Muscle Memory

In this issue of The Journal, Cyrulnik et al report that patients with Duchenne muscular dystrophy (DMD) often have delayed milestones, both language and motor. This is the first systematic study of a large cohort of patients to document that early delay does occur and can be correlated with later cognitive function.

The year 2006 marked the 20th anniversary of the discovery of the dystrophin gene and mutations that cause DMD and the allelic disorder, Becker muscular dystrophy (BMD). In the 2 decades since, we have seen molecular explanations for facts we knew but didn’t understand, such as holes in the sarcolemma visible at the electron microscopic level. We have also learned some new things, such as there are many patients with BMD who have no weakness, but present with other manifestations such as cardiomyopathy or autism. This knowledge has reinforced a concept that, although progressive muscle weakness is the hallmark of DMD/BMD, it is a multi-system disease.

Although the association between DMD/BMD and cognitive deficits was recognized in the earliest clinical descriptions, the role that dystrophin deficiency might play in brain dysfunction remains a mystery. Debate in the 1970s centered on whether the cognitive deficit was progressive and somehow related to loss of mobility and socialization; we now know this is not true (Hinton; personal communication). Studies of brain structure yielded little information, but positron emission tomography studies suggested a relationship between glucose utilization and dystrophin deficiency in the cerebellum. Few studies focused on the specifics of clinical brain dysfunction in DMD/BMD.

However, the cognitive deficits seen in DMD/BMD are not seen in other neuromuscular disorders. Spinal muscular atrophy, another common cause of weakness in infancy and childhood, is associated with excellent language development and often advanced language development. Likewise, children with various forms of congenital myopathies tend to perform extremely well academically.

Cyrulnik et al previously showed that DMD is associated with significant deficits in verbal memory that can explain poor school performance. Now, as part of their large and ambitious study of cognitive function in DMD, they have focused in this report on developmental milestones. Most neuromuscular specialists who care for patients with DMD know empirically that boys who are affected often have a history of delayed milestones and, in particular, language delay.

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However, many families experience inappropriate diagnosis and management because of failure to recognize the presence of the muscular abnormality before they get to the neuromuscular specialist. It is very important that pediatricians be aware that DMD is a common cause of developmental delay and school failure in the absence of or before the development of weakness. Serum creatine kinase levels should be included in the first screening tests for boys with developmental delay; creatine kinase screening is a cheap and quick test that will always have abnormal results in DMD/BMD during the first decade of life. Moreover, newborn screening and early diagnosis might make it possible to enroll young affected boys in early childhood intervention and appropriate classroom placement by age 3 years.

Although treatment with prednisone has been very effective in slowing the progression of weakness and preventing some of the medical complications of DMD, steroids may disrupt school performance by causing decreased attention span and irritability. The authors of the report by Cyrulnik et al do not mention whether any of their patients were taking steroids at the time of neuropsychological testing. It is clear from their work that the search for new treatments as effective as prednisone should include a consideration for effects on cognitive function, especially verbal memory.

References


Omega-3 Long-Chain Polyunsaturated Fatty Acids in Older Children

Phenylketonuria (PKU), the most prevalent inborn error of metabolism, is usually caused by low hepatic activity of phenylalanine hydroxylase, the enzyme that catalyzes conversion of phenylalanine to tyrosine. It is characterized by a high plasma phenylalanine concentration and, in the absence of adequate tyrosine intake, a low plasma tyrosine concentration. Management of patients with PKU includes early detection, primarily by mandatory neonatal screening programs, followed by a low protein diet supplemented with a low-phenylalanine or phenylalanine-free formula. Frequent monitoring and appropriate dietary changes in response to this monitoring are necessary to maintain plasma phenylalanine and tyrosine concentrations within the desired range.

Growth and development of infants and children with PKU who are treated as aforementioned do not differ appreciably from population norms. However, the IQ of treated children with PKU is somewhat lower than that of their unaffected siblings. These children also perform less well in school than their unaffected siblings, they tend to exhibit more behavioral problems, and they have problems concentrating. However, current outcomes of infants and children with PKU are far superior to the severe psychomotor retardation that occurs without treatment.

A major question concerns the extent to which the residual developmental deficits of optimally treated infants and children with PKU are an inevitable consequence of the condition. A study reported by Beblo et al in this issue of the Journal suggests that at least

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