Wohlfart Kugelberg Welander Disease: A case report with genomic analysis

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Abstract:
Spinal Muscular Atrophy (SMA) comprises a group of inherited disorders marked by hypotonia, muscle weakness and atrophy due to degeneration of anterior horn cells of spinal cord. Wohlfart Kugelberg Welander Disease or Type 3 SMA presents with milder weakness and onset after the age of 18 months. We present one such case with genetic analysis showing homozygous deletion of exon 8 sparing exon 7 in the Survivor Motor Gene 1 (SMN1) which is a rare occurrence.

Keyword: Wohlfart Kugelberg Welander Disease, exon8, SMN1 gene

Introduction:
Spinal muscular atrophies are a group of disorders inherited predominantly in autosomal recessive pattern with an incidence of 1 in 6,000 to 10,000 livebirths (1). Of the 3 variants classically described, Type 3 SMA or Wohlfart Kugelberg Welander Disease is the mildest form with onset of symptoms generally after the age of 18 months and has a chronic evolution (2). Patients present usually with insidious onset of weakness which is more pronounced in the pelvic girdle than the shoulder girdle. These children can stand and walk unaided at least in infancy. Although SMA has no known cure, the affected children can survive well into adulthood with therapy focused on symptomatic control and preventive rehabilitation stressing on the importance of early diagnosis. Molecular genomic analysis for homozygous deletion of exons 7 and 8 of SMN1 gene located on chromosome 5q13 by Polymerase Chain Reaction – Restriction Fragment Length Polymorphism (PCR-RFLP) remains the mainstay of diagnosis (3).

Case Report:
A 5 year old female child, first born of a non-consanguineous marriage was brought with complaints of frequent falls and difficulty in walking for the past 3 ½ years. The child started walking with support at 10 months of age and without support after 1 year of age with a broad based waddling gait which never became corrected to the normal gait. Child can walk and run with broad based gait till 1 ½ years of age. After that the child started having frequent falls while walking and his range of mobility decreased to walking with support at the age of 2 ½ years. Now the child can stand without support and walk only a few steps with support. History of difficulty in getting up from lying and sitting posture, lifting hands above head also present. No history suggestive of distal muscle weakness was present.

The antenatal history was uneventful with no history of reduced fetal movements. Development milestones were appropriate for age till 1 ½ years after which there is marked delay in gross motor milestones. There was no positive family history other than a spontaneous abortion at 45 days of amenorrhoea in the mother prior to this child’s birth.

On examination, the child was found to be an alert playful child with fluent speech and good comprehension. She walks with support in broad based gait and had an exaggerated lumbar lordosis. Central Nervous system examination revealed hypotonia in all limbs with lower limbs affected the worst. The power in shoulder was 3/5, elbow and wrist 4/5, hip, knee and ankle 3/5. All the deep tendon reflexes were absent and plantar was flexor. Sensory examination was normal.

Investigations:
CPK-MB showed only mild elevation (252 IU/L).
Nerve conduction study was normal.
Thyroid function test was also normal.
Genomic DNA analysis confirmed the diagnosis of Type 3 SMA with results showing deletion of 189 bp band representing deletion of exon 8 of SMN1 gene.

Discussion:
Spinal Muscular Atrophy is a clinically heterogeneous group of disorders inherited mostly in autosomal recessive pattern with the disease spectrum ranging from inutero death to survival well into adult life with minimal weakness. The International SMA Consortium (ISMAC) has divided this disease into 3 types based on age of onset of weakness and development of milestones. Dubowitz added a Type 0 with prenatal onset and intrauterine or early neonatal death. An adult form (Type 4) is increasingly being recognized with onset after 30 years of age (4).
There are 2 SMN genes namely Telomeric (SMN1) and Centromeric (SMN2) with critical sequence difference between the two is the exon 7 region. For DNA based mutation detections, one bp variation each in exons 7 and 8 forms the basis of identifying diseased gene (7).

Type 0 Inutero Decreased fetal movements Severe asphyxia at birth Inutero or early neonatal death

Type 1 (Werdnig Hoffman disease) 0 – 6 months Floppy infant with alert look, tongue fasciculation Severe proximal and respiratory muscle weakness Death in early infancy to 2 years of age

Type 2 (Intermediate, Chronic) 6 – 18 months Able to suck and swallow, nasal speech Progressive weakness, may sit but never stand Survival beyond 4 years until adolescence

Type 3 (Wohlfart Kugelberg Welander Disease) 18 months – 17 years Normal infancy Independent walking & standing – Lose this later Survival into middle adult life Type 4 30 – 50 years Insidious onset of weakness at median 37 years

Wohlfart Kugelberg Welander Disease or Type 3 SMA or Hereditary Proximal Neurogenic Muscular atrophy initially presents with gait instability which slowly progresses to the distal muscles (8). The hands are the last parts to be affected. Extraocular muscles are spared.

Minipolymyoclonus, a fine tremor of outstretched fingers may be seen. Muscle wasting is predominant but calf pseudohypertrophy may be present. Sensory system is normal.

There is no known cure for Type 3 SMA. Genetic counseling should be given to the family.

Maintaining joint mobility by range-of-motion exercises and ankle-foot orthotics at night along with passive stretching exercises are used to prevent contractures (9). Dietary advice to reduce or prevent obesity should be given as it puts undue strain on the already weak muscles. Medications for upregulation of SMN2 gene like phenylbutyrate, Valproic acid, Suberoylanilide hydroxamic acid, hydrosyurea, neuroprotective medications like gabapentin and riluzole are currently under study. Albuterol, Lithium and Thyrotropin releasing hormone are also being evaluated for treatment (10).

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