Severe childhood autosomal recessive muscular dystrophy, mental subnormality and chorea

Satish V. Khadilkar, Krishe M. Menezes, Rakesh K. Singh*, Madhuri R. Hegde**

Department of Neurology, Grant Medical College and Sir JJ Group of Hospitals, Mumbai, *Consultant Neurologist, Thane, India, **Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA

Severe childhood autosomal recessive muscular dystrophy (SCARMD) is characterized by a severe Duchene muscular dystrophy like phenotype. Most such cases represent alpha or gamma sarcoglycanopathies. Mental subnormality is very uncommon and other central nervous system deficits have not been documented in patients with SCARMD. We report a brother and sister with the SCARMD phenotype, who additionally had static mental subnormality and choreiform movements. Work-up for sarcoglycan genes, dystrophin gene and known causes of mental retardation and chorea was normal.

Key words: Chorea, mental subnormality, muscular dystrophy

Introduction

Severe childhood autosomal recessive muscular dystrophy (SCARMD) is a descriptive term denoting severe muscular dystrophy occurring at early ages and affecting boys as well as girls with similar severity. First report of SCARMD was given by Buss in 1887 and an unequivocal description of transmission and clinical features of SCARMD was given by Kloepfer and Talley in 1958. In 1983, Ben Hamida described signs, symptoms and muscle pathology findings of SCARMD. Many reports have since been published from various countries and cases and series have been described from India.[1-3] With advances in genetics and immunocytochemistry, most cases of SCARMD are now known to result from mutations of alpha and gamma sarcoglycan genes.[4] Other autosomal recessive limb girdle muscular dystrophies can rarely have a severe childhood expression.[5] However, unlike the Duchene muscular dystrophy, none of these forms of autosomal muscular dystrophies are known to be associated with abnormalities of the central nervous system. Recently, in 2005, mutations in protein O-mannosyltransferase (POMT) 1 gene have been described. Sufferers have muscular dystrophy and subnormal mentation.[6] Besides mental subnormality, no other central nervous system changes are known in these patients.

In the present case report, a family with severe muscular dystrophy, mental subnormality and previously undocumented association of chorea in two affected siblings is described.

Case Report

Proband was a 10-year-old boy born of a non-consanguineous marriage. He presented with proximal muscle weakness, beginning in both lower limbs since 3 years of age. Weakness was progressive and at the age of 10 years, both upper limbs became weak. He was noticed to be mentally dull since birth but gradually gained skills as he grew up. He also had abnormal movements of all limbs, which were noticed at age of 1 year. He was born of full term normal hospital delivery and his early motor milestones were normal. His younger sister, aged 7 years, had identical history. There was no family history of similar disorder. On examination, proband’s intelligence quotient was 67 and sister’s was 70. Both sibs had generalized chorea, which was mild in intensity and involved frequent eyebrow raising. Both patients had severe limb girdle muscular weakness, being more prominent in the lower limbs, with mild calf hypertrophy [Figure 1] and tendon Achilles contractures. Tendon reflexes could be elicited normally. Sensory examination was normal. EMG showed normal muscle biopsy confirmed dystrophic histology. Immunohistochemistry showed normal staining pattern for dystrophin I, II and III and Alpha, beta, gamma and delta sarcoglycan subunits. Electrocardiogram and 2-D
echocardiogram did not reveal any abnormality of myocardial contractility or of cardiac rhythm. Nineteen exon deletion testing for dystrophin gene using Begg’s and Chamberlein’s methods[7,8] did not reveal any deletion in dystrophin gene. All the four sarcoglycan genes were studied by direct sequencing using diHPLC method. The complete coding region of the four sarcoglycan genes, including all splice junctions, was amplified using standard sequences of primer pairs.[9]

Proband and his sister were also tested for expansions in the genes associated with Huntington's disease and fragile X syndrome. Both these analyses revealed no abnormalities and alleles sizes were in the normal range. T3, T4 and TSH levels were within normal limits. Serum copper oxidase was normal. There were no Kayser Flescher rings. No acanthocytes were detected in fresh blood on three samples and the MRI brain of both sibs was normal.

Discussion

Our patients were born to non-consangunous parents who tested normal on clinical examination and laboratory investigations. Thus the disease is probably autosomal recessive in nature. Affected sibs had very similar clinical features, which consisted of a muscle disorder and central nervous system affection resulting in chorea and mental subnormality.

The muscle disorder

Muscle disorder in these two children is SCARMD. Patients began with weakness at about 3 years of age, which was severe enough to produce disability by the age of 10 years and there was calf hypertrophy. No cardiac involvement was documented clinically or by investigations. Lack of cardiac involvement and sister having severe phenotype makes dystrophinopathy unlikely. Dystrophin immunocytochemistry was normal and no abnormality was detected in the deletion analysis of dystrophin gene, excluding the diagnosis. Autosomal recessive inheritance and the early severe phenotype strongly suggested sarcoglycanopathy. However, all four sarcoglycan subunits, including the most commonly affected ones in SCARMD - alpha and gamma - were normal on immunocytochemistry. Though no disease-associated mutations were detected in four sarcoglycan genes, these results do not exclude all known causes of SCARMD, as additional genes can be associated with the SCARMD phenotype.[5,10,11] However, none of these conditions are known to have central nervous system abnormalities seen in our patients.

Central nervous system abnormalities

These children had a movement disorder consisting of generalized choreiform movements with prominent eyebrow raising. We investigated them for various causes of chorea and excluded known etiologies. MRI of the brain showed normal basal ganglia. Huntington’s gene was normal. Work-up for Wilson’s disease and neuroacanthocytosis was normal. The other central nervous system abnormality was mild mental subnormality, which had remained static over years. Fragile X chromosomal studies were normal. Association of static mental subnormality and rapidly progressive childhood muscular dystrophy would raise the diagnosis of dystrophinopathy, but as explained earlier, it was excluded. Genes encoding for glycosyltransferases are getting to be associated with muscular dystrophies. Severe forms present early in life and have structural eye and brain changes. Mild forms present in the adulthood.[12] At least five genes (POMT1; POMGnT1; FKRP; Fukutin; LARGE) encode for proteins involved in the glycosylation of alpha-dystroglycan and abnormal glycosylation of this protein is a common link to these conditions.[12] The recent description of mental retardation and autosomal recessive muscular dystrophy resulting from a mutation in the protein O-mannosyltransferase [POMT] 1 gene needs a particular consideration. POMT 1 gene mutation affects glycosylation of alpha dystroglycan, which reflects in muscles as well as brain. The condition is allelic to Walker-Warburg syndrome. However, in these patients, choreiform movement disorder has not been described and in this respect, the present family is different. We could not test alpha dystroglycan immunocytochemistry on muscle due to technical limitations. Congenital muscular dystrophies were considered but normality of early motor milestones, development of muscular weakness after 3 years of age, normal MRI and presence of chorea made this possibility less likely. Normality of the thyroid function tests excluded a possibility of hypothyroid state with CNS and neuromuscular manifestations.

It is tempting to postulate that the gene defect, which codes for muscle disorder in these children, is also responsible for producing movement disorder and mental subnormality. However, two separate unrelated conditions cannot be excluded. Evolution of disease in these children may give further clues.

In conclusion, we document a most unusual family having a combination of autosomal muscular dystrophy with mental subnormality and generalized chorea, which has previously not been described.

References

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