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General review

Motor neuron disease in inherited neurometabolic disorders

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ABSTRACT

Inherited neurometabolic disorders represent a growing group of inborn errors of metabolism that present with major neurological symptoms or a complex spectrum of symptoms dominated by central or peripheral nervous system dysfunction. Many neurological presentations may arise from the same metabolic defect, especially in autosomal-recessive inherited disorders. Motor neuron disease (MND), mainly represented by amyotrophic lateral sclerosis, may also result from various inborn errors of metabolism, some of which may represent potentially treatable conditions, thereby emphasizing the importance of recognizing such diseases. The present review discusses the most important neurometabolic disorders presenting with motor neuron (lower and/or upper) dysfunction as the key clinical and neuropathological feature.

1. Introduction

Hereditary neurometabolic disorders represent a large, heterogeneous and growing group of neurogenetic diseases resulting from inborn errors of metabolism (IEM), leading to quantitative or qualitative defects in the production of enzymes, cofactors, vitamins and intracellular membrane transporters related to intermediary, complex molecular and energy-related metabolic pathways. In general, most IEM originate from homozygous or compound heterozygous mutations with autosomal-recessive inheritance, and their clinical manifestations are due to the lack of a specific subtrate of an affected metabolic pathway, intermediary metabolic dysfunction with accumulation of toxic metabolites causing acute and chronic cellular dysfunction, derangement of metabolic pathways related to the biosynthesis or catabolism of complex molecules in cytoplasmic organelles with partly irreversible accumulation of non-degradable complex substrates, and/or impairment of mitochondrial

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energy processes and their associated cytoplasmic pathways [1].

The neurological manifestations associated with IEM represent an extremely common group of presentations of such metabolic defects in clinical practice, including variable age of onset from perinatal to late adult cases, acute (episodic), chronic or relapsing – remitting forms and highly variable expressivity, with the age of symptom onset being a key factor of the clinical picture of most of these metabolic disorders. From a neurological point of view, the IEM can present in isolation or in association with movement disorders (especially dystonia and parkinsonism), cerebellar ataxia, spastic paraparesis, epilepsy (especially myoclonic epilepsy or certain types of epileptic syndromes of childhood), peripheral neuropathies, metabolic and mitochondrial myopathies, leukoencephalopathies, and possibly even acute cerebrovascular or encephalopathy presentations [2].

Although spasticity represents an extremely common finding in many IEM with pyramidal tract involvement, neurometabolic diseases are rarely considered in the differential diagnosis of motor neuron disease (MND), despite the wide range of different conditions that relate to dysfunction of upper motor neurons (UMNs) and lower motor neurons (LMNs). The number of new inherited metabolic disorders now recognized as important causes of early- or late-onset motor neuron dysfunction has grown noticeably over the last few decades, due to the increased availability of laboratory methods for screening and making a definite diagnosis of IEM, and the use of next-generation sequencing techniques (particularly whole-exome sequencing) [3–5].

Yet, despite the new knowledge related to metabolic disorders linked to motor neuron dysfunction, underdiagnosis of these conditions is still the rule, as they are rarely recognized as a relevant group of conditions in clinical practice. The present review discusses the main inherited neurometabolic diseases associated with patterns of involvement similar to amyotrophic lateral sclerosis (ALS), progressive muscular atrophy (PMA) and spinal muscular atrophy (SMA). However, conditions associated with a phenotype similar to primary lateral sclerosis (PLS) and hereditary spastic paraparesis (HSP) are not systematically presented, as they have already been extensively reviewed elsewhere [5–8].

2. Basic introduction to MND

MND represents a large group of neurodegenerative diseases resulting from involvement of UMNs (cortical or giant pyramidal neurons of Betz) in layer V of the primary motor cortex, of LMNs (alpha motor neurons) in the ventral (anterior) horn of the spinal cord, or both concomitantly from disease onset or throughout disease progression [9]. Primary isolated involvement of LMNs is observed in classic SMA (*SMN1/SMN2*-related), in atypical distal or proximal SMA (non-5q or non-*SMN1/SMN2*) and in PMA, resulting in weakness, proximal or distal muscle atrophy, reduced or absent tendon reflexes and fasciculations at multiple spinal or bulbar levels. SMA classically arises with a slowly progressive proximal symmetrical presentation of appendicular weakness, while PMA generally starts asymmetrically, with proximal and distal compromise and only later with bulbar involvement, despite variable ventilatory capacity commitment [10–12].

Primary isolated involvement of UMNs is observed in classic and juvenile presentations of PLS and in pure and complicated (complex) forms of HSP, causing muscle weakness, brisk tendon reflexes, pyramidal release signs (Babinski's sign and other pathological reflexes), ankle jerk reflex (clonus) and spasticity [13,14]. Sphincteral disturbances and a positive family history are more frequent in cases of HSP, as well as the occurrence of other neurological and systemic signs, in particular, ophthalmological findings, cerebellar ataxia, axonal neuropathy, movement disorders and epilepsy. Both HSP and PLS often present with a more slowly progressive clinical course than other forms of MND. Nevertheless, there is a clear difference between them based on their neuropathology: HSP represents primary retrograde dysfunction of the long descending fibers of the corticospinal tract; while PLS represents a primary neurodegenerative disorder of UMNs [7,15,16].

ALS is the most common form of neurodegenerative MND seen in clinical practice and is the result of impairment of both UMNs and LMNs, either concomitantly or at different times during disease progression, with a variable association of UMN and LMN signs. Around 90% of cases are sporadic, while only 10% of cases have a familial pattern of presentation [9,16–18]. Most cases have an adult onset at 45–65 years, with cases aged < 45 years considered early-onset ALS and those at age < 25 years called juvenile ALS [4]. There is a frequent association of genetically determined forms and familial cases with other systemic and neurological degenerative conditions, such as Paget's disease of bone, frontotemporal lobar degeneration, parkinsonisms and inclusion-body myopathy [4].

3. Basic physiopathological mechanisms associated with IEM in MND

MND can result from various acute or chronic neurometabolic disorders related to intermediary metabolism and catabolism and biosynthesis of complex molecules (Table 1) [1,5,19,20]. The main dysfunction of motor neurons is related to secondary degeneration due to chronic energy deficit (including primary mitochondrial and fatty-acid beta-oxidation disorders), amino-acid metabolic dysfunction, disorders of metabolism of purine/pyrimidine nucleotides, disturbances of vesicular and endosomal formation and trafficking, disorders of biosynthesis of complex molecules (including bile acids) and their catabolism (including late-onset glycogenosis and peroxisomal disorders), and defects of transporters of cofactors, metals and vitamins (Fig. 1) [1,5,19]. In general, motor neuron metabolic dysfunction involves the final common pathways of neuronal degeneration seen in other primary forms of MND/ALS, including activation of apoptotic pathways, increased neuronal oxidative stress, secondary dysfunction of autophagy and ubiquitin–proteasome systems, and secondary axonal degeneration in cases of defects related to biosynthesis of complex molecular components of the long descending tracts (pyramidal pathway) [4].

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