CASE REPORT

Multifactorial pathological hip subluxation in neurofibromatosis type-1 (NF1) due to intra-articular plexiform neurofibroma, lumbar radiculopathy and neurofibromatous polyneuropathy

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SUMMARY

Neurofibromatosis type-1 (NF1) is a multisystem disorder with very rare descriptions of hip instability. We report a case of a 37-year-old man with known NF1 and childhood-onset of left foot drop, who developed persistent left hip pain following a minor trauma. Physical examination revealed left-sided mild foot drop, hip abductor weakness, bilateral sensory loss in feet and an antalgic gait. Work-up revealed anterolateral subluxation of the left femoral head along with left hip plexiform neurofibroma (PN), dysplastic and degenerative changes, neurofibromatous neuropathy and chronic left L5 radiculopathy. Initial improvement after surgical resection of the PN was unsustained and followed by increasing pain and recurrent hip subluxation, prompting a total hip arthroplasty which resulted in marked improvement of symptoms. Our patient, unlike those in other reports, illustrates multiple aetiologies of hip dislocation in NF1 including local factors, lumbar radiculopathy and polyneuropathy, reinforcing the importance of a multidisciplinary approach in the management of such cases.

BACKGROUND

One of the most common inherited neurological disorders, neurofibromatosis type-1 (NF1) results from mutations in the NF1 gene, which encodes for a tumour suppressor protein, neurofibromin, a negative regulator of the Ras proto-oncogene. Neurofibromin deficiency leads to increased signalling of Ras and other signal transduction pathways, resulting in the development of many tumours, including plexiform neurofibromas (PN).^{1 2}

One of the many types of neurofibromas, PN are characterised by the proliferation of Schwann cells, perineural fibroblasts and mast cells; they develop in 25–50% of patients with NF1.³ Unlike cutaneous neurofibromas, PN arise from multiple nerve fascicles and display a potential to grow along the length of the nerve. Although benign, PN are associated with significant morbidity and mortality due to their proclivity to extend into surrounding structures, resulting in significant pain, disfigurement and even life-threatening complications including their potential for malignant transformation.⁴

Pathological hip subluxation or dislocation is a rare complication in NF-1, with 14 documented cases in the published literature.^{5–7} We describe a case of hip subluxation in a patient with known

NF1, which unlike other reported cases, was of multifactorial cause. We present, in detail, the clinicopathological associations of the different comorbidities in our case.

CASE PRESENTATION

A 37-year-old right-handed man, with a prior diagnosis of NF1, presented for evaluation of left hip pain and weakness. Eighteen months prior to presentation, following a minor fall on ice, he developed persistent sharp left hip pain with radiation to the ipsilateral groin and calf. Arising and walking were difficult due to hip instability and pain. There was mild localised low back pain, but no tingling, numbness or symptoms referable to the right leg, arms, bladder or bowels. He had noted the left foot ‘catching’ during walking since childhood, which started after a minor motor vehicle accident, with documented left foot drop by a physical therapist; this remained stable, without any intervention. Review of systems was otherwise unremarkable.

His medical history was also significant for mild developmental delay, asthma, panhypopituitarism and two separate episodes of spontaneous pneumothorax. Current medications included: testosterone gel, tiotropium and fluticasone/salmeterol inhalers, ibuprofen 200 mg every 6 hours, prednisone 5 mg/day and vitamin D3 1000 IU/day. He had 15 pack-year smoking history and denied alcohol or illicit drug use. Family history was significant for neurofibromatosis in his father; there was no family history of neuropathy.

Physical examination

General examination was significant for a thinly built, well-groomed man with multiple cafe-au-lait spots and cutaneous neurofibromas with highest density over the trunk, but with no axillary freckles. Neurological examination was relevant for mild static encephalopathy, Medical Research Council grade 4/5 weakness of left tibialis anterior, tibialis posterior and extensor hallucis longus muscles; decreased ankle reflexes; mild distal loss to pin prick and vibration in both feet. Left hip examination demonstrated pathological external rotation to about 120°; although left hip abductors could be activated, there was weakness against gravity. He could, nevertheless, stand on either leg independently with just minimal support and did not exhibit a Trendelenburg sign. He did, however,

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show a Trendelenburg gait as the abductors fatigued easily during walking.

INVESTIGATIONS

Nerve conduction studies (NCS) and electromyography (EMG) showed findings of a moderately severe, mixed axonal and demyelinating sensorimotor polyneuropathy, and a chronic left L5 radiculopathy with evidence of ongoing denervation in the L5-innervated muscles (table 1 A and B).

MRI scan of the lumbar spine, pelvis, left hip and thigh showed a large sacral meningocele without left L5 or S1 nerve root compression and no neurofibroma or mass along the course of the left sciatic nerve or lumbosacral plexus. There was, however, a constellation of findings suggestive of intra-articular and extra-articular PN involving the left ilium and capsular structures of the left hip, with caudal extension along the anterior cortical margin of the proximal femoral shaft with infiltration of the musculature of the anterior compartment of the thigh (figures 1B and C). Additional imaging findings included dysplastic features in the left acetabulum and proximal femoral shaft, anterolateral subluxation of the left femoral head and severe degenerative changes of the left hip out of

proportion to the patient's age, with greater involvement of the left as compared to the right hip (figure 1A).

Work-up for acquired aetiologies of polyneuropathy included the following normal tests: complete blood count, comprehensive metabolic profile, serum and urine protein electrophoresis with immunofixation, methylmalonic acid, folic acid, thyroid-stimulating hormone, erythrocyte sedimentation rate, antinuclear antibody, anti SSA/SSB antibodies, antitissue transglutaminase antibody, ACE inhibitors, haemoglobin A1C and antiglycolipid antibodies. Vitamin D level was mildly reduced (25 ng/mL, sufficient=10–30 ng/mL). Cerebrospinal fluid cell count, protein, glucose, ACE inhibitors, oligoclonal bands, IgG index, Lyme antibody titre, Venereal Disease Research Laboratory test (VDRL) and cytology were normal or negative.

Left sural nerve and tibialis anterior muscle biopsies revealed findings of a chronic axonopathy with mild-to-moderate loss of myelinated fibres; atrophy of type I and type II fibres and grouped muscle fibre atrophy, compatible with ongoing denervation and reinnervation (figures 2A–C). Malignant transformation was excluded by an incisional open biopsy of the left intra-articular soft tissue mass, which showed findings consistent with a diffuse type of PN (figure 2D).

Table 1 EMG/NCS and nerve/muscle biopsy showed mixed axonal and demyelinating abnormalities

(A) NCS

	Onset latency (ms)	Amplitude (mV-motor or uV-sensory)	Conduction velocity (m/s)	F-wave latency (ms)
Right tibial motor	6.5 (normal <6.1)	3.1 (ankle) (normal >3.0) 3.6: Pop. Fossa	33.0 (normal >41.0)	70.5 (normal <56.0)
Left tibial motor	7.2	4.9 (ankle) 3.8: Pop. Fossa	32.0	60.6 (normal <56.0)
Left common fibular: from extensor digitorum brevis	7.2 (normal <6.1)	1.6 (ankle) (normal >2.0) 1.5 (fibular head) 1.4 (knee)	33.0 (ankle-fibular head) (normal >41.0) 30.0 (fibular head-knee)	
Left median motor	3.5 (normal <4.4)	4.5: wrist (normal >4.0) 4.3: Elbow	54.0 (normal >49.0)	33.0 (normal <31.6)
Left radial sensory	2.5 (normal <3.4)	17.0 (normal >17.0)	47.0 (normal >51.0)	
Left median sensory	3.5 (normal <3.1)	8.0 (normal >20.0)	50.0	
Left sural sensory		No response		
Left superficial fibular sensory		No response		

(B) EMG

Muscle	Spontaneous and/or volitional activity						Recruitment Pattern
	Fibrillations	Positive waves	Fasciculations	Polyphasia	Amp	Dur	
Left tibialis ant.	1+	3+	None	Many	Increased	Increased	Discrete
Left gastroc. med H.	None	1+	None	Few	Normal	Normal	Moderate
Left vastus med.	Normal						
Left biceps femoris	Normal						
Left semitendinosus	Normal						
Left gluteus medius.	1+	2+		Many	Marked increase	Increased	Discrete
Left gluteus max.	Normal						
Left iliopsoas L.	Normal						
Left-lumb. paraspinal.	None	1+					

Axonal loss in our case was suggested by absent lower extremity sensory nerve action potentials, reduced compound muscle action potential amplitudes and neurogenic changes on EMG in distal calf muscles (ongoing denervation changes included fibrillations and positive waves while the presence of increased motor unit potentials polyphasia, amplitude and duration suggested reinnervation changes). Demyelinating features were supported by prolonged motor onset latencies, reduced conduction velocities and delayed F-wave latencies. EMG, electromyography; NCS, nerve conduction studies.

Figure 1 (A) Anteroposterior view of the left hip showing lateral subluxation of the femoral head with respect to the acetabular fossa (white arrowheads) and dysplastic features in the acetabulum and the proximal left femoral shaft (white arrows). (B) Coronal T1-weighted fat saturated MRI scan of the left hip after intravenous contrast administration showing an enhancing intra-articular neurofibroma in the medial aspect of the acetabular fossa interposed between the femoral head and the wall of the acetabulum (white arrows). In addition, there is a periarticular plexiform neurofibroma with extra-articular extension along the superolateral aspect of the acetabulum and lateral aspect of the proximal femoral shaft causing remodelling changes (white arrowheads). (C) Coronal T1-weighted MRI scan image of the pelvis without fat saturation showing asymmetric extra tissue interposed between the left femoral head and the acetabulum (white arrows), lateral subluxation of the left hip (white arrowhead) and bilateral degenerative changes, worse in the left hip. The right hip shows a normal appearance of the femoral head which is well positioned within the acetabular fossa. (D) Four anteroposterior radiographs of the left hip obtained immediately after the initial surgery for resection of the intra-articular neurofibroma, then postoperatively at 8 weeks and 6 months, and finally after total left hip arthroplasty. Note the satisfactory reduction of the hip subluxation on the first radiograph (white arrowhead), followed by recurrent lateral subluxation of the hip on the two subsequent radiographs (black arrows) with the femoral head progressively translating laterally with respect to the acetabulum (white arrowheads). In addition, one of the two screws fixing the trochanteric osteotomy has broken in the interval (white curve arrow). The last radiograph shows a well-seated left hip arthroplasty.

TREATMENT

After confirmation of the diagnosis of PN, and exclusion of malignant transformation, the patient underwent surgical dislocation of the left hip with resection of the intra-articular and extra-articular neurofibromata.

While there was initial improvement, because of the return of left hip pain within a year of the PN excision, as well as continued subluxation of the hip documented on examination and by X-ray (figure 1D), total left hip arthroplasty using a large femoral head dual mobility total hip to maximise hip stability was performed (figure 1D).

OUTCOME AND FOLLOW-UP

The patient noted excellent pain relief and greatly improved gait and functional abilities, at 6 months follow-up after arthroplasty.

DISCUSSION

In our case, there were multiple potential sources of progressive hip instability that needed attention prior to choosing an appropriate treatment course.

The following mechanisms of hip instability were considered:

(a) Local factors^{4 8} related to intra-articular growth of PN and associated mesodermal dysplastic changes. By producing chronic pressure erosions on adjacent structures, a large neurofibroma can contribute to dysplastic changes. Pertinent factors

that predisposed to subluxation of the hip included: (1) hypertrophied and degenerated labrum, which together with a shallow and poorly formed left acetabulum, resulted in uncovering of the left femoral head; (2) coxa valga deformity of the hip, which refers to the increase in the angle above 135° formed between the head and neck of the femur and its shaft, contributed by abnormal morphology from osseous erosive changes of the femoral head and neck as well as the aforementioned mesodermal dysplastic changes from NF; and (3) synovitis and a sizeable left hip joint effusion creating extrinsic mass effect on the femoral head and increased joint capsule fragility and laxity. Other reported factors in the literature, including limb length discrepancy and pelvic inclination due to scoliosis, were not identified in our case.

(b) L5 radiculopathy-related mechanical instability⁷ due to weakness of hip abductors, which were not strong enough to restrain the hip joint. The gluteus medius, an important hip abductor, is critical for smooth reciprocal gait and hip stability. The unilateral L5 radiculopathy in our patient could have resulted in Trendelenburg gait; however, it is possible that deconditioning resulted in easy fatigue of the hip abductors. The diagnosis of an L5 radiculopathy was based on clinical examination and was confirmed by EMG which showed neurogenic changes in the L5-innervated muscles (tibialis anterior, tibialis posterior, gluteus medius and lumbar paraspinals). Another possible site of localisation of the weakness, when

Figure 2 Biopsy of tibialis anterior muscle, sural nerve and plexiform neurofibroma from the patient. (A) Electron micrograph ($\times 1000$, magnification) of nerve showing loss of myelinated axons; computer-assisted morphometric analysis showed 4298 fibres/mm² (laboratory normal=8100 fibres/mm²). (B) ATPase (9.4) stained cross section of muscle showing a single group of type 2 (darkly stained) fibres at the lower left edge, denoting regeneration. (C) H&E stained cross section of muscle showing a small group of angular atrophic fibres in the centre, denoting denervation. (D) H&E section of biopsied plexiform neurofibroma showed a haphazard array of ovoid and elongated nuclei characteristic of plexiform neurofibroma, diffuse type; note absence of necrosis, mitosis or cellular atypia.

considering the prominent EMG changes in the tibialis anterior and posterior, with sparing of the L5-innervated hamstring muscles, could be a lesion in the left sciatic nerve distal to the take-off of the motor branch to the short head of the biceps femoris; however, involvement of the gluteus medius on EMG (innervated by superior gluteal nerve), argues against this possibility, as does the MRI scan of the left thigh and pelvis, which showed no neurofibroma or mass along the course of the sciatic nerve. Similarly, the normal MRI scan of the lumbosacral plexus also rules out a radiographically identified cause of a lumbosacral plexus lesion as the cause of weakness.

MRI scan of lumbar spine showed no radiographical explanation for the L5 radiculopathy. The lumbar meningocele identified in our case, a rare association of NF1, can induce erosive and lytic deformities of the spine^{8,9} through pulsed synchronous stress; however, we identified no radiological evidence of dynamic spinal instability. Infectious, infiltrative and immune-mediated aetiologies of a non-structural radiculopathy were excluded by appropriate CSF and serological studies. Our patient's chronic radiculopathy was most probably related to childhood traumatic radiculopathy, with subsequent resolution of disc herniation, albeit with persistent neurogenic changes on EMG. This assumption was based on his report of a presumed left foot drop with 'catching' since childhood after a minor motor vehicle accident, which was documented by a physical therapist a few years before the current presentation.

(c) Neuropathic arthropathy⁶ was possibly caused by the disturbance of normal sensations in the hip and contributed to by the documented peripheral neuropathy. Reported aetiologies^{6,7} in the literature, related to NF1-associated neuropathic arthropathy, include cauda equina syndrome from multiple schwannomas, scoliosis and infiltration of the joint by a neurofibroma that could impair proprioceptive sensitivity. Hip dislocation in these reported cases was not symptomatic (painless), and a reduction

of the sensitivity to pain was evident on examination of the affected limb. In our case, based on the lack of neuropathy-associated symptoms and symptomatic (painful) hip dislocation, the contribution of polyneuropathy towards the hip instability is unlikely.

In contrast to neurofibromatosis type-2 (NF2), where the clinical symptoms of peripheral neuropathy occur in almost 50% of cases, peripheral neuropathy is much less common in NF1; found in 1.3% and 2.3% of screened patients with NF1.^{10,11} Of these, the largest subgroup had either asymptomatic or pauci-symptomatic neuropathy, detected only on electrophysiological studies. The most common pattern was of demyelinating neuropathy with secondary axonal loss and superimposed radiculopathy changes.¹¹ These reports are consistent with the findings in our case, in which electrodiagnostic studies and nerve/muscle biopsies showed mixed axonal and demyelinating abnormalities. An appropriate, directed work-up, as discussed in our case, is necessary to identify neurofibromatous neuropathy in a patient with NF1.

Even though the majority of cases of neurofibromatous neuropathy may be asymptomatic, the presence of proximal large neurofibromas, peripheral neuropathy particularly of the demyelinating type and subcutaneous neurofibromas has previously been associated with a poor prognosis, related to spinal complications and malignant transformation of peripheral nerve sheath tumours.¹¹ The presence of above-mentioned features which were also present in our case emphasise the importance of obtaining histological confirmation to exclude the possibility of malignant transformation of PN. Other previously described risk factors for malignant transformation include a painful expanding lesion, change in tumour consistency, new neurological deficits, prior radiation therapy and the presence of large germline mutations encompassing the entire NF1 gene (micro-deletions).^{12,13} Besides histology, ¹⁸F-fluorodeoxyglucose

(18F-FDG)-PET and volumetric MRI analysis can be used to exclude the possibility of malignant transformation of PN.^{14 15}

There is limited evidence to guide the orthopaedic treatment of hip instability related to NF1. In cases of spontaneous dislocation, often the result of minor trauma, short-term success can be achieved with a closed relocation, but recurrent dislocation is likely to occur.^{12 16} Cases of recurrent dislocation of the otherwise normal joints can be successfully treated with casting or skeletal traction.^{16 17} These treatments were not a reasonable option in our patient, who had progressive hip subluxation and near dislocation, associated with painful arthritis. For cases of joint destruction related to NF1, the source of pain and the cause of instability must be sought to determine the appropriateness of total hip arthroplasty; the potential for dislocation after total hip arthroplasty in these cases is significant. There are two case reports in the literature of total hip arthroplasty for the treatment of NF-1 related hip subluxation,^{15 18} in both of these instances, distal advancement of the greater trochanter was required. When performing arthroplasty for NF1-related hip instability, careful planning is necessary to reduce the risk of dislocation.

Currently, the treatment of PN is largely surgical; however, further knowledge of the genetic pathways and molecular mechanisms might provide future therapeutic options for inoperable symptomatic PN.^{19–21}

In summary, our case highlights multiple aetiologies of hip subluxation or dislocation in patients with NF1 and reinforces a multidisciplinary approach in selecting the most appropriate treatment.

Learning points

- ▶ Pathological hip dislocation in neurofibromatosis type-1 (NF1) could be multifactorial including: intra-articular plexiform neurofibroma (PN) with associated mesodermal dysplastic changes, L5 radiculopathy causing mechanical instability through hip abduction weakness and neurofibromatous polyneuropathy through proprioceptive loss leading to painless hip dislocation.
- ▶ Neurofibromatous polyneuropathy, particularly demyelinating, constitutes a potentially severe complication in patients with NF1, associated with a frequent morbidity related to spinal complications and malignant transformation of an existing PN.
- ▶ Given the multifactorial issues that can cause hip instability in NF1, a multidisciplinary approach is helpful to guide treatment.
- ▶ When performing arthroplasty for NF1-related hip instability, we recommend planning to use adjuncts such as dual mobility constructs and trochanteric advancement to reduce the risk of dislocation.

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