SHORT REPORT

Familial neurofibromatosis microdeletion syndrome complicated by rhabdomyosarcoma

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Neurofibromatosis type 1 with dysmorphism and developmental delay is reported in a mother and two children. The son required treatment for a prostatic rhabdomyosarcoma. His sister has an optic pathway glioma. Fluorescence in situ hybridisation confirmed a submicroscopic deletion at 17q11.2. New evidence suggests an increased malignancy frequency in microdeletion cases.

Neurofibromatosis type 1 (NF1) is characterised by multiple neurofibromata, café-au-lait patches, axillary freckling, and Lisch nodules. In addition an increased frequency of neoplasia has been described.[1] A wide diversity of mutation types has been identified in the NF1 gene which is thought to act as a tumour suppressor gene.

Rhabdomyosarcoma accounts for two thirds of paediatric soft tissue sarcomas and can arise in the head/neck region, genitourinary tract, or extremities. It is mostly sporadic but can complicate NF1, Beckwith–Wiedemann syndrome, or Li–Fraumeni syndrome.

CASE REPORTS

Case 1 developed neurofibromata at the age of 13 but was not diagnosed with NF1 until she became pregnant at the age of 22. She left school without qualifications. Baby photographs revealed a coarse facial appearance (fig 1A). She had numerous neurofibromata and café-au-lait patches as well as Lisch nodules and some facial dysmorphism but was normocephalic.

Her daughter, case 2, was born at 37 weeks gestation with bilateral talipes. Her gross motor milestones were delayed: she sat at age 12 months and walked at 26 months after bilateral tendon achilles lengthening. She received speech and language therapy as well as one-to-one tuition at school. On examination at age 4½ her growth parameters were occipito-frontal circumference (OFC) 50.5 cm (50th centile), weight 18.1 kg (75th–91st centile), and height 104 cm (25th–50th centile). She had numerous café-au-lait patches, hemihypertrophy of her right upper and lower limbs, and was dysmorphic (fig 1B). Ophthalmological review revealed Lisch nodules, bilateral myopic astigmatism, and good binocular vision. MRI confirmed an optic pathway glioma as well as several unidentified bright objects (UBOs).

Her brother, case 3, was born at term and had mild global developmental delay: he sat at age 8 months and, when first seen at age 15 months, was bottom shuffling but not yet vocalising. His OFC (47 cm) plotted on the 9th centile, with his weight (9.42 kg) between the 9th and 25th centiles, and his height (79 cm) between the 50th and 75th centiles. He had numerous café-au-lait patches, broad thumbs, mild buttock asymmetry, and facially resembled his sister (fig 1C).

At the age of 21 months he presented with a six week history of diarrhoea and vomiting and a seven day history of abdominal swelling and decreased urine output. Obstructive renal failure secondary to a prostatic embryonal rhabdomyosarcoma was diagnosed. He was successfully treated with radio- and chemotherapy. When reviewed at age 4½ he was well with no recurrence, was walking since 25 months of age, and speaking a few single words.

Fluorescence in situ hybridisation (FISH) studies in all three cases revealed a heterozygous microdeletion of their entire NF1 gene.

DISCUSSION

The majority of germline mutations identified in patients with NF1 to date consist of intragenic mutations, which cause truncation or loss of the encoded protein neurofibromin. Microdeletions of the entire NF1 gene have been found to account for 5–10% of all cases. Their breakpoints appear to cluster at flanking repetitive sequences on either side of the NF1 gene. Unequal crossovers and homologous recombination between two ~60 kb duplicons separated by ~1.5 Mb are thought to give rise to the characteristic interstitial microdeletion at 17q11.2.[2]

Compared to patients with intragenic mutations a more severe phenotype is crystallising from the 65 microdeletion cases described in the literature. Learning difficulties are observed in a higher proportion and the early onset and/or excessive burden of cutaneous neurofibromata is remarkable. Characteristic facial dysmorphic features include hypertelorism, down slanting palpebral fissures, ptosis, a small pointed chin, and altogether coarse facial features or a "Noonan-like" face.[2]

Haploinsufficiency of the NF1 gene in combination with contiguous genes may be responsible for this particular phenotype.[3] To date at least 10 genes have been identified which are commonly co-deleted, and it is tempting to speculate whether the characteristic clinical and developmental phenotype of patients with 17q11.2 microdeletions may be caused by dose sensitive genes located in the deleted interval or close to the deletion boundaries that regulate development, organisation, and function of the brain and cellular differentiation.

NF1 associated rhabdomyosarcomata were found to be over represented among children with soft tissue sarcoma from the Manchester Children's Tumour Registry.[4] A population based study estimated rhabdomyosarcomata to occur in 1.5% of NF1 patients.[1] Data from mouse models now suggest that in NF1, rhabdomyosarcomata arise from neural crest cells rather than originating from mesoderm as traditionally believed,[5] implying that they are part of the NF1 neurocristopathy. Inactivation of both NF1 genes and/or TP53 has been shown in NF1 associated malignancies. Several models of tumorigenesis

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Abbreviations: FISH, fluorescence in situ hybridisation; NF1, neurofibromatosis type 1; UBO, unidentified bright object

Figure 1 (A) Case 1, aged 12 months: broad and coarse face with full cheeks and possible hypertelorism. (B) Case 2, age 4½: round and broad face with full cheeks, depressed nasal bridge, anteverted nares and micrognathia; note hypertelorism with left divergent squint. (C) Case 3, aged 15 months: full cheeks, depressed nasal bridge, anteverted nares, micrognathia and epicanthic folds.

suggest that mutations which activate the proto-oncogene ras, such as loss of NF1, cooperate with inactivating mutations of the p53 tumour suppressor gene during malignant transformation. Deletions of the entire NF1 gene have been found to be over represented in the germline of NF1 patients with malignant peripheral nerve sheath tumours.[6] It is currently unclear whether this might be a result of other (as yet unknown) tumour suppressor genes also being constitutionally deleted in these patients or whether the deletion in itself predisposes to a second hit in a second copy of the NF1 gene or another tumour suppressor gene, such as TP53.

Our family adds further evidence towards the existence of a dysmorphic phenotype associated with NF1 microdeletions as well as for the increased malignancy frequency previously suspected in this subgroup.[7] To our knowledge this is the first reported case of a rhabdomyosarcoma in a child with a germline deletion of the entire NF1 gene.

In summary, microdeletions of the entire NF1 gene have been found to account for up to 10% of all NF1 cases. It is important to consider FISH studies in children with NF1 who are facially dysmorphic and have significant learning difficulties, as they may be prone to develop malignancies. Formal screening for malignancies associated with NF1 is currently deemed impractical and unhelpful as there is no evidence that it improves outcome. However, annual clinical review by a paediatrician, including blood pressure measurement as well as parental vigilance, remain paramount.

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