A CASE OF GIANT AXONAL NEUROPATHY

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CASE HISTORY

• Nine year old male child
• Second born
• Born to third degree consanguineous parents
• Presenting complaints of progressive unsteadiness while walking from 4 years of age
• The difficulty in walking was progressive
CASE HISTORY

- Child took native treatment for 2 years, but the symptoms were progressive
- No h/o seizures
- No h/o recurrent vomiting
- No h/o recurrent respiratory infections
- No h/o chest pain or breathlessness
- No h/o short stature
- No h/o deafness
CASE HISTORY

- Antenatal history was uneventful
- FTNVD, birth wt – 2.75 kg
- No h/0 birth asphyxia
- No h/0 NICU admissions
CASE HISTORY

• No other significant illness in the past
• No history of similar illness among family members
• Child had a motor developmental delay
• Attained head control at age of 7 months
• Started walking at the age of 3 years
• Speech delay was also present
GENERAL EXAMINATION

• Conscious
• Oriented
• Afebrile
• No pallor/icterus/cyanosis/clubbing
• No neurocutaneous markers
• No dysmorphic facies
• No microcephaly
• No telangiectasia
• Hair is tightly curled
EXAMINATION OF NERVOUS SYSTEM

• Higher functions are normal
• Speech is normal
• Cranial nerve examination – normal
• Motor system
  – Bulk → decreased in all four limbs
  – Tone → normal in all 4 limbs
EXAMINATION OF NERVOUS SYSTEM

– Power → 3/5 in right lower limb
  3/5 in left lower limb
  upper limb – normal

• Reflexes
  – Ankle jerk is absent in both lower limbs
  – Knee jerk is diminished in both lower limbs
  – All other reflexes are present
EXAMINATION OF NERVOUS SYSTEM

- Superficial reflexes were present
- Plantar - flexor

- Sensory system
  - Touch, vibration and proprioception are diminished in distal parts of both upper limbs and lower limbs
  - Vibration over the spine is present
  - Pain and temperature are intact
EXAMINATION OF NERVOUS SYSTEM

• Romberg’s sign is positive

• Cerebellum
  – Child is ataxic
  – Horizontal gaze evoked Nystagmus is present
  – Finger nose incoordination is present
  – Tandem walking could not be done
  – Dysdiadokokinesia is present
EXAMINATION OF NERVOUS SYSTEM

• Autonomic nervous system – normal
• Spine – scoliosis is present
• Cranium – normal
• Fundus – normal
EXAMINATION OF OTHER SYSTEMS

- CVS – normal
- RS – normal
- P/A – soft, no organomegaly
CASE SUMMARY

- Nine year old child
- Third degree consanguinity in parents
- With progressive ataxia
- With tightly curled hair
- With distal weakness involving both lower limbs
- With diminished reflexes in lower limbs
- With positive Romberg's sign
- With glove and stocking sensory impairment
- With cerebellar signs
DISCUSSION

This case can be discussed as a case of peripheral neuropathy with cerebellar involvement. With the classical tightly curled hair, giant axonal neuropathy comes as the first diagnosis.

Other diagnoses includes

1) Neuro axonal dystrophy
2) Mitochondrial disorders
3) Friedricks ataxia
4) Ataxia telengiectasia
INVESTIGATIONS

- Basic blood investigations were normal
- Serum lactate, pyruvate, ammonia were normal
- Serum CPK was normal
- Cardiac evaluation was normal
IMAGING

• MRI Brain showed
  – Predominant cerebellar white matter hyperintensities
  – Also frontal and parietal subcortical hyperintensities
NERVE CONDUCTION STUDIES

• Nerve conduction studies showed the following features suggestive of axonal neuropathy
  – CMAP- grossly reduced in both tibial and peroneal nerves
  – Sensory potentials could not be obtained in all four limbs
  – Nerve conduction velocities were normal with normal latency

Nerve biopsy could not be done
GIANT AXONAL NEUROPATHY

- Chronic progressive mixed peripheral neuropathy and degeneration of central white matter
- There is generalized disorganization and aggregation of cytoskeletal intermediate filaments in multiple tissue types
  - Neurofilaments
  - Vimentin
  - Glial fibrillary acidic protein
  - Keratin

  ➔ peripheral nerve
  ➔ endothelial cells and schwann cells
  ➔ astrocytes
  ➔ hair
• Autosomal recessive disorder
• Nonsense and missense mutations or deletions occur in the \textit{GAN} gene, with allelic heterogeneity, at 16q24.
• These mutations are responsible for defective synthesis of the protein gigaxonin, a member of the cytoskeletal superfamily, crucial to linkage between intermediate proteins and the cell membrane, and in neurofilament architecture
CLINICAL PRESENTATION

• Onset is usually in infancy
• Motor developmental delay
• Sensory ataxia is the most important clinical feature
• Gait becomes broad based, clumsy and unsteady
• Progressive distal weakness and atrophy occurs
CLINICAL PRESENTATION

• Weakness starts from the lower limbs and progressively involves the upper limbs and trunk
• Slurred speech, truncal ataxia, nystagmus, intention tremor and dysmetria gradually develop
• Distal sensory functions are impaired
• Cranial nerve involvement can occur
CLINICAL PRESENTATION

• Tendon reflexes are diminished or absent
• Plantar response is extensor, indicating pyramidal tract involvement
• Mild mental retardation can be seen
• Initially, polyneuropathy is common
• Later, symptoms of spinocerebellar degeneration predominate
• Seizures can occur
CLINICAL PRESENTATION

• The striking abnormality in this disorder is the presence of tightly curled hair.

• The hair texture in the affected child is significantly different from that of the parents.

• Death usually occurs in the adolescence or in the third decade.
INVESTIGATIONS

- CSF protein is normal
- Motor nerve conduction velocities are normal or mildly decreased
- Sensory action potentials are usually absent or very much decreased suggesting an axonal neuropathy
- EEG, Brainstem evoked responses, visual evoked responses, somatosensory evoked responses are all abnormal
INVESTIGATIONS

• CT brain and MRI brain reveal wide spread white matter changes

• magnetic resonance spectroscopy (MRS) demonstrates increased ratios of choline : creatine and myoinositol : creatine, with a normally preserved ratio of $N$-acetyl aspartate : creatine, indicating demyelination and glial proliferation without axonal loss.
INVESTIGATIONS

• Nerve biopsy shows giant axonal swellings measuring upto 50 micrometre with densely packed neurofilaments, often with few or no neurotubules.

• Giant axons show no or very thin myelin sheaths

• Onion bulbs are found around some fibres
INVESTIGATIONS

• Accumulation of intermediate filaments are seen in other cell populations also

• Microscopic examination of hair shows variation in diameter of the shaft and twisting, similar to that in Menkes disease

• Scanning electron microscopy may show typical longitudinal grooves
CONCLUSION

• A child presenting with
  – Ataxia
  – Distal weakness
  – Distal Sensory impairment
  – Tightly curled hair

A diagnosis of giant axonal neuropathy should be thought of