CASE REPORT

Charcot-Marie-Tooth syndrome and neurofibromatosis type 1 with multiple neurofibromas of the entire spinal nerve roots

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SUMMARY

The coexistence of polyneuropathy which has the definite clinical and electromyographical findings consistent with Charcot-Marie-Tooth (CMT) syndrome and neurofibromatosis type 1 (NF1) has infrequently been reported. We describe a patient with both CMT and NF1, who had multiple neurofibromas involving the entire spinal neural axis. In addition, he had multiple neurofibromas distributed within the ileopsoas and gluteus muscles and subcutaneous tissues. These lesions were detected readily by MRI and the patient underwent successful surgical resection of the largest tumours compressing bilateral C2 nerve roots. To our knowledge, this is the first reported case of CMT syndrome coexisting with NF1 in which multiple neurofibromas involved the entire spinal nerve roots. We discuss the diagnostic and therapeutic challenges, emphasising the role of MRI and electrophysiology in such cases and provide a literature review.

BACKGROUND

Charcot-Marie-Tooth (CMT) syndrome is an inherited neuropathy which was named after the three investigators who independently described the condition for the first time in France (Charcot and Marie) and in England (Tooth) both in 1886. It encompasses many genetically diverse peripheral nervous system disorders classified mainly into two groups based on electrophysiological and histopathological features. Whereas CMT type 1 is marked by impeded velocities of peripheral nerve conduction and hypertrophic demyelination; CMT type 2 is associated with normal nerve conduction velocities and axonal degeneration.¹⁻³

Neurofibromatosis type 1 (NF1; OMIM 162220) alternatively known as 'peripheral neurofibromatosis' or 'Von Recklinghausen disease' accounts for 90% of all cases of NF. Fifty per cent of NF1 cases occur by spontaneous loss-of-function mutations in the NF1 gene on chromosome 17 while the rest is inherited in an autosomal dominant manner.³⁻⁵ The National Institute of Health (NIH) of the USA established the diagnostic criteria for NF1 based on the presence of two or more of the following: six or more café-au-lait macules, two or more neurofibromas (or 1 plexiform neurofibroma), two or more iris hamartomas, axillary or inguinal freckling, optic glioma, a family history of NF1 or bone dysplasia.⁶ In this report, we discuss a rare case of coexistence of CMT and NF1 with multiple neurofibromas involving the entire spinal

nerve roots. This patient underwent surgical resection of the compressive C2 neurofibromas. We discuss the diagnostic and therapeutic challenges, emphasising the role of MRI and electrophysiology in such cases, and provide a literature review.

CASE PRESENTATION

A 64-year-old retired man was clinically assessed for 2 years of worsening weakness and numbness of the arms and legs, with the upper limbs more affected than the lower limbs. He also complained of radicular pain in the lower cervical region which radiated to the upper thoracic spine and shoulders. He had received a past diagnosis of NF1 as an adolescent due to the presence of numerous café-au-lait macules, axillary freckles and subcutaneous neurofibromas distributed in the trunk. Genetic testing for NF1 mutations had never been carried out. He had also been diagnosed with CMT syndrome by a neurologist over a decade before presentation on the basis of bilateral foot drop worse on the right side, which causes difficulty with walking and is occasionally relieved by the use of bilateral ankle splints. The patient has no previous injury to the spine and there is no history of either condition in his parents or siblings. The patient's sister however has motor neuron disease.

Examination

Skin examination showed the following: multiple hyperpigmented freckles in the axillary region, numerous café-au-lait macules distributed within the trunk and arms; and three neurofibromas located in the left subcostal margin along the mid-axillary line and in the subcutaneous tissue of the posterior trunk. Upper limb neurology was grossly normal but lower limb examination revealed a high stepping gait (worse on the right foot) and inability to tiptoe or walk on heels. There was obvious wasting of both gastrocnemii and stocking sensory loss bilaterally extending to above the ankles. Vibration sense, cold perception and joint proprioception were decreased below the knees and absent in the toes. He had bilateral weakness of dorsiflexion worse on the right side, normal knee jerks, absent ankle jerks and plantar responses were down-going.

INVESTIGATIONS

Serum testing demonstrated positive antinuclear antibody titre, normal fasting glucose, normal vitamin B levels and also negative Bence Jones protein. Immunoglobulin G (IgG) κ paraprotein level was

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raised in keeping with monoclonal gammopathy without associated immunosuppression, and thought to be incidental.

Motor nerve conduction studies showed bilateral absence of tibial and peroneal responses in the feet, bilateral reduction of peroneal motor recording from tibialis anterior, and focal slowing of conduction across the right fibular head. Sensory nerve testing showed bilateral absent sural responses. Needle electromyography showed evidence of active denervation and chronic reinnervation in distal and proximal myotomes of both legs. These findings of severe sensorimotor polyneuropathy and a median/ulnar conduction velocity of 43.8 m/s are consistent with CMT 2 (table 1).

MRI showed enhancing nodules bilaterally at the C2 level which resulted in cord compression more marked on the right side. In addition, there was high T2 and low T1 signal within the spinal cord at C1–C2 levels in keeping with myelomalacia and cord compression. There were also extensive lesions consistent with neurofibromas distributed within all the neural exit foraminae of the cervical, thoracic, lumbar and sacral with only mild spinal canal stenosis at L3–L4. These lesions were hypointense on T1 and hyperintense on T2 sequences and readily enhanced with gadolinium. Neurofibromas were also seen within the iliopsoas and gluteus muscles, and the subcutaneous tissue (figures 1 and 2).

TREATMENT

The patient underwent total C1 laminectomy through a midline incision under general anaesthesia and in prone position. The

dural sac was opened and the spinal cord was seen to be deviated posteriorly from right anteriolateral compression, but no intradural tumours were seen. Large greyish-white tumours surrounded by vascular tissue were identified extradurally on either side of C1–C2 causing compression of the theca and cord on the right side. These were excised with sacrifice of the C2 nerve roots which were completely enveloped by the tumours. Dural closure was reinforced with fibrin glue.

Histological findings

Histology showed interlacing bundles of collagen fibres and spindle-shaped cells with elongated nuclei which are darkly staining due to abundance of chromatin. There are scattered large slightly abnormal looking ganglion cells in a background resembling neurofibroma. No binucleate or multinucleate forms or immature elements are identified. Hence the diagnosis of neurofibroma of spinal ganglion or benign ganglioneuroma was entertained (figure 3).

OUTCOME AND FOLLOW-UP

The patient noticed some improvement in tingling and numbness of the upper limbs, but otherwise his neurology was unchanged (due mainly to long duration of cord compression before surgery as well as the coexistent CMT syndrome). Postoperative MRI showed that there was no more compression of the spinal canal at C1–C2 level. He has continued the use of ankle splints and occasional physiotherapy, is receiving regular outpatient clinic review and is currently managing well.

Table 1 EMG/NCS data

Nerves/sites	Record site	Latency (ms)	Peak amplitude (μV)	Distance (cm)	Velocity (m/s)				
Sensory nerve conduction									
Right ulnar	Wrist-digit 5	3.40	9.8	15	44.1				
Right sural-calf left sural-calf	Lateral Malleolus	Nil response	Nil response						
Motor nerve conduction									
Right ulnar	Wrist	4.60	6.5						
Right ulnar	Below elbow	9.60	5.1	22.5	45.0				
Right ulnar	Above elbow	11.95	5.2	10	42.6				
R/L common Peroneal-EDB R/L tibial-AH	Ankle/knee	Nil response	Nil response						
Right common Peroneal-TA	Fibular head	4.90	0.3	13					
Right common Peroneal-TA	Knee	8.20	0.2	10	30.3				
F wave									
Nerve	F-M-1(MS)								
Right ulnar	37.90								
Electromyography summary									
	Spontaneous activity					MUAP			Recruitment
	IA	Fib	PSW	Fasc	H.F	Amp	Dur	PPP	Pattern
Right TA	N	2+	Nil	Nil	Nil	1+	1+	N	Discrete
Left TA	N	2+	Nil	Nil	Nil	1+	1+	N	Discrete
L Gastroc	N	2+	Nil	Nil	Nil	1+	1+	N	Discrete
R Gastroc	N	2+	Nil	Nil	Nil	1+	1+	N	Discrete
R TFL	N	Nil	Nil	Nil	Nil	2+	2+	1+	Reduced
Right VL	N	Nil	Nil	Nil	Nil	2+	2+	N	Reduced
R first DI	N	Nil	Nil	Nil	Nil	2+	2+	N	N

EMG, electromyography; MUAP, motor unit action potential; IA, insertion activity; Fib, fibrillation potential; PSW, positive sharp waves; Fasc, fasciculations; HF, higher frequency cut-off; Amp, amplitude; Dur, duration; PP, polyphasic potential; N, normal; NCS, nerve conduction study; R, right; L, left; EBD, extensor digitorum brevis; AH, abductor hallucis; TA, tibialis anterior; TFL, tensor fascia lata; VL, vastus lateralis; DI, dorsal interosseus.

Figure 1 Preoperative T2-weighted sagittal MRI of the cervical and thoracic spine. (A) Spinal canal compression and high-intensity signal within the cord at C1–C2 (blue arrow). (B and C) Multiple enhancing plexiform neurofibromas within the neural foraminae (white arrow).

DISCUSSION

CMT and NF1 each has a frequency of occurrence of 1 in 2500, so both diseases should co-exist in about 1 in 6 million cases.⁷ There have been previous reports of the co-existence of CMT and NF1. Bosch *et al*⁸ reported four NF1 patients who had peroneal muscular atrophy and axonal neuropathy, concluding that these findings represented uncommon presentations of NF1. Roos *et al*⁹ described a patient with NF1 and CMT1A, suggesting a possible genetic linkage between the two conditions. On the other hand, Koc *et al*¹⁰ in presenting a 22-year-old man with NF1 and CMT1A could not establish any genetic relationship between the two conditions. Likewise Lupski *et al*¹¹ reported two patients with NF1 and CMT1A, concluding that these conditions co-occurred possibly by chance. Lancaster *et al*, in reporting a patient with NF1 and CMT1B did not find any genetic interaction between these conditions. Chance phenomenon may therefore explain the co-occurrence of NF1 and CMT in our patient whose parents and other siblings did not manifest either condition. In a letter to the editor, Kapur *et al*¹² described the challenging anaesthetic management of a pregnant lady with NF1 and CMT.

CMT is generally classified on the basis of the ulnar or median motor conduction velocity (MCV) into demyelinating (type 1) with MCV lower than 38 m/s or axonal (type 2) with

MCV more than 38 m/s.¹³ Our patient whose median ulnar conduction velocity was 43.8 m/s qualifies to be categorised as CMT2.

The diagnosis of CMT relies on the following: symptoms and signs of limb weakness, muscle atrophy, gait abnormalities; positive family history; electrophysiological evidence of impaired nerve conduction and genetic testing for specific mutations. If these diagnostic features are inconclusive or genetic testing is negative, then peripheral nerve biopsy can be performed for histopathological evidence of abnormal myelination and degeneration. Lack of a positive family history as occurred in our patient does not rule out diagnosis of CMT.¹⁴ Since genetic testing is not yet widely available to test for all the chromosomal defects causing CMT, a negative result also does not rule it out.¹⁵

Molecular genetics advances notwithstanding, diagnosis of NF1 also relies mainly on clinical criteria as outlined by NIH above. Even though there is a positive family history in 71% of NF1 cases, our patient belongs to the minority who do not have a family history and probably acquired NF1 through spontaneous mutation. Our patient also had café-au-lait spots seen in 95% and axillary/inguinal freckling seen in 70% of NF1. Neurofibromas of the skin/subcutaneous tissues are seen in 95% while plexiform neurofibromas affecting the peripheral nerves

Figure 2 T2-weighted MRI of the lumbosacral spine. Coronal (A) and sagittal (B) views showing multiple enhancing plexiform neurofibromas within the neural foraminae (white arrows).

Figure 3 Microphotograph showing interlacing collagen fibres, darkly staining spindle cells and some ganglion cells. (H&E stain ×400).

occur in 30% of NF1.¹⁶ Both lesions were observed in our patient. The majority (72%) of paraspinal neurofibromas occur in the intradural extramedullary region as in our patient. The two major ocular features of Lisch nodule observed in 95% or optic glioma which is seen in 15% of NF1 cases were not manifested by our patient.^{17–18}

Spinal neurofibromatosis invading the entire spinal axis has been rarely reported but has been documented to occur irrespective of whether the NF1 was inherited in a familial or sporadic manner.

In a similar case to ours reported by Nakagawa *et al*, a patient who had neurofibromas affecting the entire dorsal spinal roots showed clinical improvement in sensory symptoms following resection of bilateral neurofibromas in the C4 nerve roots.¹⁹ In our case, the patient showed modest improvement as a result of myelomalacia from long duration of cord compression as well as his coexistent CMT syndrome.

Pascual-Castroviejo *et al* published a case series involving three members of a family who had asymptomatic multiple spinal neurofibromas, identifying common specific genetic mutation.²⁰ In another paper, the same authors described eight patients with sporadic (non-familial) NF1 concluding that the sporadic type presented earlier and predisposed to malignancy more.²¹ Carman *et al*²² reported multiple spinal neurofibromas in a young man with variant phenotypes associated with a single genetic mutation.

MRI of the whole spine has become a cornerstone in the diagnosis and planning of surgical treatment in multiple spinal neurofibromatosis. Paraspinal neurofibromas are isointense or hyperintense in T1 and hyperintense in T2 sequences, while dumbbell tumours readily enhance with gadolinium contrast.^{23–25}

Many authors have advocated surgical resection of symptomatic neurofibromas. During such procedures, preservation of the involved spinal nerve root may not always be feasible especially if they are completely wrapped by large tumours as in our case and complete tumour resection is intended. Surprisingly, postoperative neurological deficit is not seen indicating that the spinal roots involved in the tumour formation are dysfunctional even preoperatively; understandably, revision surgeries are fraught with more complications. The risk of postoperative tumour recurrence in NF1 cases is minimal.^{26–28}

The role of physical rehabilitation and ankle orthosis as ancillary aids to surgery in NF1 and also in CMT cases had been advocated.^{29–31}

Learning points

- ▶ Charcot-Marie-Tooth disease and neurofibromatosis type 1 (NF1) are common genetic conditions affecting the peripheral nervous system.
- ▶ The concurrence of these two conditions in the same patient is quite rare and may be due to chance phenomenon.
- ▶ NF1 with neurofibromas invading the entire spinal axis is quite rare and may cause spinal nerve compressive symptoms.
- ▶ MRI and electrophysiology play key roles in the diagnosis and management of these two conditions.
- ▶ Surgical treatment of spinal neurofibromatosis should only be confined to complete excision of symptomatic neurofibromas.
- ▶ Physical rehabilitative therapy and ankle support orthotic braces are ancillary aids to surgical treatment.

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