

Dejerine-Sottas Disease (Progressive Hypertrophic Polyneuropathy)

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Key Words

Neurology and art · Dejerine-Sottas disease · Hereditary motor and sensory neuropathy · Myelin proteins

Abstract

This paper records parts of Dejerine and Sottas's description of the syndrome that bears their names. It outlines biographical elements of Dejerine's work. The modern classification and the role of myelin protein mutations are briefly described.

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History

Joseph Jules Dejerine¹ [2] was born in Geneva in 1849 and graduated in medicine in Paris in 1879 as Vulpian's most distinguished protégé. He succeeded Raymond as Professeur de clinique des maladies du système nerveux à la Faculté de Médecine at the Salpêtrière in 1910.

¹ According to Dejerine's daughter (Mme la Dr Sorrel-Dejerine), the name is not spelled Déjerine or Déjérine [1].

In a previous note [3], I sketched one of Dejerine's best known syndromes – 'le syndrome thalamique' (Dejerine-Roussy syndrome). This paper is mainly concerned with the Dejerine-Sottas syndrome, but Dejerine spawned many signs and syndromes – a great source of material for those beloved of eponyms. They include: facio-scapulo-humeral dystrophy (Landouzy-Dejerine); hypertrophic interstitial polyneuritis (Dejerine-Sottas); olivo-pon-to-cerebellar atrophy (Dejerine and André-Thomas). He also described alexia without agraphia (pure alexia) and alexia with agraphia. The precipitation of root pain by sneezing and coughing is known as Dejerine's sign.

Not only did he contribute to the expanding field of clinico-pathological studies of the nervous system, but he also had a keen interest in functional disorders and psychotherapy, stimulated by Paul Dubois of Berne whom he would visit on holidays to Thalgut. He taught his students: 'It is rare you will be able to use subtle logic; it is your heart that carries you along (...) In man, emotion is almost everything and reason very little.'

Dejerine

Dejerine married Dr Augusta Klumpke (1859–1927), herself a distinguished physician [4], who in 1885 left another eponym (Klumpke's palsy) for posterity [5] (this

publication won her the Godard Prize of the Medical Academy in 1886). He owed much to Augusta, who had studied medicine in Paris and whose scientific ability and perseverance enabled her – despite fierce opposition – to become the first woman to receive the title of ‘interne des hôpitaux.’ The Dejerine marriage comprised two intellectual giants collaborating and inspiring each other. Only the Curies and the Vogts could boast of comparable achievements [1]. Jules was elected to the Academy of medicine in 1908 and died on February 26, 1917. After his death, Augusta continued much of his practice and research. The centenary of Dejerine’s birth was celebrated at the Fourth International Neurological Congress in Paris in 1949 with a discourse from André-Thomas.

Dejerine-Sottas Syndrome

In 1893, Dejerine and Jules Sottas (1866–1943) presented autopsy studies of a brother and sister with progressive atrophy of the muscles of the extremities [6]. Sottas was ‘chargé de laboratoire’ at the Hospice de Bicêtre, and at the Salpêtrière under Dejerine. The long title of their publication encapsulates the essential features: *On the interstitial hypertrophic and progressive neuritis of childhood; often a familial affection beginning in infancy, characterized by a muscular atrophy of the extremities with marked disturbances of sensation and ataxia of movement and caused by an interstitial hypertrophic neuritis that ascends with consecutive medullary [cord] lesions.*

Also named ‘hereditary motor and sensory neuropathy type III’, it is transmitted as either an autosomal dominant or recessive trait. The onset is usually with weakness and deformity of the feet and lower limbs.

Original Cases

In 1893, Dejerine and Sottas described a brother and sister of presumably unaffected parents. The onset in Fanny Roy was in infancy; in Henri Roy, it was recorded when in hospital for spinal surgery at the age of 14. However, his mother had noticed spine deformities already at the age of 4–5 years. Both had clubfoot, kyphoscoliosis, generalized weakness and muscular atrophy with fasciculations beginning first in the leg muscles. They showed decreased reactivity to electric stimulation, areflexia, marked distal sensory loss in all four extremities, and incoordination in the arms, Romberg’s sign, miosis, decreased pupillary reaction to light, and nystagmus. Fanny died aged 45. Autopsy showed the peripheral nerves to be increased in size, firm and gelatinous. Only rare nerve

fibres contained myelin. Thirteen years earlier, François Gombault (1844–1904) had described a similar subacute or chronic parenchymatous neuropathy in 1880 [7].

Classification and Variants

Dyck [8] characterised this as an autosomal recessive form: HMSN type III or Dejerine-Sottas disease: a severe, demyelinating neuropathy, presenting in infancy with delayed motor development, very slow nerve conduction velocities (<10–12 m/s) and elevated CSF protein. Progression was severe and walking ability was lost early. Hypomyelination and classic onion bulbs were the pathological hallmarks.

Many phenotypic variants have been reported. In 1962, Andermann et al. [9] described Dejerine-Sottas neuropathy in three generations with nystagmus, distal muscular weakness, distal sensory change, pes cavus and exacerbations and remissions. By contrast, sensory loss was notably absent in the family of Russell and Garland [10], restudied by Croft and Wadia [11], who traced the disorder through five generations. Spinal nerve root enlargement is demonstrable by myelography and MRI, often with raised CSF protein. Thomas et al. [12] studied 9 kindreds in which two variants were suggested. In one, the onset was in childhood with leg weakness, foot deformity, and mild sensory changes. In the other, sensory loss was severe, often associated with chronic trophic foot ulcers. Ionasescu et al. [13] reported a 55-year-old black male of a family with 9 severely affected patients in an autosomal dominant pattern. Onset had occurred at 2 years of age with steppage gait. He showed pes cavus, hammertoes, progressive severe weakness and atrophy of the legs, and claw hands. He developed Charcot joints at both shoulders. A brother, aged 47, had similar findings and Charcot joints of the interphalangeal joints of the fourth and fifth fingers.

Both autosomal dominant and recessive forms of Dejerine-Sottas syndrome are now classed as a severe degenerative neuropathy of the Charcot-Marie-Tooth (CMT) type with onset by 2 years of age. It is caused by several mutations in the myelin protein zero gene, the peripheral myelin protein gene, the periaxin gene, and the early growth response gene. In addition, CMT-IV (regarded as a form of Dejerine-Sottas syndrome) is conventionally an autosomal recessive form of demyelinating CMT disorder that has several different subtypes, including CMT type IVA, caused by mutation in the gene encoding ganglioside-induced differentiation-associated protein-1 on chromosome 8q21. Periaxin proteins necessary for Schwann-cell function are depleted.

The morphological hallmark is the onion-bulb appearance of extensive nerve and root hypertrophy; this results from demyelination-remyelination of surviving, originally myelinated axons and profuse Schwann-cell proliferation. Wide variations in clinical manifestations of chron-

ic demyelinating polyneuropathies of early onset in children born to unaffected parents have now been reported, and at least seven genes encoding the myelin proteins have been implicated [12] (Gene map locus: 19q13.1-q13.2, 17p11.2, 1q22, 10q21.1-q22.1).

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