CASE REPORT

Spinal neurofibromatosis associated with classical neurofibromatosis type 1: genetic characterisation of an atypical case

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SUMMARY

Spinal tumours are observed in about 40% of neurofibromatosis type 1 (NF1) patients and occur within two subgroups: (1) NF1 patients carrying classical diagnostic criteria and only one or few spinal tumours and (2) patients with few NF1 stigmata but multiple bilateral spinal tumours, an entity called spinal neurofibromatosis. We report a young patient whose classical NF1 stigmata and numerous spinal neurofibromas matched both groups. He carried a single base deletion, c.389delA in exon 4a, which creates a premature termination at codon 164. This case illustrates the possibility of variant phenotypes and a novel NF1 mutation associated with spinal neurofibromatosis.

3 months. Performance in school was poor. Upon physical examination, head circumference was 56 cm (75–95 percentile), while his height and weight were at the third percentile. He had multiple café au lait spots, axillary freckling, Lisch nodules, soft and mobile subcutaneous nodules, a large (6×8 cm) plexiform neurofibroma on the right thigh, a webbed neck and thoracic kyphoscoliosis. Upon neurological examination, neck movements were restricted, arms could be abducted up to the shoulder level, muscle tone was generally increased, but deep tendon reflexes were normoactive and plantar responses, flexor. He was walking with assistance. NF1 was diagnosed based on NIH criteria.¹

BACKGROUND

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with specific clinical features including hyperpigmented spots, neurofibromas, Lisch nodules, skeletal abnormalities and tendency to develop neoplasms.¹ Neurofibromas can develop from dorsal nerve roots as well as peripheral nerves, and in about 36–40% of patients, in the spinal canal. Spinal neurofibromas can be identified in two different phenotypes of NF1 patients: (1) classical NF1 features and only one or few spinal tumours and (2) multiple bilateral spinal tumours, but only few NF1 criteria. The latter has been classified as a subgroup of NF1, the spinal neurofibromatosis.^{2–3} This may be inherited in an autosomal dominant fashion called familial spinal neurofibromatosis (FSNF), although this term is also used for sporadic cases.^{2–3}

Patients with spinal tumours possess a relatively specific germline mutational spectrum, mostly missense and splice-site mutations and some frameshift mutations. In a study of familial (n=12) and sporadic (n=7) patients with FSNF, a truncating mutation was found in 6/12 (50%) and 1/7 (14%); a missense mutation in 5/12 (42%) and 4/7 (57%) and a partial or whole gene deletion in 1/12 (8%) and 2/7 (29%), respectively. In comparison, missense changes are rare in classical NF1 (28/278, 10%).⁴ We present a patient severely affected by spinal neurofibromas carrying a frameshift mutation (c.389delA) and fulfilling the NIH criteria for classical NF1.

CASE PRESENTATION

Case

A 14-year-old boy was referred because of fatigue, abdominal pain and progressive weakness for

INVESTIGATIONS

Routine laboratory investigations including blood count, biochemistry and bone investigations were normal. Electromyography showed asymmetrically reduced nerve conduction velocity in all extremities. Brain MRI revealed the presence of masses at the right medullo-pontine corner, in the cerebellum and basal ganglia. Bilateral neurofibromas were observed on the ophthalmic branches of the trigeminal nerves, a brain stem glioma at the medullo-pontine corner; intradural and extramedullary neurofibromas with compression of the cervical cord and enlargement of the cervical spinal canal. In addition to this multiple neurofibromas were affecting the entire spinal cord. Those at the C2–C3 and L4–L5 levels had dumbbell configuration with extraspinal and intraspinal components producing cord compression and foraminal enlargement (figures 1 and 2). Multiple bilateral chain-like neurofibromas were found occupying the pelvis (figure 3).

Genomic DNA was extracted from peripheral blood samples by salting out procedure after informed consent. PCR was performed with intronic primers for all exons of the NF1 gene. Primer sequences were available on request. Primers designed by primer3 programme (<http://frodo.wi.mit.edu/>). DNA samples were sequenced to detect variations in each exon by using the Big Dye Terminator 3.1 Kit (PE Applied Biosystems, Foster City, California, USA) and ABI-PRISM 3130 Genetic Analyzer (PE Applied Biosystems), according to the manufacturer's instructions. Mutation nomenclature follows the Human Genome Variation Society (<http://www.hgvs.org/mutnomen/>) recommendations.⁵

We identified a single base deletion, c.389delA in exon 4a which causes a frameshift and eventually premature termination at codon 164. This is a

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Figure 1 Sagittal T2-weighted cervical spinal MRI showing intradural and extramedullary neurofibromas, with compression of entire cervical cord and enlargement of cervical spinal canal.

novel mutation, previously unreported in classical NF1 or FSNF.

DIFFERENTIAL DIAGNOSIS

The patient matched the clinical diagnostic criteria of NF1. Similar features can be encountered in an overlap syndrome

Figure 2 Axial T2-weighted spinal MRI: dumbbell tumour at the L4–L5 spinal level.

Figure 3 Coronal T2-weighted spinal MRI shows multiple bilateral neurofibromas, at lumbar and sacral levels with invasion of the entire pelvis.

called neurofibromatosis-Noonan syndrome although clinical differentiation is possible. Legius syndrome carries similar skin findings but no neurofibromas.

TREATMENT

The progressive symptoms were attributed to the tumour at the medullopontine junction which was inoperable, and no chemotherapy or radiotherapy was indicated.

OUTCOME AND FOLLOW-UP

Quadripareisis and pyramidal signs progressed within 6 months. He became unable to sit, walk and self-care without assistance after 6 months. The physical examinations and spinal MRI scans of the other family members (mother, father and sister) were normal.

DISCUSSION

Spinal tumours take part in the wide clinical spectrum of NF1; however, only 2% of patients, and even fewer of children, experience symptoms. In a series of 53 children with NF1 undergoing spinal MRI, spinal neurofibromas were found in 7 (13.2%), all asymptomatic.⁶ The frequency of neurological manifestations increases with age. Therefore the severe and progressive symptoms and the tumour load of our patient are unusual for his age.^{7 8} Another particular feature of our patient was the presence of all peripheral signs of classical NF1 including short stature, bone lesions, café au lait spots and plexiform neurofibromas in the presence of spinal neurofibromatosis, a phenotype unlike FSNF. We therefore consider the classification of the spinal manifestations of NF1 into two phenotypic groups may not be valid for all cases, and overlapping cases may exist.

The mutation identified in this patient causes a frameshift and eventually a stop codon. This novel mutation has not previously been identified in spinal or classical NF1 patients. Kluwe *et al*⁹ found two truncating mutations in patients with spinal neurofibromas, both located in the last couple of exons of the gene. Our findings differ from the literature.

At present, the management of spinal neurofibromas consists of careful observation, resection being reserved for the most severe cases: the anatomical location, degree of invasion and risk of recurrence at the surgical site affect the decision regarding surgery. In our case the progressively symptomatic tumour was inoperable. No definitive chemotherapy has been reported for plexiform neurofibromas. Rapamycin, imatinib, sorafenib, interferon are all used in the treatment of plexiform neurofibromas with varying degrees of success.^{10–12}

Research into new chemotherapeutic agents may ultimately lead to more treatment options and higher success rates.¹³ The severity of spinal tumours in this young patient with full-blown clinical NF1 feature calls attention to the variability of NF1 with spinal involvement.

Learning point

- This case illustrates a need for revised clinical classification and genetic characterisation of these patients and families, which could also help understand the molecular alterations underlying spinal tumourigenesis in neurofibromatosis type 1.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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