Neuroimaging Highlight

Unusual Neuroimaging Findings in Two Families with Giant Axonal Neuropathy

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Case Presentation

Family 1

An 8-year-old boy, born to a third-degree consanguineous couple with no adverse perinatal events, presented with complaints of delayed development and gait abnormalities. He had global developmental delay with independent ambulation achieved at two years of age and monosyllables at 2.5 years of age. There was no regression. His hearing and vision were normal. He had had two episodes of generalized tonic-clonic seizures in the previous year. His examination revealed normal fundus and absence of musculoskeletal deformities. He had frizzy hair, mild global hypotonia, no motor weakness, absent muscle-stretch reflexes, and positive cerebellar signs. He had an older male sibling (not investigated) with a similar illness who was now bedridden.

Magnetic resonance imaging of the brain showed T2 hyperintensities in the bilateral cerebellar dentate nuclei, posterior limb of the internal capsule, and the globus pallidi (Figure 1). Nerve-conduction studies were suggestive of sensorimotor axonal polyneuropathy. Nerve biopsy showed giant axons. Echocardiography was unremarkable.

Family 2

An 8-year-old boy, the first of twins, born to a second-degree consanguineous couple, presented with difficulty in walking and

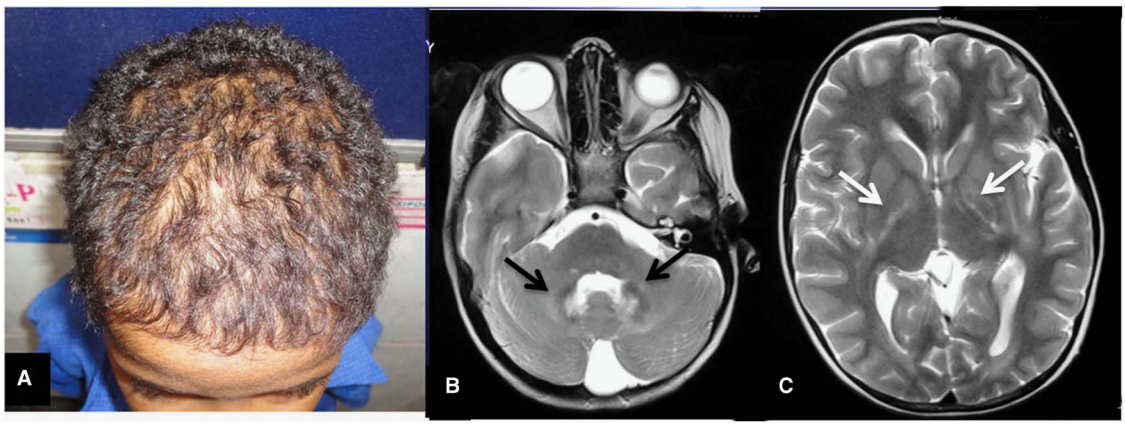

Figure 1: *Child (family 1) with giant axonal neuropathy showing frizzy hair (A). Magnetic resonance imaging of the brain (done at 7.5 years of age) shows T2-weighted hyperintensities in the bilateral cerebellar dentate nuclei (B, black arrows), posterior limb of internal capsule, and globus pallidi (C, white arrows).*

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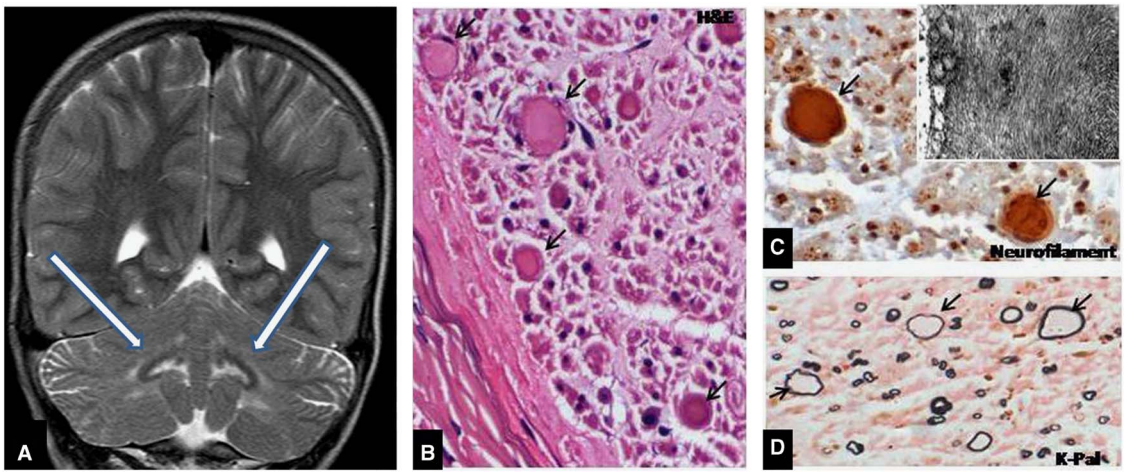

Figure 2: *Index case in family 2. (A) T2-weighted coronal magnetic resonance imaging images (at 8 years of age) show bilateral dentate hypointensities surrounded by hyperintensities (white arrows). Nerve biopsy (B-D): Several giant axons of varying sizes (arrows) dispersed within the fascicles (20-200 μm) (B). These contain abundant phosphorylated neurofilaments distending the axoplasm to giant proportions (C). Electron microscopy: closely packed aggregates of neurofilaments distending and displacing normal organelles within the axoplasm (B, inset). Myelin stains (C): thinned out attenuated myelin sheaths surrounding the giant axons (D). (A) Hematoxylin and eosin × objective 20; (B) Immunostain neurofilament × objective 40; (B) inset: uranyl acetate–lead citrate ×28665; (C) Kulchitsky Pal stain × objective 40.*

delayed milestones. He started walking at two years and dragged the legs while walking. For the past two years, his gait had worsened, with frequent falls. He had poor school performance with normal vision and hearing and no history of seizures. Examination disclosed frizzy hair and normal head circumference. Neurological examination showed an everted foot, spastic diplegia, and areflexia with positive cerebellar signs. Funduscopy revealed bilateral optic atrophy with retinitis pigmentosa.

Magnetic resonance imaging of the brain revealed signal changes in the dentate nuclei (Figure 2A) and hyperintense internal capsule on T2/fluid-attenuated inversion recovery sequences. Nerve biopsy showed giant axons (Figure 2B-D). The other twin was an 8-year-old girl who had similar complaints (less severe) and neuroimaging. One elder sibling died at 16 years of age with a similar illness.

The diagnosis of giant axonal neuropathy was made on the basis of clinical phenotype, radiology, electrophysiology, and nerve biopsy findings.

Discussion

Giant axonal neuropathy presents within the first few years of life with delayed development, gait abnormalities, progressive weakness, hyporeflexia, cerebellar signs, spasticity, epilepsy, learning difficulties, and cranial nerve palsies. Most patients become bedridden by the second to third decade of life.[1,2]

Histological findings in peripheral nerve biopsies include "giant" axons with an accumulation of neurofilaments and onion bulb formations of the Schwann cells. Giant axons have also been described in neuropathies resulting from SH3TC2 (Charcot-Marie-Tooth disease 4C) and NEFL mutations (Charcot-Marie-Tooth disease 2E/1F), BAG3 mutations, the juvenile form of neuroaxonal dystrophy, amyotrophic lateral sclerosis, and infantile spinal muscular atrophy.[2,3]

The classic neuroimaging findings include variable cerebral and cerebellar white matter involvement. There may be variable cerebral, cerebellar, and brainstem atrophy. Cavum septi pellucidi has been reported frequently.[4] Nonspecific abnormalities have been reported on magnetic resonance spectroscopy.[5-7] Involvement of the globus pallidus and cerebellar dentate nucleus (T2 hyperintensities and hypointensities) has rarely been described previously.[3,7,8] Increased apparent diffusion coefficient values in the basal ganglia has been described without T1 or T2 signal changes.[9] Signal changes have been described in the posterior limb of the internal capsule, pyramidal tracts, medial lemniscus in the brainstem, and middle cerebellar peduncles.[8]

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Statement of Authorship

SS, MK, PJ, and BP worked up the case under the supervision of SA. VH provided radiological inputs. AM performed the neuropathology. PJ drafted the manuscript, which was then critically reviewed and approved by all of the authors.

Disclosures

The authors have no disclosures to declare. Informed consent was received from the parents for publication of this case report.

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