Updates in Floppy Infant Syndrome

Essay

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in

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الحديث فى متلازمة حديث الولادة الرخوى

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توطئة للحصول علي درجة الماجستير فى
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مقدمة من

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List of Abbreviations

AAV	Adeno associated virus
AchR	Acetyl choline receptor
ASOS	Antisense oligonucleotides
CDG	Congenital disorder of glygosylation
CFTD	Congenital fiber disproportion disease
CGH	Comparative genomic hybridization
CK	Creatine kinase
CMAP	Compound muscle action potential
CMD	Congenital muscular dystrophy
CMS	Congenital myasthenic syndrome
CNS	Central nervous system
CRIM	Cross reactive immunological material
CSF	Cerebrospinal fluid
DNA	Deoxyribonucleic acid
DS	Down syndrome
EEG	Electroencephalogram
EGR2	Early growth response 2 gene
EMG	Electromyography
ERT	Enzyme replacement therapy
FISH	Fluorescent insitu hyridization
GAA	Acid alpha glucosidase
HIE	Hypoxic ischemic encephalopathy
MEB	Muscle-eye-brain

MELAS	Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episode
MERRF	Myoclonus, epilepsy and ragged red fibers
MN	Motor neuron
MTM	Myotubularin 1 gene
MPZ	Myelin protein zero gene
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
OCRL1	Oculocerebralrenal 1 gene
PWS	Prader-Willi syndrome
PC	Pyruvate carboxylase
PDH	Pyruvate dehydrogenase
RNS	Repetitive nerve stimulation
RYR1	Ryanodine receptor 1 gene
SMA	Spinal muscular atrophy
SEPN1	Seleno protein 1 gene
SNE	Sub acute necrotizing encephalomyelitis
TPM3	Tropomysin 3 gene
WWS	Walker-Warburg syndrome
VLCFA	Very long chain fatty acid

Introduction

The term ‘floppy baby or infant’ is used to denote an infant with poor muscle tone affecting the limbs, trunk and the cranio–facial musculature. The condition is usually evident at birth or is identified during early life as poor muscle tone results in an inability to maintain normal posture during movement and rest ***(Prasad and Prasad, 2003).***

When lying supine, all hypotonic infants look much the same, regardless of the underlying cause or location of the abnormality in the nervous system. Spontaneous movement is lacking, full abduction of the legs places the lateral surface of the thighs against the examining table, and the arms lie either extended at the sides of the body or flexed at the elbows with the hands besides the head. Pectus excavatum is present when the infant has long standing weakness in the chest wall muscles. Infants who motionless eventually develops flattening of the occiput and loss of hair on the portion of the scalp that constant contact with crib sheet. When placed in a sitting posture, the head falls forward, the shoulders droop, and the limbs hang limply ***(Gordon et al., 2006)***.

Floppy infants may be due to central hypotonia, hypotonia of neuromuscular origin and others that are uncharacterizable ***(Prasad and Prasad, 2003).***

Central hypotonia includes chromosomal disorders, genetic disorders, brain dysgenesis, acute hemorrhagic or other brain injuries, hypoxic encephalopathy, peroxisomal disorders, metabolic defects, drug intoxications and benign congenital hypotonia. Peripheral hypotonia includes Werding Hoffman disease, poliomyelitis, neonatal Guillan-Barre syndrome, myasthenia gravies, Pomp disease, and muscle disorders. In certain cases, however, central and peripheral defects coexist as in congenital myotonic dystrophy, congenital muscular dystrophy, lipid storage diseases, and mitochondrial encephalomyopathies ***(Richer et al., 2001).***

Three features are generally useful in establishing the locus of hypotonia at anatomical level above the lower motor neuron, first, hypotonia is usually more severe than weakness and, in dead, some affected infants although "floppy" exhibit strong movements when stimulated. Second, tendon reflexes are usually preserved, although it is unusual to observe the hall mark of central hypotonia as seen after the first weeks and months of life: hyperactive tendon reflex. Thus, as with weakness hypotonia is more

marked than is involvement of tendon reflex. Third, other signs of central involvement are frequently present, particular note: should be made of seizure ***(Joseph, 2008).***

The diagnosis can be improved by including a karyotype and cranial imaging in addition to a clinical assessment. Newer cytogenetic tests such as array comparative genomic hybridization (array CGH) and second generation sequencing studies (exone sequencing) will enhance and facilitate the genetic investigation of hypotonia The detection rate for chromosomal abnormalities with array CGH with a normal karyo-type is in the range of 5-17%, a significant improvement. The principal limitation of this technique apart from its cost is its inability to detect balanced rearrangements (translocation and inversions). In addition, due to its high sensitivity, a proportion of detected copy number variants may be of unclear clinical significance. Parental sampling may be required to further delineate the pathogenicity of the changes seen. That being said, array CGH is a powerful diagnostic tool and is replacing both conventional cytogenetic, as well as other labor-intensive techniques such as fluorescent in-situ hybridization (FISH) ***(Shinawi and Cheung, 2008).***

The technique of electroneuromyography (EMG/nerve conduction study) retains relevance in the investigation of disorders of the lower motor unit. Although earlier technical challenges precluded their use in very young infants, they remain valuable for two reasons: first, they can help categorize central from peripheral hypotonia; second, nerve conduction and EMG studies are very helpful in distinguishing between a peripheral neuropathy and a motor neuropathy ***(Darras and Jones, 2000).***

Performing a muscle biopsy is recommended in neonates with weakness without electrophysiological evidence of an anterior horn cell, nerve or neuromuscular junction disorder, even if the needle EMG examination is normal. Muscle biopsy should be considered in the diagnosis of suspected myopathies and muscular dystrophies, even if the electrophysiological studies are normal ***(Richer et al., 2001).***

Cranial CT/MRI studies of the brain are helpful in the identification of structural malformations, neuronal migration defects (e.g. lissencephaly), altered signal characteristics of white matter (e.g. laminin deficiency). Signal abnormalities in the basal ganglia (e.g. mitochondrial cytopathies) as well as the detection of brain stem and cerebellar abnormalities (e.g. pontocerebellar

hypoplasia) are findings that may be pathognomonic for specific disorders ***(Prasad and Prasad, 2003).***

The treatment approaches for genetic disorders resulting in hypotonia are mostly symptomatic and supportive. Specific interventions such as anticholinesterase inhibitors and 3, 4- diaminopyridine are currently in use for the treatment of congenital myasthenic syndromes (CMS), while ephedrine is being tried for CMS associated with DOK7 mutations. The epigenetic modifying effects of valproic acid have been effective in animal models of SMA in improving survival and function and have been tried in patients in initial trials ***(Swoboda et al., 2009).***

The use of hydroxyureas may enhance splice function and increase nuclear gems (small nuclear organelles**)** ***(Darras and Kang, 2007).***

The future of antisense oligonucleotide therapy in the realm of congenital muscular dystrophy remains speculative at present. The timely delineation of an accurate diagnosis for urea cycle defects, fatty acid oxidation disorders and organic acidemias will allow dietary manipulations and use of specific medications. Another important disorder presenting with hypotonia is Pompe disease where early detection and use of myozyme can help with the course ***(Chien et al., 2009).***

There are challenges with cross-reactive immunological material (CRIM)-negative status where more extensive immunomodulation treatment may be required ***(Kishnani et al., 2010)***.

Nevertheless focus has now begun on early detection through newborn screening of Pompe disease in some countries, notably Taiwan ***(Chien et al., 2009)***.