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Case Report

A Child Hereditary Motor Sensory Neuropathy and Mutation of Heat Shock Protein *HSPB1*

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INTRODUCTION:

Diagnosis of distal lower limb weakness with atrophy of muscles in children is challenging. The differential diagnoses are primary distal myopathies and neuropathies. Hereditary motor sensory neuropathy (HMSN) is an important cause and

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can be expressed in childhood. Apart from clinical examination and electromyography, genetic analysis is important for diagnosis. Hereditary neuropathies are genetically heterogeneous. Mutations of several genes are known to cause distal hereditary neuropathy.

Heat Shock protein beta-1 is a ubiquitously expressed, multifunctional protein chaperone. Mutations in HSPB1 result in the development of a late onset, hereditary motor neuropathy type II (HMN) and axonal Charcot-Marie Tooth disease with sensory involvement (CMT2F).[1] We describe a case with weakness of the distal lower limbs. Exome sequencing identified a novel mutation in the conserved a-crystallin domain of HSPB1. The multiple tissues involved in this disorder are important for both the clinical classification of distal weakness and the development of new treatments.

CASE REPORT:

A 5 year old boy presented with instability during walking. From the beginning, he had delayed milestones of motor development. He started to sit at 1 year of age and started to stand with support at 4 years of age, he can now walk with support,but he can not climb stairs or jump. He does not have any numbness in his both lower limbs. He had no history of disturbance in feeding, swallowing or combing his hair. No diurnal variation of motor symptom was present. He had no history of trauma in the back or head, no history of taking any toxic substance or heavy metal. He is the 2nd issued of his consanguineous parents; none of his family members had similar type of illness. Regarding birth history, he was born by lower uterine caesarian section at term with average birth weight without any perinatal complication. Regarding his developmental history, he achieved his neck control at 3 months, sitting at 1 year. He can speak age appropriately but

speech is slurred. His cognition, fine motor, vision and hearing function was in normal range.

On examination, he was alert, vitals within normal limit, anthropometrically normal. There was no abnormality in the cranial nerves. Higher psychic function was normal except the slurred speech. Cerebellar function was normal except gait which could not be evaluated and slurred speech. Examination of the motor system of lower limbs revealed that, bulk of the muscle was reduced more in the muscles bellow knee. Pes cavus was observed. Tone of the muscles were decreased, power was 3/5, more obvious in distal part. The muscle strength was decreased particularly knee flexor, extensor, dorsiflexor muscles. Knee and ankle jerks were diminished symmetrically, planter reflex was flexor. He was unable to stand on tip toe or balance on either leg. Gait could not be evaluated. However, he can walk with orthotic aid to a certain distance. Sensation of light touch, pain, temperature, vibration and position was normal. Examination of the upper limbs showed that the bulk is normal, tone decreased , power 4/5 and jerks diminished. He did not have any abnormal autonomic disturbances like urinary incontinence and orthostatic hypotension.

Work up: The complete blood count was normal. CPK , liver function test and renal function test was normal. Vitamin B12 level was normal. Nerve conduction study showed, distal latencies were prolonged in both ulnar and median nerve and normal in tibial and peroneal nerve. CMAP was low in ulnar, tibial, peroneal and median nerve. Conduction velocity was reduced in ulnar, peroneal, tibial and right median nerve and prolong in left median nerve. F wave was inexitable in right median nerve and absent in left median nerve, both ulnar, tibial and peroneal nerves. Sensory Nerve Action Potential (SNAP) were absent in superficial peroneal, sural, medina and ulnar nerves . Thus NCV of all four limb suggested motor

sensory polyneuropathy (axonal, motor>sensory). MRI of brain was normal.

Gene analysis of the case:

Karyotyping by G banding of the peripheral blood was normal. A novel mutation in HSPB1 was found . Along with this, exon 1 deletion was found. A panel of 10 genes known to cause hereditary neuropathy were screened (HSPB 1, HSPB 3, HSPB 8, GARS, SATX, IGHMBP2, NEFL, DCTN1, ATP7A,BSCL2)

DISCUSSION:

Till date, very few cases have been reported of HSPB 1 gene mutation causing HMSN. The phenotype of our case is similar to other cases reported till date but slurring of speech is an additional finding in this case.[2,3] The speech abnormality can not be explained by HSPB1 gene deletion.

HSPB1 is a stress-inducible, adenosine triphosphate–independent small heat shock proteins expressed in skeletal muscle and neurons.[4] It is a chaperone protein and forms oligomers to maintain a misfolded protein in a refolding-competent state. The upregulation of HSP27 has been reported to be required for the survival of motor and sensory neurons injured by apoptotic stress. [5] Individuals with mutations in the C-terminal domain of HSP27 show a more severe phenotype, with ages at onset as young as four and seven years. [6] Mutation of HSPB1 along with HSPB3 and HSPB 8 are clinically associated with motor neuropathy. [7] The genes associated with HMSN disease may have a specific role in Schwann cells or in the peripheral neurons. Although some genes are expressed in every tissue and cell, the HMSN causing mutations selectively affect peripheral nerves. [8]

Our child is the first reported case from Bangladesh having HSPB1 mutation causing HMSN. The age of onset of previously reported cases were mostly late adulthood. [2,3] First reported case was by Ikeda et al. [9] Compared to these patients, our patient has an early age of onset. Our patient never started to walk steadily, also he had no sensory impairment in examination however neurophysiology was suggestive of sensory impairment. This feature coincide with the previous case report by DJ Lewis – Smith et al who reported normal sensation but decreased sensory muscle action potential (SNAP) with normal conduction. [2]

In a case reported earlier, patient had myopathic clinical feature with increased CPK and histological change in the muscle suggestive of myopathy along with HMSN . This was an unusual feature of HSPB1 mutation. [2] However, our patient did not have any such feature. In another case, patient had severe dysfunction of the autonomic nervous system.[9] Our patient did not have any form of dysautonomia.

CONCLUSION:

This is the first case reported from Bangladesh with HMSN due to HSPB1 mutation. Such case gives broader consideration of the underlying disease mechanisms particularly the relevance of key interacting proteins. This will assist in the prioritization of novel variants for further functional studies. Also it will help to establish pathogenicity and broadening our understanding of the relationship between genotype and phenotype. A deeper knowledge of the cell types involved in widely expressed genes is critical for the development of novel therapies.

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