SHORT REPORT

Focal amyotrophy in neurofibromatosis 2

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Abstract

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder characterised by bilateral vestibular schwannomas and other CNS tumours including meningiomas and spinal schwannomas. Occasionally, peripheral neuropathy occurs in these patients but this is the first report of focal amyotrophy. Clinical, electrophysiological, and imaging data from four NF2 patients seen at a specialist neurofibromatosis clinic over a 4 year period are described in whom symptomatic focal amyotrophy preceded the diagnosis of NF2. Two presented with wasting and weakness of a single muscle group, several years before NF2 was diagnosed. In one patient a mononeuritis multiplex was the presenting feature of NF2, and in one patient focal wasting and weakness developed after the diagnosis of NF2 was made. In none of the four cases could a focal peripheral nerve or root neurofibroma be identified despite extensive imaging with MRI, and the limitations of neuroimaging for identifying a structural cause in patients with NF2 with a focal peripheral nerve lesion is discussed. It is likely that NF2 may affect peripheral nerve structures in a manner distinct from a compressive schwannoma.

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Neurofibromatosis type 2 (NF2), formerly known as bilateral acoustic or central neurofibromatosis, is established as a distinct disease on clinical, genetic, and pathological grounds.¹ Stringent diagnostic criteria are employed to aid differentiation from neurofibromatosis type 1 (NF1), formerly known as von Recklinghausen's disease or peripheral neurofibromatosis.^{2,3} Large clinical studies have defined the various clinical, demographic, and epidemiological features of both conditions, and guide the continued management of these patients.⁴⁻⁷

Neurofibromatosis 2 (NF2) has an estimated birth incidence of 1 in 33 000,⁴ and is inherited in an autosomal dominant fashion. Most patients with NF2 are diagnosed after presentation with symptoms referable to their bilateral vestibular schwannomas. It is not uncommon,

particularly in patients with severe NF2, to find they have had previous problems that can be related retrospectively to the disease. These include previous surgery for meningiomas, spinal or peripheral schwannomas, and symptomatic ophthalmic problems including cataracts and retinal hamartomas. Although the cutaneous lesions in NF2 are less marked than in NF1, occasionally patients will have been given a possible diagnosis of NF1 because of the presence of cafe au lait spots and of cutaneous nerve tumours clinically indistinguishable from neurofibromas. Non-tumorous peripheral nerve lesions are uncommon, being described in only 6% of patients with NF2.^{4,6} In three of those there was good clinical and neurophysiological evidence of a mixed sensorimotor neuropathy and in the other three evidence of a mononeuritis multiplex on clinical grounds only. The authors note that in none of the cases could a discrete tumour be found to account for the nerve lesions, although they do not indicate how extensively they investigated this possibility.

Reports of symptomatic peripheral neuropathy in patients with NF2 are rare and there are conflicting views on the pathogenesis.⁸⁻¹¹ There has been only one report of NF2 initially presenting as a symptomatic polyneuropathy, in which the underlying diagnosis was made 5 years subsequently, when the patient started to become deaf.⁸ Although previous reports have noted generalised muscle wasting in patients with NF2 with either a polyneuropathy or mononeuritis multiplex, there have been no previous reports of patients with NF2 presenting with symptomatic focal amyotrophy. We describe a series of four patients with NF2 and symptomatic focal amyotrophy.

Material and methods

The case notes were reviewed of patients who have been seen at the Oxford NF2 clinic between 1995 and 1999. Seventeen patients with definite NF2; and 17 at 50% risk were assessed. Three patients (cases 1-3) with clinical data suggesting the presence of either a mononeuritis or a polyneuropathy who fulfilled the diagnostic criteria for NF 2 were identified. Case 4 was a boy who presented with mononeuritis whose mother was found to have NF2.

All of the patients were examined by at least one of us, with three being evaluated by a consultant neurologist. Additional neurophysiological and neuroradiological studies were performed in those patients in whom adequate nerve conduction and imaging studies were not

available. Nerve biopsies were not performed on any of the patients because of the absence of an accessible yet affected peripheral nerve.

CASE HISTORIES

Case 1

This 26 year old man gave an 8 year history of sudden onset progressive left thigh wasting and difficulty straightening his left leg. He complained of falling because his left knee gave way. Also, he reported numbness on the inner and anterior aspects of the left thigh. Systematic enquiry disclosed increasing left sided deafness from the age of 13, undiagnosed despite previous ear, nose, and throat assessment. There was no relevant family history of neurological disease.

Examination showed severe left sensorineural deafness, profound wasting of the left quadriceps muscle, an absent left knee jerk, and sensory loss in the skin territory of the anterior cutaneous nerve of the thigh. Detailed neurological examination of the limbs was otherwise normal. There were no palpable lesions along the course of the femoral nerve below the inguinal ligament. On cutaneous examination he had one café au lait spot and an NF2 plaque lesion just above his left buttock.

Nerve conduction studies showed sural nerve action potentials of 4 μ V (right) and 7 μ V (left) (normal >4 μ V). The left posterior tibial F wave latency was normal (53 ms). Motor nerve conduction velocities were normal. Electromyography showed profound denervation of the left vastus medialis and lateralis but not the adductor muscles. No spontaneous activity was recorded from the right vastus group. There was no response to stimulation of the left femoral nerve at the inguinal ligament. MRI (figure) of the left femoral nerve, lumbar plexus, lumbosacral nerve roots, and cauda equina showed patent exit foramina, with a small unrelated mass noted on the S2 root but no focal enlargement along the femoral nerve. Cranial MRI showed bilateral vestibular schwannomas. No NF2 gene mutation has yet been identified.

Case 2

This 29 year old woman initially presented to the ear, nose, and throat department with an 18 month history of sensorineural deafness in the left ear. Brain MRI at that time showed multiple meningiomas and a unilateral schwannoma and she was referred to our NF2 clinic. A symptomatic bilateral papilloedema had been detected at 21 years by her optician while she was taking the oral contraceptive pill and ascribed to benign intracranial hypertension. Brain CT had shown a grossly dilated right lateral ventricle, with no obvious obstructing mass lesion identifiable on ventriculography.

She re-presented 18 months later with sudden onset of weakness and wasting of her left hand which had worsened over 6 months and also with wasting and weakness of her right quadriceps muscle. There were no sensory symptoms and no family history of neurological or other disease. Examination showed wasting of the intrinsic muscles of the left hand

with relative sparing of the thenar eminence. She had marked weakness of the left first dorsal interosseous compared with the abductor digiti minimi, with normal power in the abductor pollicis brevis. Sensation and the arm reflexes were normal. Palpation of the supraclavicular fossae and ulnar nerve at the elbow were normal. There was marked wasting of the medial aspect of the right vastus medialis with weakness of the quadriceps, an absent knee jerk, and a patch of sensory loss over the anterior aspect of the thigh above the knee. The other upper lumbar root territories and the obturator, gluteal nerves, and sciatic nerves were normal.

Nerve conduction studies showed a left ulnar sensory action potential of 23 μ V (normal >5) and a normal compound motor action potential over abductor digiti minimi (13 mV) with a normal conduction velocity (61 m/s). The femoral nerve was inexcitable; the right posterior tibial F wave latency was 52 ms. Electromyography showed denervation in the left first dorsal interosseus and in the right vastus medialis but not the right thigh adductor muscles. Her CSF was normal. In the absence of a unifying cause, she was thought to have a form of spinal muscular atrophy.

After diagnosis of NF2, MRI of the right lumbar plexus, lumbar roots, and right femoral nerve showed normal roots, exit foramina, and femoral nerve from groin to knee, and marked wasting of the entire quadriceps group. An MRI of the cervical spinal canal showed no mass lesions; the brachial plexus was not examined. The patient now has small bilateral vestibular schwannomas; no NF2 gene mutation has been identified yet.

Case 3

This 16 year old girl was referred with a 12 month history of right sided tinnitus and progressive sensorineural deafness. Three years earlier she underwent surgery for removal of two cutaneous lesions shown histologically to be plexiform schwannomas. There was no family history of neurological or other disease. Cranial MRI had shown bilateral cerebello-pontine angle masses extending into the internal auditory meati, that on the asymptomatic left side measuring 4 cm, whereas the right side lesion was small. An additional mass was noted at the skull base encroaching the left vertebral artery at the foramen magnum. Analysis showed a Cys37→Stop (nc IIIC→A) NF2 gene mutation.

Over the next 12 months she became progressively unsteady on her feet and serial MRI showed a further enlargement of her right but not her left acoustic neuroma. In addition, wasting was noted of the anterior tibial compartment of her right leg below the knee accompanied by marked asymptomatic weakness of right foot dorsiflexion. Tendon reflexes and sensation were normal and there were no further deficits attributable to her lumbosacral plexus or roots. There were no palpable masses in the popliteal fossa or at the fibula head.

Case 1: A series of MRIs showing (A) conus and cauda equina, (B) lumbar plexus, and (C) proximal femoral nerve. (A) There is no compressive lesion affecting the lumbar nerve roots within the cauda equina. (B) The upper plexus is seen on a coronal gadolinium enhanced T1 weighted image and the L2 and L3 roots (arrows) are seen under their respective vertebral pedicles. (C) The femoral nerve can be identified between the psoas and iliacus muscles (arrow). (D) Extensive wasting of the left quadriceps muscle is evident on a T1 weighted coronal MRI.

Nerve conduction studies showed normal sural nerve action potentials (16 μ V right, 21 μ V left) and a reduced right superficial peroneal sensory nerve action potential of 9 μ V compared with the left (29 μ V). Electromyography showed fibrillations of the right tibialis anterior, complex polyphasic units in the short head of biceps, and large (10 mV) units in

extensor digitorum brevis. F waves were absent from the right common peroneal nerve territory.

Sagittal, coronal, and axial MRI of the lumbar spine, pelvis, and right thigh showed normal exit foramina and no pathological enhancement or swelling of the lumbosacral plexus, nerve roots, or peripheral nerves.

Case 4

A 7 year old boy was referred because of sudden onset progressive right foot drop. He also had a severely amblyopic divergent squint in his left eye. There was severe weakness of right foot dorsiflexion and eversion accompanied by an absent right ankle jerk but no sensory loss. There was no right sided quadriceps weakness and the right knee jerk was present. The remainder of his neurological examination was normal. An MRI of the lumbar spine was normal. On enquiry his mother had a 5 year history of unilateral sensorineural deafness, for which she had never been investigated.

His symptoms progressed over the next year before stabilising. His mother had a brain MRI showing bilateral cerebellopontine mass lesions, thought to represent vestibular schwannomas, and was diagnosed with NF2. Mutation analysis in the mother showed a base pair deletion in her NF2 gene.

Further MR images of the brain and sagittal, coronal, and axial sequences of the lumbar spine, pelvis, and right thigh were normal. Nerve conduction studies showed an absent right sural sensory nerve action potential (left 15 μ V), an inexcitable right lateral popliteal nerve, and prolonged F waves in the right (43 ms) compared with the left (34 ms) posterior tibial nerve. Needle EMG of the right tibialis anterior muscle showed denervation changes.

Although we cannot formally diagnose case 4 until other disease features develop, given his mother's diagnosis and similarity to all of the other cases, we think that the amyotrophy is the presenting feature of NF2. The diagnosis has not been confirmed yet by gene studies or neuraxis scanning as he is otherwise well.

Discussion

We describe a small series of patients with NF2 and the previously undescribed presentation of focal amyotrophy. Focal compressive neuropathy radiculopathy or a neurofibroma could not be shown to underlie this wasting despite thorough MRI of the course of the peripheral nerves and electrophysiological studies. Although symptomatic peripheral nerve lesions have been described occasionally in patients with NF2, the underlying pathogenesis is unknown and other reports have not included MRI studies. Many cases of focal wasting and weakness in NF2 are secondary to compression of a proximal nerve or root by a schwannoma. Yet multiaxial neuroimaging with MRI in our four patients showed patent vertebral exit foramina and no peripheral nerve schwannomas causing focal compression. The disparity between first dorsal interosseous and abductor digiti minimi involvement in patient 2 suggested a deep palmar branch lesion of the ulnar nerve, but no mass was palpable in the wasted hand.

A compressive cause for peripheral nerve involvement in NF2 was first mooted after description of a patient who developed progressive distal mixed polyneuropathy.¹⁰ A sural nerve biopsy showed lamellated "onion bulb" structures, which the authors attributed to

reactive Schwann cell hyperplasia, as previously described in chronic demyelination.¹² Review of this histology refuted this origin for these structures, and suggested they were of perineural origin, raising an alternative hypothesis of a diffuse neurofibromatous process to explain the peripheral nerve involvement.¹¹ In other patients with sensorimotor polyneuropathy and neurofibromatosis the sural nerve histology was either in keeping with a diffuse neurofibromatous process in two, who were more likely to have NF1 or resembled the histology of an excised acoustic schwannoma in a third patient with NF2.¹¹ Although diffuse neurofibromatous change might account for polyneuropathy in NF2, it could only explain the localised amyotrophy in our four patients if it had developed more focally in the relevant peripheral nerves, possibly rendering the nerve more vulnerable to potential sites of compression. Recently, a 24 year old man with NF2 has been reported who presented with a mononeuritis multiplex affecting all four limbs, in whom a neurofibroma was reported in a single fascicle.⁹ Despite visualisation of only two masses in the cervical spine, numerous masses were noted in the same region at operation. This highlights the limitations of current neuroimaging in detecting small neurofibromas. A possible humoral basis for that patient's polyneuropathy was suggested by a dramatic response to immunomodulatory treatment; it seems probable that this was an idiopathic polyneuropathy unrelated to the NF2.

Our cases highlight the problem of recognising the underlying diagnosis of NF2 in otherwise asymptomatic patients with peripheral nerve lesions. Nerve biopsy of an affected motor nerve is not feasible and there is no consensus for interpreting peripheral nerve histology in NF2. Our view is that a patchy neurofibromatous process affecting peripheral nerves, without discrete neurofibromatous swellings, probably accounts for the focal amyotrophy seen in this subset of NF2 patients with focal amyotrophy. However, we have no histopathological evidence to support this hypothesis. None the less such patients should be investigated initially with MRI because excision of a compressive mass lesion remains the only potential therapeutic option to limit the progression of a focal neuropathy. We conclude that focal amyotrophy may develop several years before the underlying diagnosis of NF2 becomes apparent. Undiagnosed sensorineural deafness should be sought in the patient and first degree relatives when assessing obscure focal amyotrophy, especially affecting the femoral nerve territory.

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