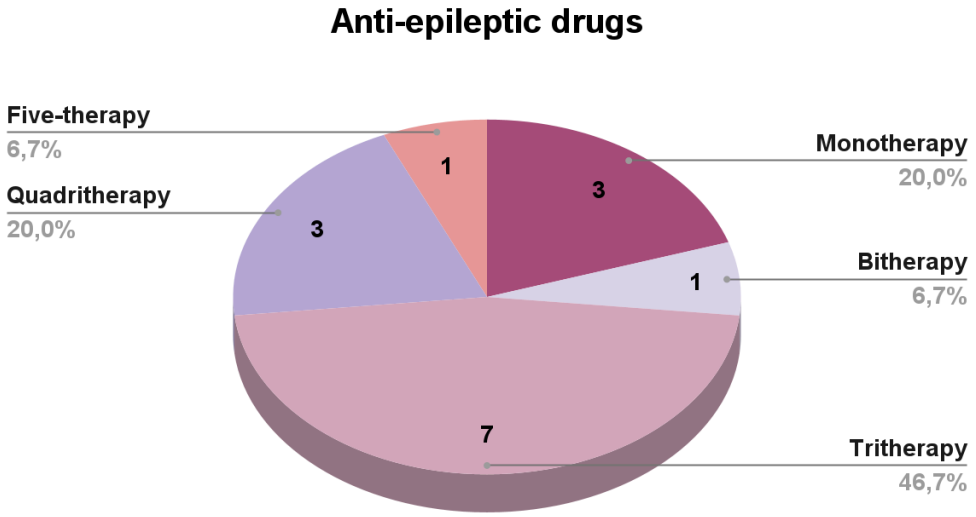

Figure 44: Distribution according to used anti-epileptic drugs number

2.20.Complications

Many complications were reported, the most frequent are repetitive head trauma and falls due to myoclonus and cognitive decline.

Previous studies made the point upon the high frequency of intellectual impairment as part of the disease evolution **(Kälviäinen, 2015)** and traumatic injuries secondary to myoclonus and seizures **(Michelucci et al., 2016)**.

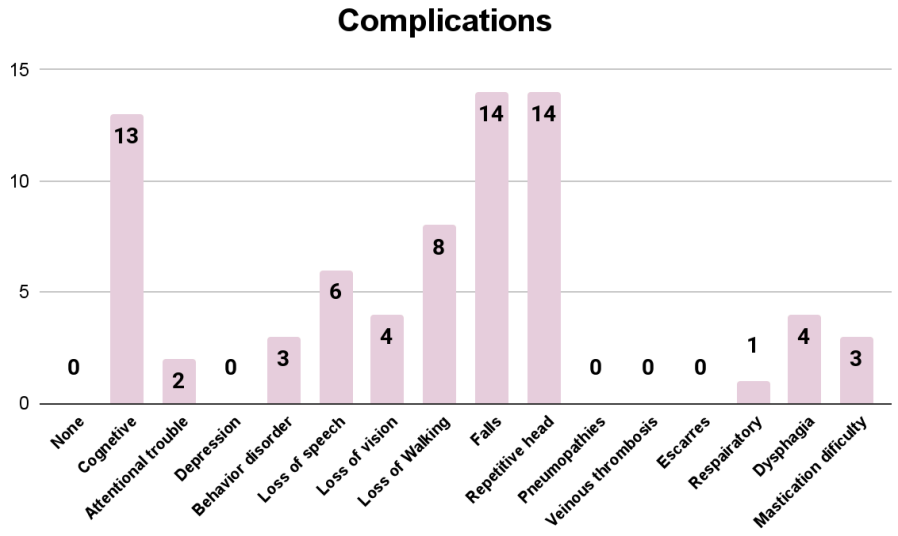

Figure 45: Distribution according to complications

2.21.Diagnosis

Based on PMEs hallmarkers and specific signs, we had an approximate clinical phenotype. We confirmed the diagnosis in 3 patients of the 04 analysed and we expect to have **06 ULD**, **01 LD** and **04 CLN** diagnosis in the remaining subjects.

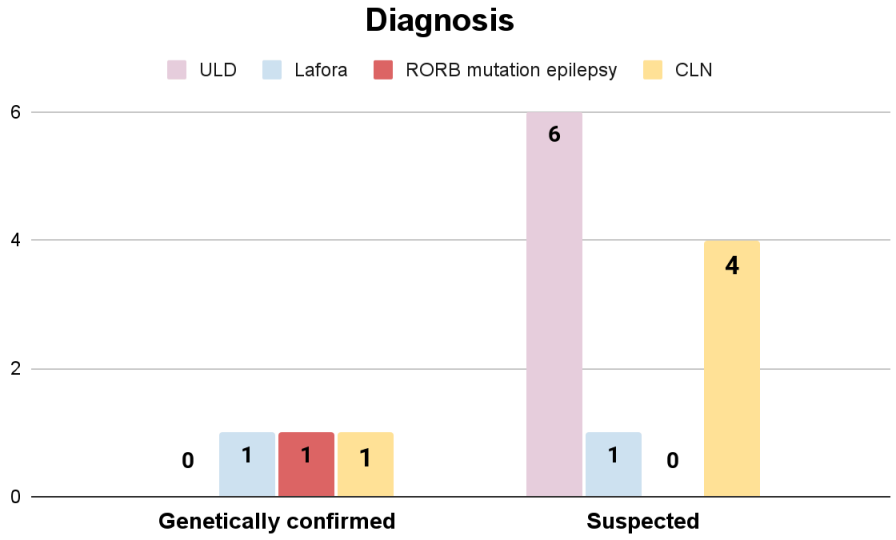

Figure 46: Distribution according to diagnosis

3. Genetic results

3.1.DNA extraction results:

DNA extraction quality measures are resumed in the following table:

- We had good DNA concentrations. A concentration above 40 ng/ml is preferable for exome sequencing.
- A260/A280 and A260/A230 ratio were in the normal values, it means that the purity of our DNA is optimal and is not contaminated by proteins, RNA and other contaminants.

The table below summarises results.

Table 03: DNA extraction quality measures

Proband	DNA concentration	A260/A280	A260/A230
F7.1	108.7	1.85	2.28
F1.1	43.3	1.82	2.43
F6.1	66.6	1.82	2.15
F2.1	73	1.84	2.38

3.2.Exome sequencing results

WES was performed for **04** patients; however, we had only **03** positive results. Two of the three variants identified are strongly known pathogenic variants and have good reads. The Inflame deletion biallelic variant ***CLN6*:c.791CCT[1] (p.Ser265del)** in proband **F7.1** is a known pathogenic variant in the ***CLN6*** gene with very rare frequency in the African population and very good sequencing reads **(See Table 4)**. Subject **F6.1** had also a known biallelic pathogenic splice acceptor variant ***RORB*:c.94-1G>A** absent in the African population and having very good sequencing reads **(See Table 4)**. In subject **F2.1** a novel missense variant ***EMP2A*:c.659T>A (p.Leu220Gln)**, was identified. Its sequencing reads and prediction scores are good and the variant is classified as Unknown significance. However, skin biopsy results and the fitting clinical phenotype are strong elements to consider this variants as likely pathogenic, other reports in the literature are needed to draw a final conclusion.

The genetic test for the **F1.1** proband having an **ULD** phenotype using **WES** was negative because the genetic method was not adapted, it required the use **RP-PCR** or **Southern-blot** to look for the dodecamer expansion.

Results are resumed in the next table.

Table 04: Genetic study results

Subject	Clinical diagnosis	Gene	Nucleotide change	Protein change	Sequencing reads number	Mutation	Frequence in African population[1]
F7.1	PME (CLN?)	*CLN6*	c.791CCT[1]	p.Ser265del	[0, 75]	Inframe deletion	0,00005338
F1.1	PME (ULD?)	/	/	/	/	/	/
F6.1	PME (ULD?)	*RORB*	c.94-1G>A	/	[19, 27]	Splice acceptor variant	0
F2.1	LD	*EMP2A*	c.659T>A	p.Leu220Gln	[0, 77]	Missense variant	0
[1] Frequency in the African population using gnomad 4.0.1.							

4. Pheno-genotype correlation

Based on our practical study and the literature review presented in the bibliographic part above, we can conclude that there is not an absolute gynotype-phenotype correlation, ie, similar mutations of the same gene or mutations in different genes can give similar phenotypes **(Subject F6.1)** whereas mutations in the same gene can give quite different phenotypes **(Family F8)**.

5. Study obstacles

Local in-house verification of the variants identified by sanger sequencing wasn't done because of delayed delivery of primers ordered. This step is a quality control requirement for WES to avoid false positive results as the technique may generate false reads. However, the variants identified in our patients are all of a high quality with high reads in both strands **(>10)** and good quality measures which renders the possibility of false detection very low.

One patient **F6.1** having the ***RORB*** mutation was not contactable to deliver testing results and to complete full phenotypic description, this is unlikely to alter our results as the data initially

collected is clear and concordant to its phenotype and the variant identified is strongly pathogenic and has good reads. The patient **F1.1** had negative testing and should receive adapted genetic testing to screen for **ULD** by **RP-PCR** or **Southern blot**, however cost and limited access to these technics is a major issue.

CONCLUSION AND PERSPECTIVES

Progressive myoclonus epilepsy (PME) is a rare, diverse and heterogeneous group of genetic diseases characterised by their progression and having in common myoclonus, epilepsies, ataxia and cognitive decline.

It is divided into typical PMEs which include more than 12 forms and reproduce PME hallmarks and PMEs-like represented by other neurological or metabolic affections that may manifest in some rare cases PME symptomatology.

Most PMEs are inherited as AR disease mode favorating by consanguinity, with some transmission exceptions as AD and mitochondrial modes.

Phenotype, progression rate and severity differ according to each type.

Treatment is still symptomatic based especially on anti-epileptic drugs.

Researches are in progress in order to discover a curative treatment.

After having done a sightseeing tour on PMEs bibliography and making a humble practical approach, we observed that:

- PMEs are still underdiagnosed and often confused with other epilepsy forms.
- PME frequency in eastern Algeria is not negligible and favoured by consanguineous marriage.
- The majority of PME families are not aware about their state and continue in consanguineous marriage.
- There is no special care for the patients with altered life quality and cognitive decline.

That's why we suggest to:

- Make a genetic and statistical study about PMEs in Algeria to have a better idea and plan a road map.
- Well train doctors in order to have an early diagnosis and better care for PMEs patients.
- Establish awareness companies to reduce consanguinity and educate PMEs family.
- Instaure specific care for PME patients and rehabilitation programs.

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APPENDIX

Appendix 01 : Consent for the use of biological data

I, the undersigned: ……..….. born on ..…/…../……

in ……

Certify that I have received from ……. exhaustive and understandable information concerning the possible causes of my health problem. I had the opportunity to ask all the questions I wanted.

I understand that a genetic analysis is offered to me from a blood sample from which my DNA will be extracted. The purpose of this analysis is to determine if my genome has an anomaly or a variation related to my health problem. I fully understood the possible implications of this study and I could obtain, if I wished, any additional information.

The results of these analyzes will be sent to me if I wish. They will remain confidential and can only be communicated with my exclusive authorization.

I can at any time decide not to pursue this process. The genetic data and biological material concerning me may be destroyed at my request.

I agree that my biological samples will be kept and used for medical and/or biological research purposes without restriction under cover of anonymity.

Made in ……..… on …./…../……

Applicant signature (tutor if minor) Signature of the researcher/ Doctor

Appendix 02: SARA score

Rater: _____date: _____patient:_____

Scale for the assessment and rating of ataxia (SARA)

1) Gait

Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.

0 **Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)**
1 **Slight difficulties, only visible when walking 10 consecutive steps in tandem**
2 **Clearly abnormal, tandem walking >10 steps not possible**
3 **Considerable staggering, difficulties in half-turn, but without support**
4 **Marked staggering, intermittent support of the wall required**
5 **Severe staggering, permanent support of one stick or light support by one arm required**
6 **Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)**
7 **Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)**
8 **Unable to walk, even supported**

Score	

2) Stance

Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.

0 **Normal, able to stand in tandem for > 10 s**
1 **Able to stand with feet together without sway, but not in tandem for > 10s**
2 **Able to stand with feet together for > 10 s, but only with sway**
3 **Able to stand for > 10 s without support in natural position, but not with feet together**
4 **Able to stand for >10 s in natural position only with intermittent support**
5 **Able to stand >10 s in natural position only with constant support of one arm**
6 **Unable to stand for >10 s even with constant support of one arm**

Score	

3) Sitting

Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.

0 **Normal, no difficulties sitting >10 sec**
1 **Slight difficulties, intermittent sway**
2 **Constant sway, but able to sit > 10 s without support**
3 **Able to sit for > 10 s only with intermittent support**
4 **Unable to sit for >10 s without continuous support**

Score	

4) Speech disturbance

Speech is assessed during normal conversation.

0 **Normal**
1 **Suggestion of speech disturbance**
2 **Impaired speech, but easy to understand**
3 **Occasional words difficult to understand**
4 **Many words difficult to understand**
5 **Only single words understandable**
6 **Speech unintelligible / anarthria**

Score	

Rater: _____date: _____patient:_____

5) Finger chase

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband´s reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

- **0 No dysmetria**
- **1 Dysmetria, under/ overshooting target <5 cm**
- **2 Dysmetria, under/ overshooting target < 15 cm**
- **3 Dysmetria, under/ overshooting target > 15 cm**
- **4 Unable to perform 5 pointing movements**

Score	**R**ight	**L**eft
mean of both sides (R+L)/2		

6) Nose-finger test

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

- **0 No tremor**
- **1 Tremor with an amplitude < 2 cm**
- **2 Tremor with an amplitude < 5 cm**
- **3 Tremor with an amplitude > 5 cm**
- **4 Unable to perform 5 pointing movements**

Score	**R**ight	**L**eft
mean of both sides (R+L)/2		

7) Fast alternating hand movements

Rated separately for each side
Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

- **0 Normal, no irregularities (performs <10s)**
- **1 Slightly irregular (performs <10s)**
- **2 Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s**
- **3 Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s**
- **4 Unable to complete 10 cycles**

Score	**R**ight	**L**eft
mean of both sides (R+L)/2		

8) Heel-shin slide

Rated separately for each side
Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

- **0 Normal**
- **1 Slightly abnormal, contact to shin maintained**
- **2 Clearly abnormal, goes off shin up to 3 times during 3 cycles**
- **3 Severely abnormal, goes off shin 4 or more times during 3 cycles**
- **4 Unable to perform the task**

Score	**R**ight	**L**eft
mean of both sides (R+L) / 2		

Appendix 03 : Rankin score

Points	Grade of disability
0	No symptoms
1	No significant disability. Some symptoms but able to carry out all usual activities
2	Slight disability. Able to perform daily activity without assistance, but unable to carry out previous activities.
3	Moderate disability. Requires some help, unable to walk alone without assistance.
4	Moderate severe disability. Needs for assistance for own bodily needs, unable to walk alone without assistance.
5	Severe disability. Unable to attend own body needs without constant assistance, nursing care and attention. Incontinent.
6	Dead.

Appendix 04 : Informations form

	Family N°	
	Proband	……
Family name		
first name		
Sex		
Status (alive=0, dead=1)		
Dexterity		
Consanguinity		
Other family members affected		
Status (alive=0, dead=1)		
City of origin		
Ethnicity		
Date of birth		
Age at inclusion		
Age of onset		
Age of diagnosis		
Diagnosis delay		
Age of death		
Cause of death		
Pregnancy		
Normale		
RCIU		
Maternal infection		
Maternal diabetes		

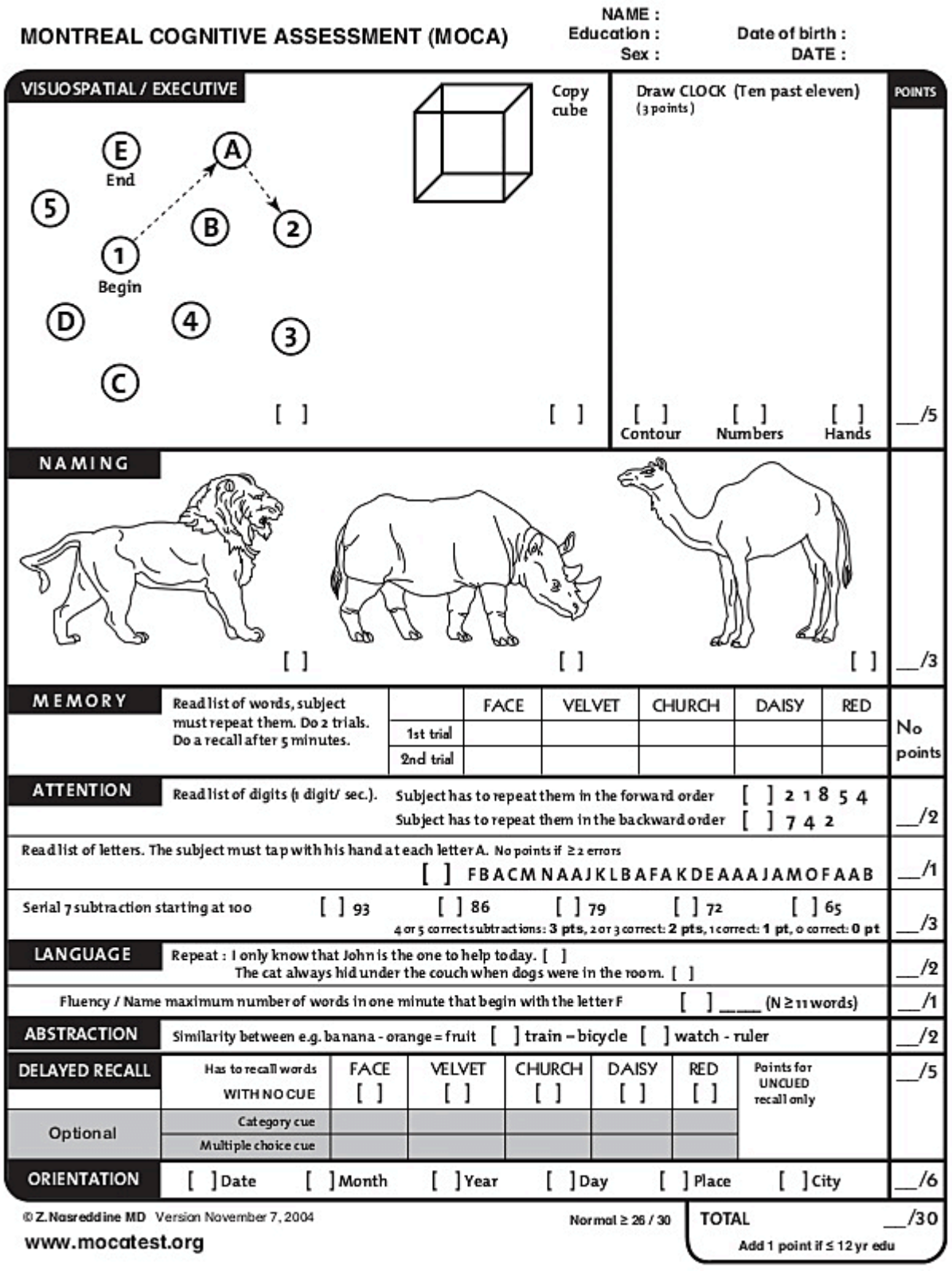
Maternal HTA		
Delivery		
Normale		
C-section		
Early delivery (week)		
Delivery complications		
Forceps		
Neonatale anoxia		
Neonatale seizures		
Medical history		
Delayed Psychomotor development		
Delayed Speech acquisition		
Mental retardation		
Febrile seizures		
Signe of onset		
Myoclonus		
Generalized seizures		
Absence seizures		
Occipital seizures		
Other seizures		
Ataxia		
Clinical features severity or frequency of seizures		
Myoclonus		
Generalized seizures		
Absence seizures		

Occipital seizures		
Other seizures		
Dysarthria		
Nystagmus		
Limb Ataxia		
Static ataxia		
Action tremor		
Myoclonic tremor		
Vision loss		
Hearing loss		
Cognitive decline **(MOCA)**		
insomnia		
Walking		
Normal		
Assisted one side		
Assisted both sides		
Loss of walking/wheelchair		
Bedridden		
Progression rate		
Stationary		
Slow		
Quick		
EEG		
Background Activity		
General slowness		
Focal slowness		

PSW		
GSWC		
Absence seizures		
Occipital spikes		
Normal		
Other		
MRI		
Focal lesion		
Lobar atrophy		
Generalized atrophy		
Others		
Normal		
Other		
Genetics testing		
WES		
DNA extraction		
Pathology		
Other complementary exams		
Quality of life score		
Sara score		
Modified Rankin		
Treatment		
Valproate		
Gardenal		
Leviteracetam		
Lamotrigine		

Topiramate		
Clonazepam		
Urbanyl		
Other		
Complications		
Dementia		
Depression		
Loss of speech		
Loss of vision		
Loss of Walking		
Falls		
Repetitive head trauma		
Pneumopathies		
Veinous thrombosis		
Escarres		
Respiratoty distress		
Others		
Suspected/confirmed diagnosis		

Appendix 05 : Montreal Cognitive Assassement (MoCA)



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE

Copy cube

Draw CLOCK (Ten past eleven) (3 points)

POINTS

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ]

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

 Version November 7, 2004

www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Appendix 06 : Miller's DNA extraction method

1. **Leukocytes' preparation:** the leukocytes are separated from the blood by red blood cells hypotonic lysis in a Tris-EDTA (TE) 20:5 buffer (containing 20 mmol Tris, 5 mmol EDTA, pH 7.5) for 10 minutes on ice. After washing, the pellet is resuspended in TE 20:5.
   a. In a 50 ml tube we added a total blood sample and completed up to 25 ml with Tris-EDTA (TE) 20:5 to obtain red blood cells lysis for 10 minutes on ice.
   b. We centrifuged the tube for 10 min at 3900 revolutions per minute (RPM).
   c. We aspirated the supernatant liquid with a vacuum pipette.
   d. Then we resuspended it in a TE 20:5 solution for 10 min with a total volume of 25 ml on ice.
   e. We proceeded to do a second centrifugation under the same conditions.
   f. Finally we aspirated the supernatant using a vacuum pipette to obtain the leukocytes flow.
2. **DNA extraction:** is done by adding a lysis buffer (400 mmol NaCl, 2 mmol EDTA, 10 mmol Tris,pH 8.2), 10% Sodium Dodecyl Sulfate (SDS), 10 mg/ml proteinase K and 4 ml of 4 mol NaCl.
   a. After obtaining the leukocytes flow, we put it into a 15 ml tube.
   b. We added 3 ml of a lysis buffer (400 mmol NaCl, 2 mmol EDTA, 10 mM Tris,pH 8.2).
   c. We dispensed and mixed the continent with sterile pastette.
   d. Then we added 200 µl of 10% Sodium Dodecyl Sulfate (SDS) which is an organic sodium salt and anionic surfactant used as detergent, protein denaturant, fat emulsifier and wetting agent. Here we used it for leukocytes lysis and proteinase K activation, it inactivates nucleases and denatures proteins in order to digest DNA associated proteins, and 10 mg/ml proteinase K.
   e. After that the tube is rotated on a wheel at 37°C overnight and cooled on ice the day after for 5 min.
   f. We added 4 ml of 4 mol NaCl and agitated manually to allow the release of the nuclear DNA in the lysate and proteins precipitation with the solvent.
   g. We put it again for 5 min on ice.
   h. Then we centrifuged it for 15 min at 2500 RPM.
3. **DNA precipitation:** using high concentrations of pure and cold ethanol (-80°C and 2.5x sample volume concentration) and TE 10:1.
   a. We put the supernatant into a 15ml tube.
   b. We added Isopropanol to lead DNA precipitation.

c. We mixed and centrifuged.
d. DNA is on the tube bottom, we took off the supernatant.
e. We added a double supernatant volume of pure and cold ethanol at -80°C with rotatory agitation.
f. The DNA pellet is formed in the supernatant by precipitation with pure ethanol.
g. We recovered it with a Pasteur pipette and rinsed it twice in 70% ethanol in order to eliminate salt and isopropanol and then we dried it.
h. After that we placed it in a 1.5 ml Nunc® tube, we added TE 10:1 (or bidistilled water) to rehydrate it.
i. We can conserve it at 4°C or -20°C.
j. NB: If the DNa concentration is law (< 50 µg / ml), we should prolong the precipitation > 10h. We can use sodium acetate to increase the ionic force.

4. **Solubilization:** using TE (10:1) or bidistilled water.
   a. The DNA obtained is dissolved in the aqueous phase, by adding between 300 and 1000 µl of TE 10:1 or bidistilled water depending on the size of the DNA ball and the wanted concentration.
   b. The mixture is left overnight on a rotator-stirrer at 37° C then at ambient temperature until complete dissolution (1 to 2 days).

Appendix 07 : UV spectrophotometry

UV spectrophotometry is used to check DNA purity and concentration.

The technique used is to put in two transparent UV light cuvettes, respectively a volume of (244µl) of water for control and a volume of (5 µl) from the sample.

First we test the "control" UV absorption which must be null, then the sample UV absorption and concentration which must be multiplicated by the dilution ratio to get the right value.

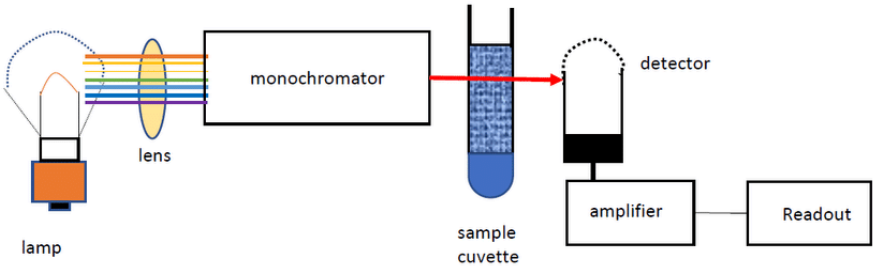


Figure: UV spectrophotometry DNA quantitation and quality process **(Rahman et al., 2020).**

DNA absorbs at 260 nm vs 280 nm for proteins and 230 nm for phénol, l'EDTA… which are considered as contaminants. So the absorption or Optical Density (OD) must be measured at 230, 260 and 280 wavelengths.

To get the DNA purity, the A260/A280 and A260/A230 ratio (R) are automatically calculated, looking for proteins, RNA and other substances (phénol, l'EDTA…) contamination.

If A260/A280 Ratio is between $1.6 < R \leq 2$, DNa is sufficiently pure. We consider proteins contamination if $R < 1, 6$ and RNA contamination if $R > 2$.

If A260/A230 Ratio is between $2 < R \leq 2.2$, DNA is sufficiently pure, if it's lower than 2, we consider phénol, l'EDTA or other substances that absorb at that wavelength contamination. **(García-Alegría et al., 2020; Kargar, 2014; Shen, 2023).**

DNA concentration is estimated using a specific equation after measuring the absorbance at 260 nm.

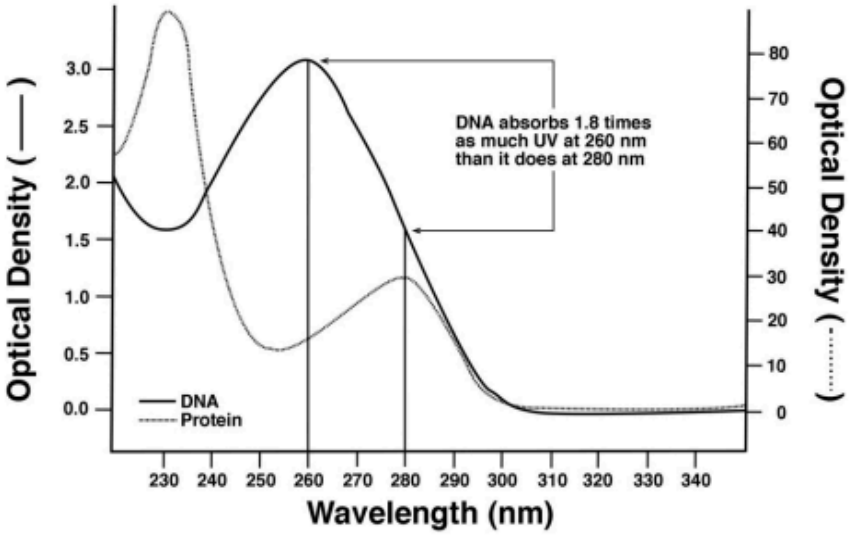


Figure: UV spectrophotometry **(Kargar, 2014)**

ABSTRACTS

التشخيص الجيني للمرضى الذين يعانون من الصرع الرمعي العضلي التدريجي

خلاصة:

الصرع الرمعي العضلي التدريجي هو كيان نادر وغير متجانس لمتلازمة الصرع الوراثية، ينتقل بشكل أساسي في الوضع الجسدي المتنحي.

يتم تعريف الصرع الرمعي العضلي التدريجي الذي ينتج عن زواج الأقارب من خلال وجود الرمع العضلي والصرع والترنح مع الاضطرابات المعرفية التي تتطور تدريجياً.

كل نوع من هذه الأمراض له جيناته الخاصة وتطوره.

إلى جانب الأشكال النموذجية، قد تحاكي بعض الأمراض العصبية أو الأيضية في بعض الحالات أعراضا مماثلة وبالتالي تشكل مجموعة غير نمطية.

في جميع الحالات، يظل العلاج بمضادات الصرع، في انتظار علاجات جديدة فعالة وعلاجية بما في ذلك الجينية.

لقد اخترنا معالجة موضوع الصرع الرمعي العضلي التدريجي نظرًا لعدم تجانسه وعدم وجود دراسات جزائرية عنه. تتعلق دراستنا المقطعية بأثر رجعي بـ 14 مريضًا يستوفون المعايير السريرية، والتي شوهدت في استشارات طب الأعصاب المختلفة في شرق الجزائر وتم جمعها، كما تم النظر في أفراد الأسرة الآخرين، سواء كانوا أحياء أو متوفين، للحصول على فكرة عن مدى انتشار المرض الذي تراوح في دراستنا في حوالي 4 بالمليون.

و منه كان ما مجموعه 33 فردًا موزعين على 11 عائلة في الغالب ناتجة عن زواج الأقارب حيث كان متوسط عمر العينة (14 مريضًا) 21.85 عامًا وقت الدراسة و 9.07 عامًا عند بداية الأعراض.

اخترنا استخدام تسلسل الجيل التالي لدراسة الإكسومات المتغيرة في 04 مريضى و كانت النتائج إيجابية في 03 حالات أظهرت على التوالي مرض لافورا، وداء الليبوفوسيني العصبي، والصرع الرمعي العضلي التدريجي عن طريق طفرة RORB التي تعد غير نموذجية.

. في حين أن التقنية لم تكن مناسبة للحالة الرابعة التي تعاني مع نمط ظاهري لمرض Unverricht Lundborg.

تضمنت دراستنا مكونًا سريريًا ومكونًا وبائيًا ومكونًا بيولوجيًا، وخاصة وراثيًا، يهدف إلى وصف المرض بشكل أفضل لدى السكان الجزائريين من خلال البدء بعينة صغيرة وتوسيعه لاحقًا إلى بحث وطني.

الكلمات المفتاحية: الصرع الرمعي العضلي التدريجي، مرض Unverricht Lundborg، مرض ،Lafora Neurolipofuschinose، الوراثة الجسدية المتنحية، تسلسل الإكسوم الكامل.

Le diagnostic génétique des patients atteints d'épilepsie myoclonique progressive

Résumé:

Les épilepsies myocloniques progressives constituent une entité rare et hétérogène de syndrome épileptiques héréditaires, se transmettant majoritairement selon le mode autosomique récessif. Favorisées par la consanguinité, les épilepsies myocloniques progressives se définissent par la présence de myoclonus, d'épilepsies, d'ataxie avec troubles cognitifs qui progressent graduellement.

Chacune de ces pathologies a sa propre génétique et évolution.

A côté des formes typiques, certaines pathologies neurologiques ou métaboliques peuvent mimer dans certains cas une symptomatologie pareille formant ainsi un groupe atypique.

Dans tous les cas le traitement demeure symptomatique dominé par les anti-épileptiques, dans l'attente de nouvelles thérapies efficaces et curatives notamment géniques.

Nous avons choisi d'aborder le thème des épilepsies myocloniques progressive vu son hétérogénéité et le manque d'études Algériennes à propos.

Notre étude transversale rétrospective a concerné 14 patients remplissant les critères cliniques, vus dans les différentes consultation des neurologie de l'est Algerien et prélevés, ainsi qu'on s'est intéressé aux autres membres atteints de la famille qu'ils soient vivants ou décédés pour avoir une idée sur la prévalence. Donc un total de 33 individus répartis sur 11 familles majoritairement consanguines pour une prévalence calculée à 4/1000000 habitants.

La population réellement incluse (14 patients) avait une moyenne d'âge de 21.85 ans, pour une moyenne d'âge de début à 9.07ans, présentant une description clinique et progression typique.

On a choisi d'utiliser le séquençage de nouvelle génération pour étudier les exomes variants sur 04 patients. Les résultats étaient positifs dans 03 cas présentant respectivement la maladie de Lafora, la neuro-lipofuscinose et une épilepsie myoclonique progressive par mutation du RORB qui fait partie des atypie. Alors que la technique n'était pas adaptée pour le 4e cas présentant un phénotype de la maladie de Unverricht Lundborg.

Notre étude comprenait un volet clinique, un volet épidémiologique et un volet biologique notamment génétique et ayant pour but de mieux caractériser la maladie au sein de la population algérienne en commençant par un petit échantillon pour l'élargir ultérieurement vers un Cohort nationale.

Mots clés: épilepsies myocloniques progressive, Maladie d'Unverricht Lundborg, Maladie de Lafora, Neurolipofuschinose, Autosomique récessive, Séquençage de l'exome entier.

Academic year : 2023-2024	**Presented by :** BEHLOUL SoundousMalek

Genetic diagnosis of patients with Progressive Myoclonic Epilepsy

Graduation Genetic Science Master's degree Diploma Thesis

Progressive myoclonic epilepsy (PME) is a rare and heterogeneous entity of hereditary epileptic syndrome, mainly transmitted as autosomal recessive mode. Favored by inbreeding, progressive myoclonic epilepsies are defined by the presence of myoclonus, epilepsy, ataxia with cognitive disorders that progress gradually.

Each of these pathologies has its own genetics and evolution.

Besides the typical forms, some neurological and metabolic affections may mimic in some cases similar symptomatology as PMEs forming an atypical group.

In all cases the treatment remains symptomatic dominated by antiepileptics, waiting for new effective and curative therapies especially gene therapy.

We chose to talk about progressive myoclonic epilepsy because of its heterogeneity and the lack of Algerian studies about it.

Our transversal retrospective study concerned 14 patients clinically diagnosed as PME, seen in the various neurology consultations in eastern Algeria, and their other affected family members, whether they are alive or not, in order to calculate the prevalence. So a total of 33 individuals spread over 11 families mostly inbred with a prevalence of 4/1000000.

The real study population included (14 patients) having a medium age of 21.85 years old at inclusion and 9.07 years old at the onset of the disease. We noticed that they present clinical description and progression as described in the literature..

We chose to use next-generation sequencing (whole exome sequencing) to study variant exomes in 04 patients. Results were positive in 03 cases presenting respectively Lafora's disease, neuro-lipofuscinosis and progressive myoclonic epilepsy by mutation of the RORB which is part of the atypical group, whereas the technique was not adapted for the 4th case with a phenotype of Unverricht Lundborg disease.

Our study included a clinical, epidemiological and biological part, particularly genetic, aiming to better characterize the disease in the Algerian population by starting with a small sample and subsequently extending it to a national cohort.

Key Words : Progressive myoclonus epilepsy, Unverricht Lundborg disease, Lafora disease, Neuronal ceroid lipofuscinosis, Autosomal recessive, Whole exome sequencing.

Research Laboratory : Molecular genetics laboratory

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