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PROGRESSIVE MYOCLONUS-ATAXIA SYNDROMES: DIAGNOSTIC CHALLENGES AND PRACTICAL APPROACHES

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ABSTRACT

Background: Progressive myoclonus-ataxia syndromes (PMAs) are a heterogeneous group of rare neurological conditions characterized by the coexistence of myoclonus and cerebellar ataxia, frequently associated with epilepsy and cognitive decline. Their rarity, phenotypic overlap, and genetic variability create major diagnostic difficulties.
Aim: This article provides a narrative review of the principal PMA syndromes, emphasizing clinical features, diagnostic strategies, and management options.
Methods: A narrative review of PubMed and Embase publications (2013–2023), supplemented with earlier landmark studies, was conducted. The review highlights diagnostic algorithms and therapeutic approaches across the PMA spectrum.
Results: Classic syndromes include Unverricht–Lundborg disease, Lafora disease, sialidosis, neuronal ceroid lipofuscinoses, North Sea progressive myoclonus epilepsy (GOSR2), and mitochondrial disorders (MERRF, MELAS). Key diagnostic clues involve age of onset, epilepsy phenotype, ophthalmologic findings, and neuroimaging. Next-generation sequencing has revolutionized diagnostic precision, although accessibility remains a challenge.
Conclusion: Early recognition of PMAs improves patient management and avoids harmful therapies. A structured diagnostic approach is essential, and recent developments in molecular genetics and enzyme replacement provide hope for future targeted interventions.

KEYWORDS

Progressive Myoclonus Ataxia, Diagnostic Algorithm, Unverricht-Lundborg Disease, Lafora Disease, Neuronal Ceroid Lipofuscinosis, Mitochondrial Disorders

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Introduction

Myoclonus-ataxia syndromes represent a heterogeneous group of rare neurological disorders characterized by the coexistence of myoclonus- sudden, involuntary muscle jerksand ataxia, a lack of motor coordination affecting voluntary movements. Their clinical complexity often complicates diagnosis, as these symptoms may reflect diverse genetic and neurodegenerative conditions [1]. A notable subgroup, progressive myoclonus ataxias (PMAs), typically emerges in childhood or adolescence and combines progressive myoclonus, cerebellar ataxia, epilepsy, and cognitive decline. Compared to progressive myoclonus epilepsies (PMEs), PMAs generally progress more slowly, with fewer seizures and milder cognitive deterioration [2]. Despite advances in next-generation sequencing, the etiology of many PMA cases remains unresolved, underscoring the diagnostic challenge. Although rare, PMAs cause significant disability, impairing motor function, autonomy, and quality of life [2] Management is symptomatic and multidisciplinary, relying on anticonvulsants, muscle relaxants, and supportive rehabilitation therapies. Research into the molecular and genetic mechanisms continues to offer hope for more targeted treatments. [3]. This review provides an overview of myoclonus-ataxia syndromes, focusing on diagnostic pathways, genetic background, clinical features, and management strategies. Classic syndromes such as Unverricht-Lundborg disease, Lafora disease, and Sialidosis are highlighted to illustrate the spectrum of PMA phenotypes and their clinical relevance [4].

Methods

A narrative review of the literature was conducted. The PubMed and Embase databases were searched for the period 2013–2023, using the following keywords: progressive myoclonus ataxia, Unverricht-Lundborg disease, Lafora disease, Sialidosis, Neuronal ceroid lipofuscinosis, GOSR2, MERRF, MELAS. Earlier seminal publications were also included when relevant.Inclusion criteriawere studies describing clinical features, diagnostic approaches, or management of PMA syndromes. Case reports, cohort studies, systematic reviews, and expert consensus papers were all considered.The results are presented as a structured overview of major PMA subtypes, followed by an integrated diagnostic approach and discussion of therapeutic implications.

Results:

Unverricht–Lundborg Disease (ULD)

Unverricht–Lundborg disease (ULD) is considered the archetypal form of progressive myoclonus epilepsy and is caused by autosomal recessive mutations in the CSTB gene on chromosome 21q22.3 [5]. Disease onset typically occurs between 6 and 16 years of age and is initially characterized by stimulus-sensitive myoclonus and generalized tonic-clonic seizures, with progressive ataxia, tremor, and mild cognitive decline developing later in the disease course [6]. Genetic testing is essential for diagnosis, as the characteristic dodecamer repeat expansion in CSTB may not be detected by standard next-generation sequencing, requiring targeted molecular assays [7]. While MRIs taken during the onset of the disease are generally similar to those of individuals without ULD, MRIs taken once the disease has progressed show characteristic damage. [8] These progressive changes in MRI findings could potentially aid in distinguishing ULD from other epileptic disorders as the disease advances.Management is primarily symptomatic, with valproic acid, levetiracetam, clonazepam, and piracetam demonstrating efficacy, whereas phenytoin, carbamazepine, vigabatrin, and gabapentin should be avoided due to the potential for exacerbating symptoms [9].

Lafora Disease (LD)

LD is an autosomal recessive disorder caused by mutations in the EPM2A or NHLRC1 (EPM2B) genes [10] Clinically, it typically presents during adolescence with a wide spectrum of seizure types, accompanied by visual hallucinations, progressive cognitive decline, and cerebellar ataxia [11]. Diagnosis relies on the identification of pathognomonic Lafora bodies in skin biopsy specimens and is confirmed through genetic testing. MRI may show normal findings initially, but FDG-PET can reveal posterior hypometabolism early in the disease and extensive areas of decreased glucose metabolism in advanced stages, particularly in the thalamus, temporal, frontal, and parietal lobes. [12]. Management remains purely symptomatic, with antiepileptic agents such as valproic acid, benzodiazepines, and levetiracetam commonly employed to control seizures. Despite treatment, the prognosis is poor, and affected individuals usually succumb to the disease within approximately ten years of symptom onset. [13]

Sialidosis

Classified as a lysosomal storage disorder caused by mutations in the NEU1 gene, resulting in deficiency of lysosomal neuraminidase [14]. The disease manifests in two primary forms: Type I, or juvenile/adult onset, which is characterized by a later onset and a milder phenotype including myoclonus, seizures, and visual disturbances, and Type II, or infantile onset, which presents as a severe early-onset disease with coarse facial features, hepatosplenomegaly, and rapid clinical progression. A hallmark feature of sialidosis is the presence of a cherry-red spot in the retina [15].MRI does not typically show any abnormalities in early stages. Laboratory diagnosis is process usually supported by increase urinary bound sialic acid excretion and confirmation is done by genetic analysis or demonstration of neuraminidase enzyme deficiency.[16]. Management is largely supportive, with symptomatic treatment of neurological and systemic manifestations; enzyme replacement therapy remains experimental [17].

Neuronal Ceroid Lipofuscinoses (NCLs)

Neuronal Ceroid Lipofuscinoses (NCLs) are a group of autosomal recessive, progressive neurodegenerative lysosomal storage disorders primarily affecting children. Mutations in at least eight genes (CLN1, CLN2, CLN3, CLN5, CLN6, CLN7, CLN8, CLN10) have been identified, leading to abnormal accumulation of ceroid lipopigments in neurons and other cell types. Clinically, NCLs are characterized by progressive vision loss, seizures, cognitive decline, motor dysfunction, sleep disturbances, and premature death. The disorders are traditionally classified according to age of onset as infantile, late-infantile, juvenile, or adult, although variant forms may present later or exhibit milder phenotypes. CLN2 disease, formerly recognized as classical late-infantile NCL or Jansky-Bielschowsky disease, results from biallelic mutations in the TPP1 gene. [18] Symptom onset in classic CLN2 typically occurs between 2 and 4 years of age, beginning with language delay, followed by myoclonic seizures, ataxia, neurodevelopmental regression, cognitive decline, and progressive vision loss. Atypical or juvenile presentations account for approximately 13% of cases, with onset around 6 years, often beginning with seizures and evolving to include ataxia, language regression, visual disturbances, and cognitive impairment.[19]EEG reveals abnormalities, including enhanced photo-paroxysmal responses at low-frequency light stimulation (1–2 Hz), abnormal background activity, and seizure-like discharges, with changes often more pronounced during awake and asleep recordings and diminishing as disease progresses [20]. Brain MRI typically demonstrates cerebral and cerebellar atrophy, reduced gray matter volume, and periventricular white matter hyperintensity, with findings correlating closely with disease severity; in atypical CLN2, similar neuroimaging abnormalities are observed but may be less pronounced. [21]Treatment of Neuronal Ceroid Lipofuscinoses (NCLs) remains largely supportive, aimed at seizure control, preservation of motor and cognitive function, and management of spasticity and vision loss. For CLN2 disease, enzyme replacement therapy with intraventricular cerliponase alfa slows the progression of motor decline. [22] Symptomatic care includes antiepileptic drugs, physical therapy, and interventions for spasticity and visual impairment. Experimental approaches, including gene therapy, are under investigation but not yet clinically available. [23]

North Sea Progressive Myoclonus Epilepsy (NSPME, GOSR2)

NSPME is an autosomal recessive disorder caused by a homozygous missense mutation in the GOSR2 gene (c.430G>T, p.Gly144Trp), encoding a Golgi membrane trafficking protein. The disorder typically presents in childhood with early ataxia and areflexia, followed by progressive myoclonus and epilepsy, while cognitive function is often relatively preserved [24]. Additional features may include dysarthria, scoliosis, and foot deformities. Neurophysiological studies suggest sensory neuronopathy and anterior horn cell involvement, and EEG commonly demonstrates cortical myoclonus with occipital-predominant epileptiform activity [24]. Brain MRI is usually normal. Management is symptomatic, relying on antiepileptic drugs such as clonazepam, valproic acid, and levetiracetam; ketogenic diet may reduce seizures, whereas deep brain stimulation has shown limited benefit. The disease is progressively disabling, often necessitating wheelchair use and assistance with daily activities [24].

Mitochondrial Disorders – MERRF and MELAS

Myoclonic Epilepsy with Ragged Red Fibers (MERRF)

MERRF is a mitochondrial disorder most commonly caused by the m.8344A>G variant in the MT-TK gene, although pathogenic variants in other mitochondrial tRNA genes have also been reported [25]. Clinical onset ranges from childhood to adulthood and typically begins with myoclonus, followed by seizures, ataxia, muscle weakness, and exercise intolerance, with additional manifestations including sensorineural hearing loss, cardiomyopathy, optic atrophy, and peripheral neuropathy. Muscle biopsy demonstrates ragged red fibers and cytochrome c oxidase–deficient fibers, while neurophysiological studies reveal myopathic features, and EEG often shows generalized spike-and-wave activity. Brain MRI may show cerebral and cerebellar atrophy or basal ganglia lesions. Laboratory findings include elevated blood and CSF lactate and pyruvate, as well as reduced activity of mitochondrial respiratory chain complexes. Management is primarily supportive, encompassing anticonvulsants such as levetiracetam or clonazepam for myoclonus (avoiding valproic acid), cardiac therapy for cardiomyopathy, cochlear implants for hearing loss, metabolic supplements, physiotherapy, and avoidance of mitochondrial toxins. [26]

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS)

Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like Episodes (MELAS) is a maternally inherited mitochondrial disorder most commonly caused by the m.3243A>G mutation in the MT-TL1 gene, leading to impaired oxidative phosphorylation.[27]. Clinical onset usually occurs before age 40 and predominantly affects high-energy-demand organs, presenting with stroke-like episodes, seizures, migraine, ataxia, hearing loss, and cardiomyopathy[28]. Laboratory findings often include elevated blood and CSF lactate, while neuroimaging reveals migratory cortical and subcortical lesions, basal ganglia involvement, and variable cerebral and cerebellar atrophy. Diagnosis is aided by MRI, MRS, and CT, which detect acute ischemic-like lesions and chronic sequelae.[29] Management is largely supportive, focusing on seizure control, avoidance of mitochondrial toxins such as valproic acid and metformin, and supplementation with L-arginine, citrulline, coenzyme Q10, creatine, and L-carnitine to optimize mitochondrial function and reduce the frequency of stroke-like episodes [30].

Differentiation

A structured approach is essential in the diagnosis of rare genetic disorders. The first step involves considering the age of onset. In infancy, conditions such as CLN2 and sialidosis type II are most commonly observed, while in childhood, disorders like ULD, NCL7, or NSPME may present. In adolescence, diseases such as Lafora disease or MERRF are more characteristic. The second step focuses on clinical clues that can guide further investigations. The presence of a cherry-red spot is suggestive of sialidosis, whereas occipital seizures and hallucinations may indicate Lafora disease. Areflexia combined with scoliosis can point toward NSPME, and stroke-like episodes are often associated with MELAS. Additional investigations are also critical. EEG may show generalized discharges or photosensitivity, though these findings are nonspecific. MRI often reveals progressive cerebral and cerebellar atrophy or white matter abnormalities. Enzyme assays are confirmatory in lysosomal forms of the disease. Ultimately, genetic testing remains the gold standard, with next-generation sequencing (NGS), whole-exome sequencing (WES), or whole-genome sequencing (WGS) providing definitive diagnosis.

Discussion

Progressive myoclonus-ataxia syndromes (PMAs) pose significant diagnostic and therapeutic challenges due to marked clinical and genetic heterogeneity [1]. While hallmark features such as cherry-red spots in sialidosis, Lafora bodies in Lafora disease, or stroke-like episodes in MELAS remain valuable, atypical phenotypes limit reliance on clinical clues alone. A structured diagnostic approach integrating neurophysiology, imaging, and molecular genetics is therefore essential [27]. Next-generation sequencing has greatly improved diagnostic accuracy, though limitations in accessibility and variant interpretation persist.Treatment remains largely symptomatic. Antiepileptic agents such as levetiracetam, benzodiazepines, and clonazepam are most commonly used, while drugs that may exacerbate myoclonus, including phenytoin or carbamazepine, should be avoided. [4] Recent therapeutic advances include intraventricular cerliponase alfa for CLN2 disease and metabolic supplementation (e.g., L-arginine, citrulline) in mitochondrial syndromes, though evidence remains limited. Gene therapy and molecular approaches are under investigation and may offer disease-modifying potential in the future.Overall, PMAs remain progressive and disabling, but early recognition and structured diagnostic strategies improve management, while emerging therapies provide cautious optimism for more targeted interventions. [1]

Conclusions

Progressive myoclonus-ataxia syndromes remain diagnostically and therapeutically challenging due to their rarity, heterogeneity, and clinical overlap. Early recognition, systematic diagnostic algorithms, and careful avoidance of harmful therapies are essential to patient care. While management is largely symptomatic, recent advances in genetics, enzyme replacement, and experimental molecular therapies provide cautious optimism for future targeted treatments.

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