DEJERINE-SOTTAS SYNDROME WITH EARLY ONSET IN CHILDHOOD

Diana Epure[1], Ana-Maria Geanta[1], Daniela Vasile[1], Daniel Teleanu[2], Raluca Teleanu[1,3]

[1]Department of Pediatric Neurology, "Dr. Victor Gomoiu" Children's Hospital, Bucharest
[2]Department of Neurosurgery, Emergency University Hospital, Bucharest
[3]"Carol Davila" University of Medicine and Pharmacy, Bucharest

ABSTRACT

Dejerine-Sottas syndrome (DSS) is a progressive hypertrophic interstitial neuropathy of childhood characterized by defects in the myelin structure, with motor nerve conduction velocities below 10 m/sec.Thephenotype is genetically heterogeneous with autosomal dominant and autosomal recessive inheritance but "de novo"mutations are also described. Nerve pathology is highly variable. The clinical course is severe, leading tosensory loss, distal followed by proximal weakness, foot deformities, scoliosis and contractures, cranial nerve deficits and occasionally spinal cord compression. In this case study we evaluated a case of DSS at a ten year old boy and we outlined the importance of the electrophysiological investigationstogether with magnetic resonance neurography in diagnosing the Dejerine-Sottas syndrome.

Keywords: hypertrophic interstitial neuropathy, progressive evolution, child, electroneurophysiology, magnetic resonance neurography

INTRODUCTION

Hereditary peripheral neuropathies have been classified based upon their clinical and electrophysiologic features, mode of inheritance, metabolic defects and genetic markers. The hereditary motor sensory neuropathy (HMSN) also known as Charcot-Marie-Tooth (CMT) disease is a spectrum of disorders that result in defects in the myelin structure, formation and maintenance. Dejerine-Sottas syndrome is classified together with congenital hypomyelinating neuropathy as HMSN 3. These are severe, early-onset peripheral neuropathies in which the Schwann cells are, to a variable point, uncapable of forming normal myelin, resulting in thin and poorly formed myelin. Therefore patients with Dejerine-Sottas syndrome have thin myelin sheaths and large "onion bulb" formation. (1,4,5)

ETIOLOGY

Dejerine-Sottas syndrome (DSS) is also known asprogressive hypertrophic interstitial neuropathy of childhood caused by a genetic defect either in the proteins found in axons or in the proteins found in myelin.The phenotype is genetically heterogeneous and autosomal dominant, but autosomal recessive and the novo inheritance are also described, affecting genes that are involved also in CMT type 1 and 4. (1,2)

CLINICAL FEATURES

DSS is a severe demyelinating neuropathy which is clinically evident in early infancy because of the hypotonia. Phenotype symptoms include delayed motor development, sensory loss, distal fol-

Author for correspondence:
Assoc. Prof. Raluca Ioana Teleanu MD, PhD, Department of Pediatric Neurology, "Dr. V. Gomoiu" Children's Hospital, 21 Basarabia Bd, 022102, Bucharest
E-mail: ralucate@gmail.com

lowed by proximal weakness (as the disease progresses), absent reflexes, ataxia, foot deformities, occasionally limitation of eye movements or other eye problems, mild hearing loss and profound slowing of nerve conduction velocities (to < 10 m/sec). Curvature of the spine appears early and progresses with time and contractures develop.Other reported symptoms include cranial nerve deficits and occasionally spinal cord compression resulting from the hypertrophic neuropathy of the spinal roots. The progression of the disease is slowuntil teen age, oftenimplying a severe disability or wheelchair dependency in adult life. (1,2,3,4)

GENETICS

A common finding in the peripheral neuropathies group is the association of different mutations within the same gene with various clinical phenotypes (Table 1). This variability suggests that these disorders represent a spectrum of related phenotypes which are caused by an underlying defect in peripheral nervous system myelination.Autosomal recesive and several dominant heterozygous forms of DSS have been described to be affecting genes that are also involved in CMT1 and CMT4 and they include mutations in the PMP22 gene, the MPZ gene, PRX and the EGR2 gene. (1)

ELECTROPHYSIOLOGICAL INVESTIGATIONS – ENG, EMG

The electrophysiological investigations in DSS show specific polyneuropathy sensory and motor pattern of demyelination, with profound slowing of nerve conduction velocities (to < 10 m/sec). Moreover it associates an important and severe damage to the ulnar and cranial nerves (especially the trigeminal and facial nerve). As mentioned, the goal of the electrophysiological study is to confirm the presence of a neuropathy and to determine whether motor, sensory or a combination of fibers are involved. (6)

IMAGING STUDIES

MR imaging is considered the technique of choice in order to determine the extent of the nerves involvement. On imaging, the affected nerves (the nerves of the extremities and in some cases cranial nerves) appear thickened and with edematous neural and/or perineural inflammation or infiltration.

Cervical and/or lumbosacral plexus nerves damage is often associated with damage of the cranial nerves, especially of the trigeminal and facial nerve. Also the spinal lymph nodes may be affected together with the lymph nodes situated in the cranial nerves path. (3)

CASE PRESENTATION

We present the case of a ten year old boy who was admitted for recurrent episodes of nocturnal headache followed by vomiting (possible signs of intracranial hypertension) and left periorbital pain with irradiation in the left hemicrania.

From his personal history we specify that he presented no neonatal events, birth at 37 weeks of gestation, with a normal motor and cognitive development and normal language development. His medical history revealed: at the age of two he started walking on his tiptoes due to spastic paraparesis; at the age of six he performed an EMG which showed a hereditary axonal sensorimotor polyneuropathy and an impairment of the peroneal nerve bilaterally (left > right) and of the right ulnar nerve for which it was performed a left pes cavus surgery. Since the age of four he presentedrecurrent episodes of nocturnal headache and vomiting and at the age of nine he started to present an ophtalmo-

TABLE 1. *Clinical features and genetics of DSS: (1)*

Disorder – CMT 3 –	**Gene**	**Chromosome**	**Clinical features – severe, early onset –**
1. Dejerine-Sottas syndrome	PMP 22	17p11.2-p1	Hypotonia in early infancy Delayed motor development
	MPZ	1q22	Initial sensory loss and distal weakness
	EGR2	10q21.1-q22.1	Ataxia NVC profoundly slowed (10 m/sec)
2. Congenital hypomyelinating neuropathy	PMP22	17p11.2-p1	Profound hypotonia and contractures at birth
	MPZ	1q22	Feeding difficulties Respiratory distress
	EGR2	10q21.1-q22.1	Death in infancy NCV extremely slowed or absent

plegic migraine (possible signs of Claude-Bernard-Horner syndrome) which lead him to perform a cerebral MRI (the results came out normal).

The neurological examination showed a left peripheral facial palsy (facial asymmetry, left lagophthalmos, slight synkinesis, perioral fasciculation and a slight mouth asymmetry). The gait showed a high-stepping with "foot slapping", with an inability to walk on his heels and tiptoes with his right lower limband with no mobility on his left ankle after the pes cavus surgery. He also presented muscle weakness localized in the territory of the right ulnar nerve and bilateral peroneal and tibial nerves. He presented bilateral brisk tendon reflexes, muscle atrophy (localized at the right hypothenar eminence and bilateral peroneal muscles), hypotrophy of the left lower limb and no sensitivity disturbance.

The electrophysiological investigations (ENG, EMG) of the facial nerves (Fig. 1 a, b, c) revealed an axonal lesion with a normal motor latency and CMAP with a low amplitude bilaterally. The needle

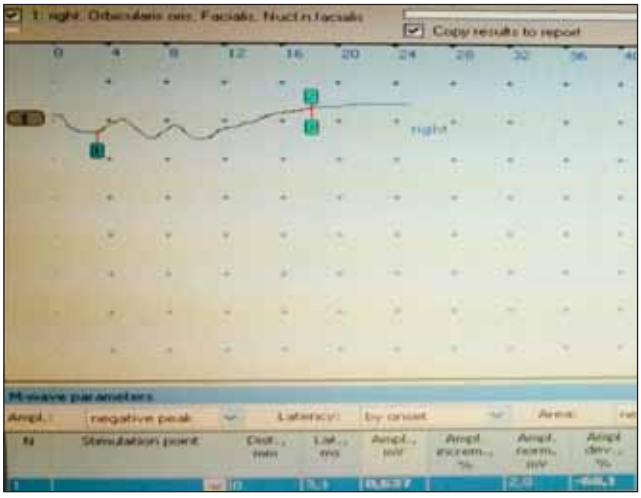

FIGURE 1A. *Right facial nerve: low amplitude of CMAP*

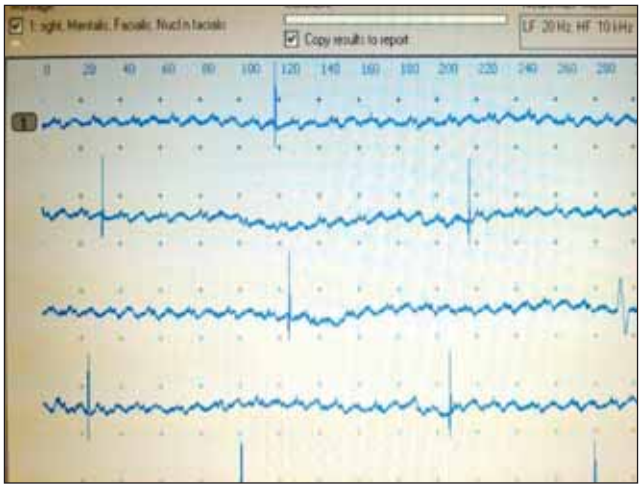

FIGURE 1B. *Right facial nerve: fibrillation potentials at rest*

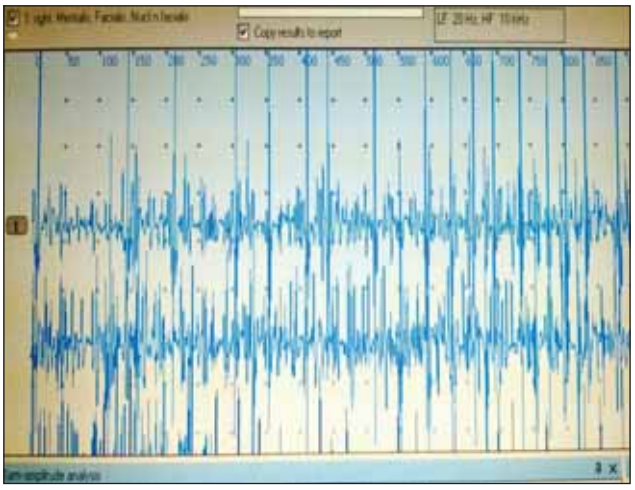

FIGURE 1C. *Needle EMG. Right mentalis muscle: neurogenic recruitment pattern*

EMG of mentalis muscle showed fibrillation potentials at rest, normal MUPs duration and amplitude. It also revealed a neurogenic recruitment pattern bilaterally (evidence of chronic and ongoing axonal loss with the typical neuropathic pattern: long, large MUPs with reduced recruitment).

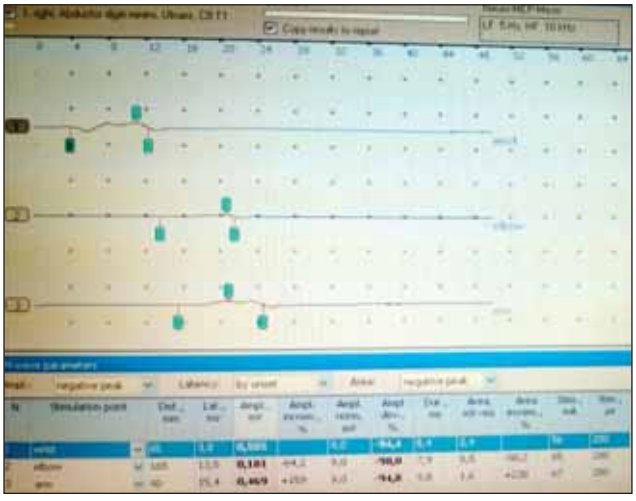

FIGURE 2A. *Right ulnar nerve: motor conduction study*

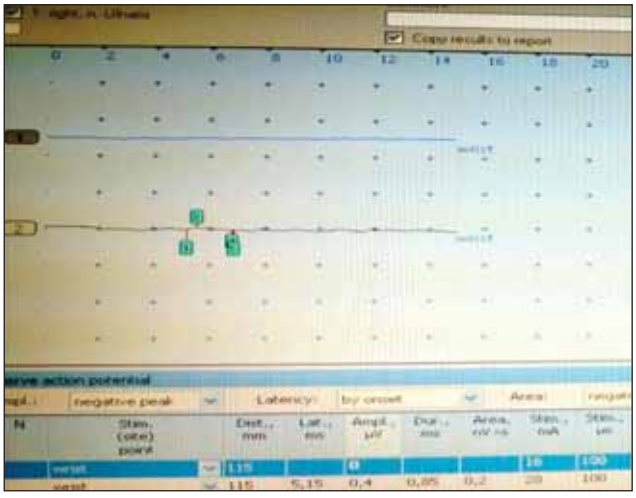

FIGURE 2B. *Right ulnar nerve: sensitive conduction study*

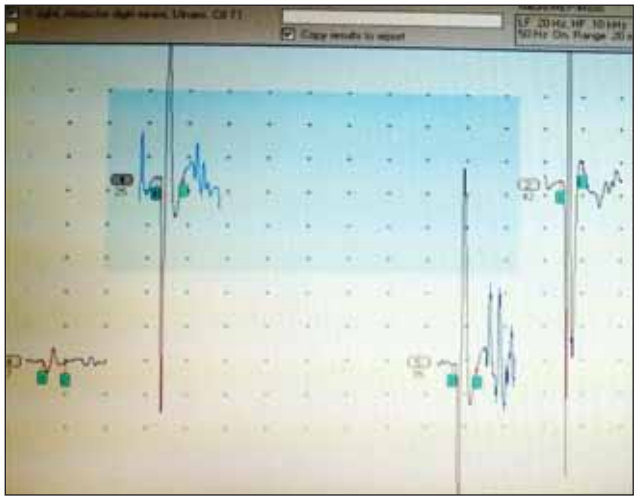

FIGURE 2C. *Needle EMG. Abductor digiti minimi muscle: PUM with high amplitude and duration*

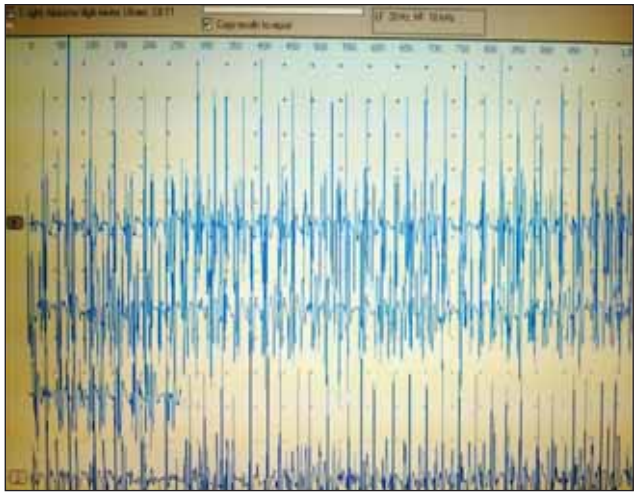

FIGURE 2D. *Needle EMG. Abductor digiti minimi muscle: neurogenic recruitment pattern*

The electrophysiological investigations (ENG, EMG) of the right ulnar nerve (Fig. 2 a, b, c, d) revealed an axonal sensorimotor lesion, with a normal motor distal latency, very low CMAP amplitude and a low SNAP amplitude, the absence of the F wave, no conduction block and normal sensory distal latency and sensory velocity. The needle EMG of the right abductor digiti minimi muscle showedno spontaneous activity at rest, a high amplitude and duration of MUPs and neurogenic recruitment pattern.

The ENG of the peroneal nerve (Fig 3 a, b) revealed a bilateral axonal lesion, with no distal or proximal response at stimulation. The right tibialis anterior muscle presented spontaneous activity (PSW +++), positive fibrillation potentials, fasciculation, high MUPs amplitude and durations and neurogenic recruitment pattern.

Axonal lesion of the right tibial nerve, with normal motor distal latency, low CMAP amplitude and low motor velocity. (Fig. 4)

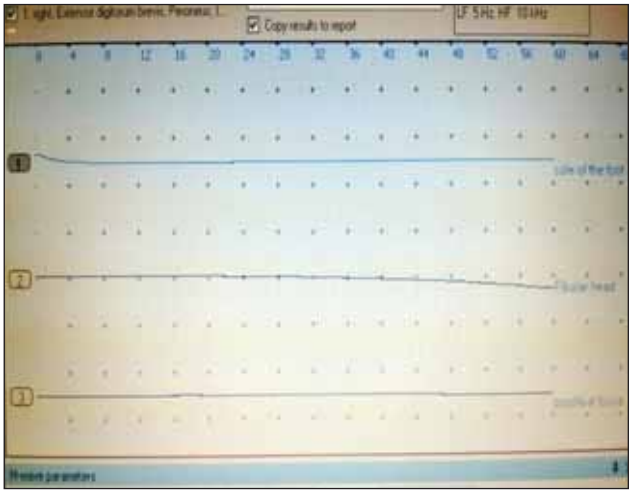

FIGURE 3A. *Right peroneal nerve: motor conduction study*

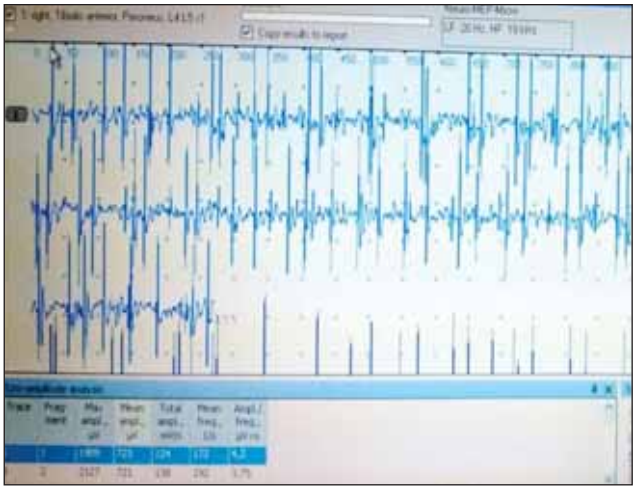

FIGURE 3B. *Tibilalis anterior muscle: neurogenic recruitment pattern*

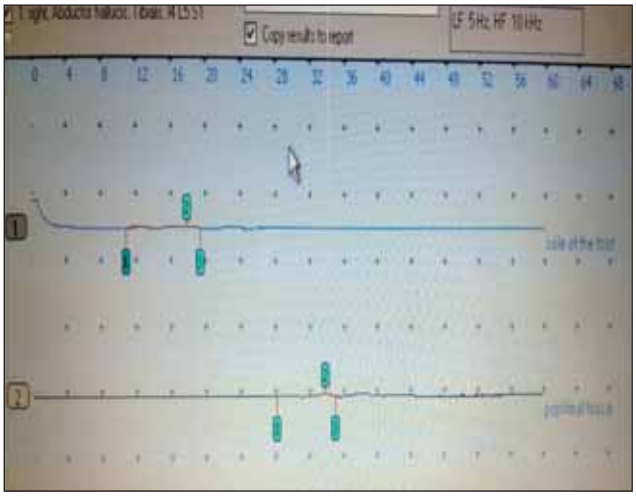

FIGURE 4. *Right tibial nerve: motor conduction study*

Axonal lesion of the right sural nerve, with normal sensory distal latency, low SNAP amplitude and normal sensory velocity. (Fig. 5)

The paraclinic exams revealed a normal CK level, normal EKG, EEG, cardiac and abdominal ul-

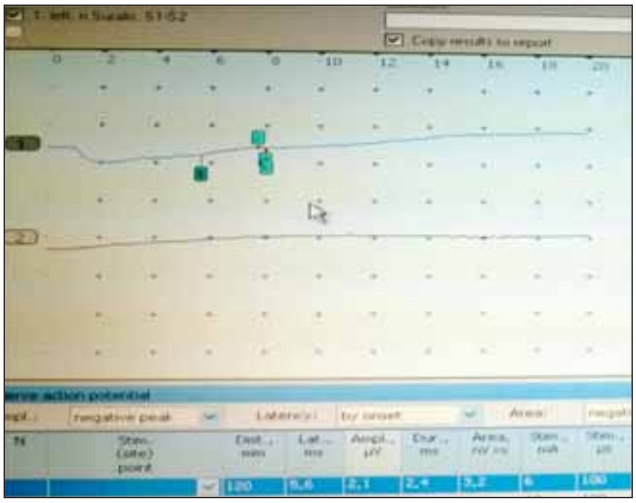

FIGURE 5. *Left suralis nerve: sensitive conduction study*

trasound. Also the results of the ophthalmological examination came out normal.

So far we have a case of a ten year old boy who came into our clinic for signs of intracranial hypertension with the clinical evaluation showing a bipiramidal syndrome associated with signs of impaired peripheral motor neurons in the territory of the cranial nerves.

The electrophysiological investigations lead us to chronic axonal sensorimotor polyneuropathyof unknown etiology. Therefore, in order to elucidate the etiology we performed tests in order to determine a cause of infection (Borellia, HIV, HVB, HVC), metabolic disease (diabetes), paraneoplastic etiology, hypothyroidism, vasculitic neuropathies, paraprotein etiology and IgM monoclonal gammopathies – all the results came out negative.We continued with the neuroimaging investigations.
The cerebral MRI result was normal, except of a gadolinium enhancement of the trigeminal nerves (left > right) and of the facial nerve bilaterally and also the MRI revealed a hypertrophy of the left pterygopalatine ganglion and right geniculate ganglion.A magnetic resonance neurography was performed and the results showed a normal left brachial plexus and the right brachial plexus (Fig. 6 a, b, c) with a slight thickening of roots C5-T1, moderate thickening of trunks, bundles and emerging nerves to the axilla. It also revealed a thickening of the right ulnar nerve from emergence to the hypothenar eminence and an intense progressive gadolinium enhancement of the elements of the right brachial plexus.The lumbosacral plexus (Fig. 7 a, b, c, d) showed a thickening of the sciatic nerves in their portions of the pelvis and thighs with fascicular thickening and edematous infiltration of perineural tissue (possible perineurinoma). It also re-

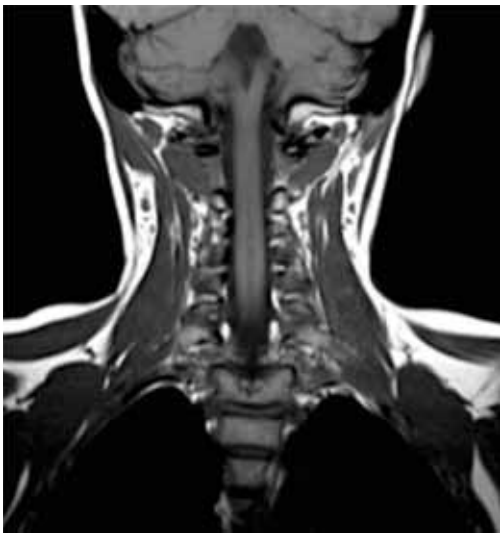

FIGURE 6A. *The thickening of the cervical roots C5-T1*

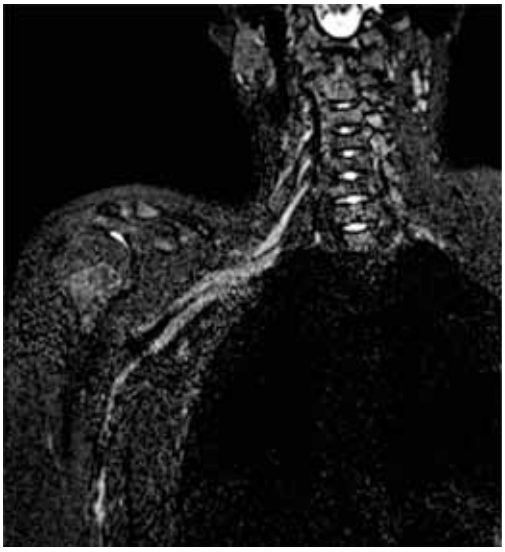

FIGURE 6B. *Thickening of trunks and bundles of cervical plexus*

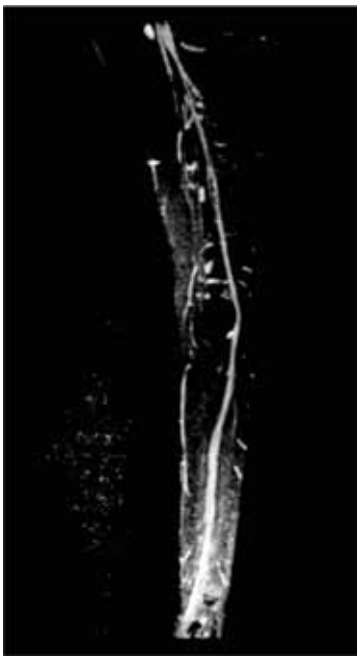

FIGURE 6C. *The thickening of the ulnar nerve from emergence to the hypothenar eminence*

vealed an important hypotrophy of left calf muscles with fatty degeneration and edematous infiltration in the triceps surae.

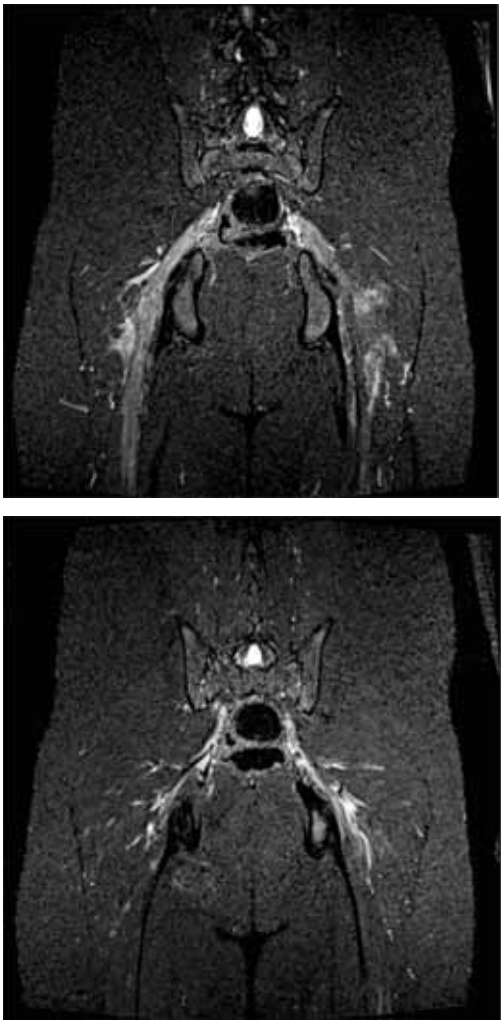

FIGURE 7 A, B. *Thickening of the sciatic nerves in their portions of the pelvis*

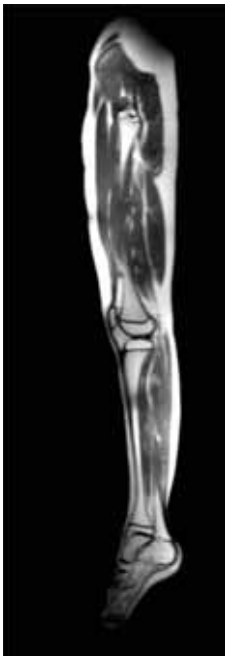

FIGURE 7C. *Thickening of the sciatic nerve path*

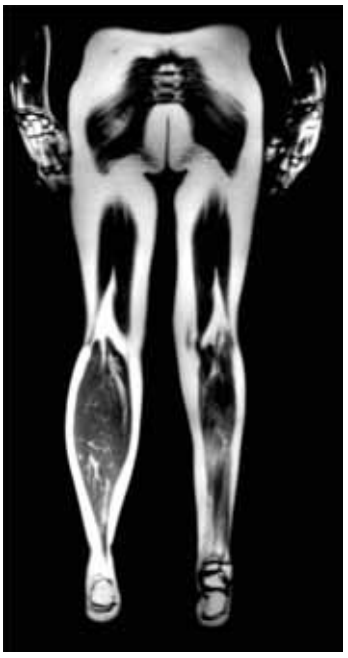

FIGURE 7D. *Trophic muscle modifications*

We also performed a nerve and muscle biopsy. The nerve biopsy was performed from the sural nerve and it showed a demyelination/remyelination aspect, axonal degeneration/ regeneration and with no inflammatory lesions. The muscle biopsy performed from the gastrocnemius muscle showed neurogenic muscle injury with interstitial cellular reaction.

Finally, the electrophysiological investigations-together with magnetic resonance neurography and the nerve and muscle biopsy lead us to the diagnosis of Dejerine-Sottas syndrome: a sensorimotor polyneuropathy with cranial nerve damage, hypertrophic aspect of nerve and plexus with severe damage to the ulnar nerve, aspect of demyelination/ remyelination at the nerve biopsy and with early onset in childhood. At this point we considered the recurrent episodes of nocturnal headache to be possible secondary to hyperproteinorachie caused by episodes of demyelination (pseudotumor cerebri) and also it may be secondary to trigeminal neuralgia like syndrome (periorbital headache and with the cerebral MRI revealing enhancement of the trigeminal and of the facial nerve bilaterally).

CONCLUSIONS

We presented the case of a boy who showed signs of intracranial hypertension and left periobital pain and for whom the investigations reveal modifications of the trigeminal and facial nerves bilaterally also with specific signs of axonal sensorimotor polyneuropathy. In this particular case, where the pyramidal syndrome associated damage of the peripheral motor nerves, the electrophysiological investigations (ENG, EMG) and the magnetic resonance neurography lead us to the diagnosis.

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