Review article

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Sialidoses

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ABSTRACT – Sialidoses are autosomal recessive disorders caused by NEU1 gene mutations and are classified on the basis of their phenotype and onset age. Sialidosis type II, with infantile onset, has a more severe phenotype characterized by coarse facial features, hepatomegaly, dysostosis multiplex, and developmental delay while patients with the late and milder type, known as "cherry red spot-myoclonus syndrome" develop myoclonic epilepsy, visual impairment and ataxia in the second or third decade of life. The diagnosis is usually suggested by increased urinary bound sialic acid excretion. We recently described genetically diagnosed patients with a specially mild phenotype, no retinal abnormalities and normal urinary sialic acid. This observation suggests that genetic analysis or the demonstration of the neuraminidase enzyme deficiency in cultured fibroblasts are needed to detect and diagnose mildest phenotypes.

Key words: cortical myoclonus, neuraminidase, NEU1, cortico-muscolar coherence, progressive myoclonus epilepsies

Sialidosis was first recognized as a specific neurological disorder in a patient presenting with muscular hypotonia and hypotrophy, ataxia, myoclonus, and seizures, who was later confirmed to have neuraminidase deficiency (Cantz *et al*., 1977; Spranger *et al*., 1978). However, it was first recognized as a clear causative factor for progressive myoclonus epilepsy (PME) (Minassian et *al*., 2016) by Rapin *et al*. (1978) who reported this disorder as 'cherry-red spot-myoclonus syndrome' because of the characteristic aspect of the fundus oculi, resulting from storage material in perifoveal ganglionic cells.

Aetiology

The disease presents with variable phenotypes, giving rise to at least two main age-related conditions: sialidosis type I and II. Both conditions exhibit autosomal recessive inheritance and are caused by mutations of the same gene, *NEU1*, localized on chromosome 6p21.3 (Bonten *et al*., 1996; Pshezhetsky *et al*., 1997), which encodes lysosomal neuraminidase (sialidase). Different mutations may account for the variable severity of the disease (Bonten *et al*., 2000). Indeed, patients with the severe infantile type II disease typically have inactive sialidase, while patients with the milder type I disease have some residual activity.

Sialidase is part of a multienzyme complex containing other lysosomal enzymes such as cathepsin A, b-galactosidase, and N-acetylgalactosamine-6-sulfate sulfatase. The integrity of the multi-enzyme complex ensures the normal catalytic activity of sialidase and protects it against proteolysis.

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NEU1 gene mutations can directly affect the active site or the central core of sialidase, leading to folding defects and retention of sialidase in the endoplasmic reticulum/Golgi compartment, but may also affect the surface region involved in binding to the multienzyme lysosomal complex (Lukong *et al*., 2001; Pattison *et al*., 2004).
Sialidase has a central role in removing terminal sialic acid molecules from oligosaccharides and glycoproteins, and its deficiency therefore leads to sialic acid-rich macromolecular storage and urinary sialyloligosaccharide excretion.

Neuropathology

Light and electron microscopy reveal cytoplasmic vacuolation involving neurons and perineuronal and interfascicular oligodendroglia, and endothelial and perithelial cells. Vacuolations are associated with diffuse neuronal intracytoplasmic storage of lipofuscin-like pigment which is detectable in the neocortex, basal ganglia, thalamus, brainstem, and spinal cord, as well in extra-nervous organs (Allegranza *et al*., 1989).
The accumulation of the sialic acid-rich substrates prominently contributes to the pathogenesis of the disease, however, other 'indirect' mechanisms are possibly involved. For instance, it was recently discovered that neuraminidase is a negative regulator of the lysosomal exocytosis of catalytically-active hydrolases (Yogalingam *et al*., 2008). The resulting increase in extracellular proteolytic activity may lead to premature degradation of other molecules implied in various cellular activities.

Laboratory findings

The laboratory diagnosis is usually supported by increased urinary bound sialic acid excretion and confirmed by genetic analysis or the demonstration of neuraminidase enzyme deficiency in cultured fibroblasts (Lowden & O'Brien, 1979).

Clinical presentation

Sialidosis type I presents with the typical features characterizing PMEs (Rapin *et al*., 1978; Lowden & O'Brien, 1979), while the phenotype of *sialidosis type II* includes dysmorphic features (coarse facial features, short trunk, barrel chest, spinal deformity, and skeletal dysplasia), sometimes associated with corneal clouding, hepatomegaly, and inner ear hearing loss. The characteristic macular change found in this metabolic disorder, leading to the definition of 'cherry-red spot', may lead to late visual failure resulting from ganglionic degeneration. The cherry-red spot can, however, be clinically undetectable for many years and may, moreover, disappear in later stages of the disease (Kivlin *et al*., 1985). Young-onset cataract formation was also identified in a few patients with type I sialidosis (Thomas *et al*., 1979).
Both types of sialidosis present with progressively worsening multifocal myoclonus, usually occurring in the second decade of life and variably associated with seizures and ataxia (Lowden & O'Brien, 1979).
Recently, we observed 6 adult patients from 2 different families, presenting high-frequency myoclonus, but no seizures. The disorder progressed slowly and myoclonus was recognized after an interval of many years, although patients displayed a prominent gait disorder with occasional but repeated falls. At the time of our initial diagnostic observation, none of the patients had the cardinal signs suggesting sialidoses, such as macular cherry-red spot or significant urinary sialic acid excretion. Diagnosis resulted from the detection of *NEU1* mutation through genome-wide screening (Canafoglia *et al*., 2014). Our observation, together with a recent similar report (Schene *et al*., 2015), points towards the possibility that mild and late forms present with 'cortical myoclonus' and are possibly misdiagnosed.
Most of the patients, with either sialidosis type I or II, become wheelchair-bound within a few years due to severe motor impairment, mainly resulting from severe myoclonus.

Imaging

MRI findings in sialidoses are normal in the early stages, while cerebellar, pontine, and cerebral atrophy can appear during disease progression (Palmeri *et al*., 2000).

Myoclonus and associated neurophysiological features

In the earliest description of classic PME resulting from type I sialidosis, the authors reported findings similar to those for Unverricht-Lundborg disease, with the exception of photosensitivity that is typically present in Unverricht-Lundborg but not in sialidosis (Engel *et al*., 1977). As for other types of PME, the subsequent description revealed some degree of phenotypic variability both in terms of the severity of myoclonus and the associated signs of cortical hyperexcitability. In general, the cortical origin of the myoclonus is confirmed by the results of simple back-averaging techniques showing a sharp transient preceding the myoclonus (Franceschetti *et al*., 1980; Tobimatsu *et al*., 1985). Since, in patients with sialidosis, myoclonus is often subtle but highly rhythmic and the EEG correlate

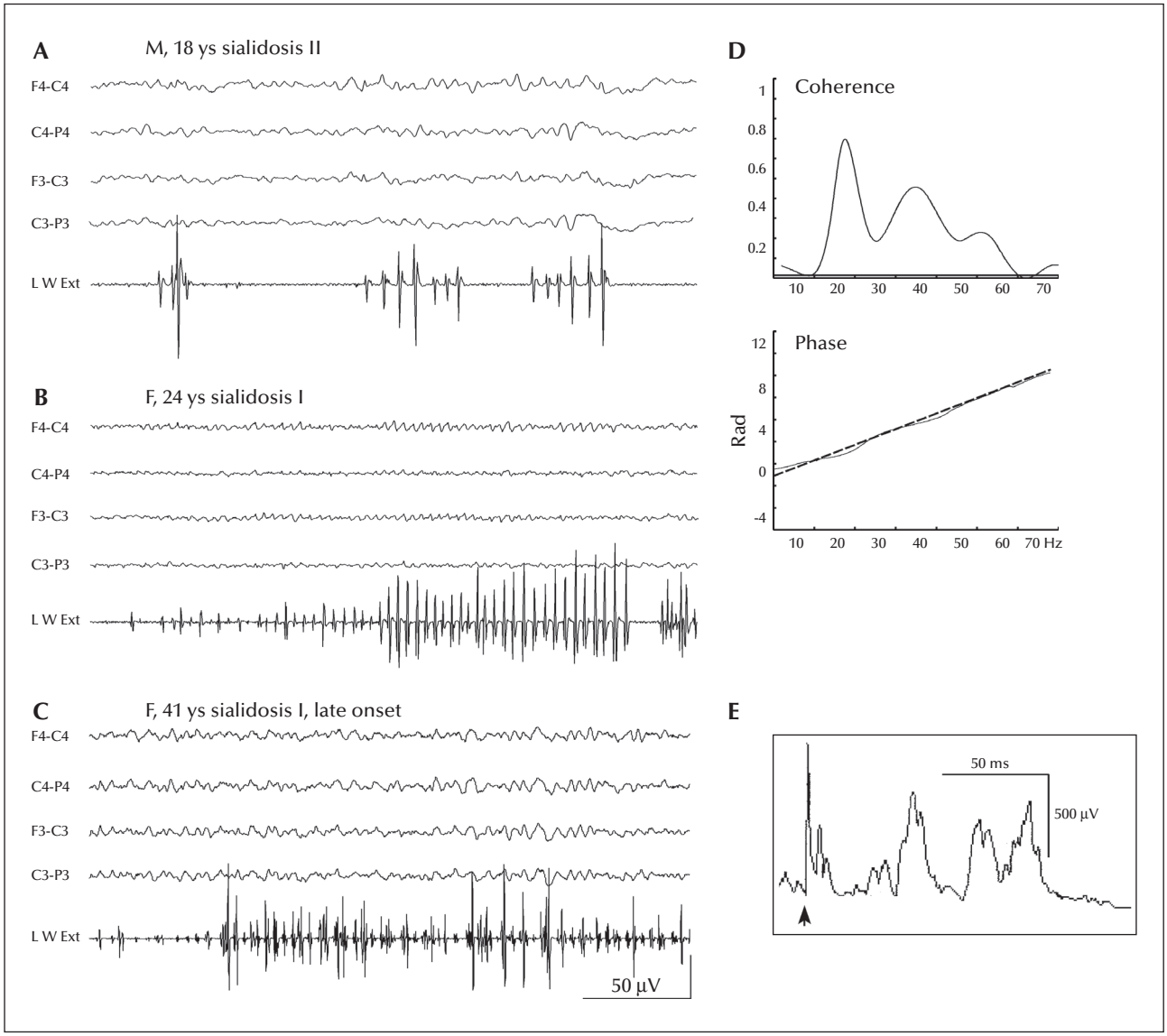

Figure 1. (A, B, C) EEG-EMG recordings performed in 3 patients with sialidosis type II or I. Even if the jerks show a rhythmic course in the all patients, the less severely affected patient with a late onset (C) shows a combination of brief rhythmic sequences and isolated jerks. The panel D shows the coherence and phase function evaluated on EEG-EMG traces in patient B, with an extremely high coherence value and a linear course of the phase indicating a cortical origin of the myoclonic jerks. The panel E shows the multiphasic long-loop response to median nerve stimulation.

consists of a discharge of fast activity, the EEG-EMG coherence analysis appears to be a more reliable method to unequivocally reveal a consistent temporal relationship between the EEG spikes and myoclonic jerks through fast cortico-muscular transfer (Panzica *et al*., 2003). A study comparing between patients with both type I and II sialidosis and patients with Unverricht-Lundborg disease suggested that this strong rhythmicity and the higher cortico-muscular coherence in sialidoses might account for the particularly severe motor impairment observed in sialidosis patients (Canafoglia *et al*., 2011). The EEG background is usually almost normal in patients with type I sialidosis, but polyspike-waves (often associated with spontaneous jerks) are present on the EEG of patients with infantile type II sialidosis.

In some of the reported patients, the presence of high-amplitude somatosensory evoked potentials and enhanced long-loop reflexes (LLR or C-reflex) further confirms the marked neocortical hyperexcitability, which is responsible for 'cortical reflex' and action myoclonus.

The strongly rhythmic recurrence of the jerks reflects on the characteristics of the so-called long-loop

reflexes evoked by median nerve stimulation, which include multiple components resulting from recurrent jerks (Canafoglia *et al*., 2011). *Figure 1* shows the neurophysiological features of the myoclonus in 3 patients with sialidosis.

Differential diagnosis

Sialidosis type II, presenting in infancy or early childhood with dysmorphic features and skeletal abnormalities, should be differentiated from other storage diseases sharing similar features.
Sialidosis type I, presenting with cortical myoclonus as the main symptom, should be differentiated from other forms of progressive myoclonus epilepsy.

Management

Pharmacological treatment is similar to that for other PMEs (see Nirenberg & Frucht [2005] for a review). Valproate can be considered as the first-line drug, but the treatment of severe myoclonus usually requires two or three additional drugs, including benzodiazepines, levetiracetam, zonisamide or topiramate.
The diversity of clinical phenotypes appears to depend on the type of mutation and the percentage of normal sialidase activity that may protect against most severe forms of the disease. Hence, enzyme replacement therapy is a possible approach to treatment. To date, the effect of enzyme replacement therapy has been evaluated in mouse models. In mice, restored neuraminidase activity persisted for some days, resulting in a significant reduction in lysosomal storage, however, the injected enzyme could not cross the blood-brain barrier. Furthermore, the injected recombinant protein may have induced severe anaphylactic responses (Wang *et al*., 2005). □

Disclosures.
None of the authors have any conflict of interest to disclose.

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