Familial neurofibromatosis type 1 associated with an overgrowth syndrome resembling Weaver syndrome

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Abstract

The simultaneous occurrence of familial neurofibromatosis type 1 (NF1) and an overgrowth syndrome resembling Weaver syndrome was observed in two related cases (a mother and her son). NF1 was confirmed by molecular genetic analysis showing a large deletion at 17q11.2, encompassing the entire NF1 gene. The other symptoms in the two cases were similar to the features reported in Weaver syndrome.

Although the combination of NF1 and an overgrowth syndrome resembling Weaver syndrome in this family may be fortuitous, we favour the hypothesis that the deletion of the entire gene has caused this combined phenotype. Possible pathogenetic mechanisms are discussed. The observation suggests a relation between NF1 with an extraordinarily large gene deletion and a Weaver(-like) syndrome. This warrants investigation for deletions in the 17q11.2 region in Weaver(-like) syndrome patients.

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Key words: neurofibromatosis type 1; entire gene deletion; overgrowth; Weaver syndrome

in a Watson syndrome patient¹⁰ and in a family with features fitting Watson and Noonan syndromes.¹¹ However, no linkage to the NF1 or NF2 loci has been found in families with only Noonan syndrome.¹²⁻¹³ In NF1 patients with mild dysmorphic features, variable mental retardation, exceptionally large numbers of neurofibromas, and very large de novo deletions (>700 kb) including the entire NF1 gene have been described.¹⁴⁻¹⁶ In a recent series of 84 Dutch patients, five complete deletions were found, including three sporadic patients with features confirming the earlier reports.¹⁷ Two other related patients, however, showed a different picture, including overgrowth.

The association of NF1 with an overgrowth syndrome has not been previously reported. In this report we present these latter patients in detail. Detailed molecular genetic data are reported elsewhere.¹⁷

Case reports

Case 1 was the first born child of non-consanguineous parents. Paternal and maternal ages at his birth were 32 and 30 years, respectively. Weight at birth was 3830 g (95th centile) and length was 52 cm (between the 50th and 95th centile). His motor development has always been normal (walking at 15 months) but his parents described him as clumsy. Talking started at 20 months of age. At that age he was referred to the Neurofibromatosis Working Group because the infant welfare centre suspected him to have NF.

Anthropometrics showed height, weight, and head circumference to be at or above the 90th centile (fig 1A, B). He had six café au lait spots of over 5 mm in diameter and no Lisch nodules or neurofibromas. Furthermore, he had a remarkable, coarse face (fig 2A, B) including a broad forehead, hypertelorism, epicanthic folds, prominent philtrum, large ears, and slight micrognathia. Further physical examination showed prominent finger pads and hyperextensible fingers. An x ray of the left wrist showed the osseous maturation to be one year advanced.

At 2 years 2 months of age he developed visual disturbances, which appeared to be caused by a glioma involving both optic nerves and the chiasm. A policy of careful ophthalmological and MRI follow up was adopted and no changes were apparent in the following years. Extensive endocrine studies were undertaken because of the continuing overgrowth. Hormonal studies showed a normal curve for growth

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Neurofibromatosis type 1 (NF1) is a common, autosomal dominantly inherited disorder characterised by café au lait spots, Lisch nodules, and neurofibromas. The NF1 gene has been cloned and maps to chromosome 17q11.2 and is probably a tumour suppressor gene. The protein was named neurofibromin.^{1,2} In 40-50% of cases, NF1 results from a spontaneous mutation.

There are more than 10 clinical syndromes that should be considered in the clinical evaluation of NF1, and numerous other disorders that share at least some features with NF1. For the most part, these conditions are fairly distinct and the differences from NF are relatively obvious.³

Some patients with classical NF1 have, in addition, features of dysmorphic syndromes, such as Noonan syndrome or Watson syndrome.⁴⁻⁸ The overlapping features of Watson syndrome, Noonan syndrome, and NF1 may imply a series of contiguous genes for NF1, vessel anomalies including pulmonary stenosis, and lymphatic abnormalities, and perhaps short stature and macrocephaly.⁹ This was supported by the finding of NF1 mutations

Figure 1 (A) Growth curve for height of case 1. (B) Head circumference curve of case 1. In retrospect overgrowth seems to have started after the first 6 months of life.

hormone although there was an increased reaction of prolactin after the fasting TRH test. The levels of all other investigated hormones, T3, free T4, TSH, somatomedin, prolactin, IGF 1, IGF 2, IGFBP-3, LH, FSH, and testosterone, were normal. He had a normal male karyotype (46,XY); molecular studies showed no signs of fragile X syndrome.

Figure 2 (A, B) Remarkable coarse face of case 1 at the age of 2 years. (All photographs reproduced with permission.)

Figure 3 Face of case 1 at the age of 5 years.

In subsequent years moderate psychomotor retardation and behavioural problems became apparent. There was a further growth acceleration and the skeletal age became even more advanced (at the age of 4 years his bone age was 7 years). He developed axillary freckling and neurofibromas on the upper limbs. No Lisch nodules have been detected as yet. His face has become longer and less distinctive (fig 3).

Case 2 was the mother of case 1. A diagnosis of NF1 was made by a dermatologist at 31 years of age based on multiple café au lait spots and numerous neurofibromas. Remarkably, in early reports by her general practitioner, she was described as a girl with "gargoylism" (M Hurler). A conspicuously coarse face and tall stature were also evident on young photographs (fig 4A, B). She had an operation for an umbilical hernia at 1 year of age. At the age of 4½ years she was said to have had a normal skeletal age. Unfortunately these x rays were no longer available. Menarche took place at the age of 14 years. No further details have been available about her growth curve. She has had mild learning problems. At the time of investigation she had a normal height of 1.76 m (90th centile), a weight of 74 kg (90th centile), and a head circumference of 59.5 cm (98th centile). Her NF1 features consisted of café au lait spots, more than 200 neurofibromas, Lisch nodules, and freckling (fig 5). An MRI showed no cranial abnormalities and no optic pathway glioma. Numerous subcutaneous neurofibromas were also seen around the carotid artery sheath. By history, there were no other family members affected with NF1. Unfortunately the parents of case 2 were not available for further investigations.

Figure 4 (A, B) Photographs of case 2 at a young age (exact age not known).

MOLECULAR GENETIC STUDIES

Molecular genetic studies were performed in both cases with intragenic polymorphic markers and Southern analysis, as described in detail elsewhere.¹⁵ Both cases had a large deletion of approximately 700 kb, including the whole NF1 gene between marker D17S117 (VAW212R2i) and cDNA probe GE2 situated on the centromeric side of the NF1 gene, and between D17S115 (VAW210M1) and cDNA probe B3A situated on the telomeric side of the NF1 gene.

Discussion

The diagnosis of NF1 is obvious as the international diagnostic criteria are fulfilled in both cases.¹⁸ Case 1 had more than six café au lait spots, freckling, optic pathway glioma, and several neurofibromas; case 2 had café au lait spots, Lisch nodules, freckling, and numerous neurofibromas. In both cases the diagnosis of NF1 was confirmed by the molecular genetic results showing a large deletion at 17q11.2, encompassing the entire NF1 gene.

Case 1 shows many features of an overgrowth syndrome and some of these features are also present in case 2. Although the boy in our report had an optic pathway glioma involv-

Figure 5 Face of case 2 as an adult.

ing the chiasm, which could cause hormonal disturbances of hypophyseal functions, we have been unable to find any evidence for such a relationship.

In general, classification of overgrowth syndromes is difficult because of the lack of hard diagnostic criteria.^{19,20} In a recent review of Sotos syndrome and Weaver syndrome, it was stated that the main method to establish a diagnosis is evaluation (of photographs) of the "facial gestalt" between 1 and 6 years of age.^{21,22}

In the present family, the face of case 1 shows a strong resemblance to the craniofacial features reported in Weaver syndrome, and a photograph from childhood of case 2 shows this as well: ocular hypertelorism, epicanthic folds, large ears, long philtrum, and slight micrognathia. Other features often reported in patients with Weaver syndrome and present in this family were developmental delay, prominent fingerpads, and an umbilical hernia (in case 2). Case 1 had no widening of the metaphyses. Although this is reported in most cases of Weaver syndrome, it is not an obligatory feature.^{21,23} A comparison of the present cases with the major features in Weaver syndrome is shown in table 1.^{20,24}

Other overgrowth syndromes such as Simpson-Golabi-Behmel syndrome and Perlman syndrome can be reliably ruled out, particularly by their differing facial phenotypes and the absence of internal abnormalities in the present patients.^{21,25}

Endocrinological investigations have been normal in most cases with Weaver syndrome. Acquired hypothyroidism, however, has been reported in one case,²⁶ and in a familial case of Weaver syndrome the son had a low basal and stimulated human growth hormone level and the affected mother had hyperprolactinaemia.²⁷

Table 1 Major features of 39 published patients with Weaver syndrome^{19,23} compared with present cases. Only features occurring in at least 75% of cases are included

	Percentage	Case 1	Case 2
Excessive growth postnatally	92	+	+
Performance motor delay	95	+	?
Hoarse and low pitched cry	90	-	?
Developmental delay or mental retardation	80	+	±
Craniofacial			
Micrognathia	97	+	+
Ocular hypertelorism	97	+	+
Large ears	96	+	+
Increased bifrontal diameter	96	+	+
Telecanthus	96	-	-
Long and prominent philtrum	82	+	+
Macrocephaly	79	+	+
Extremities			
Prominent finger pads	93	+	?
Hyperextensibility of fingers	80	+	?
Deep set or narrow nails	77	-	?
Limited extension of joints	79	-	?
Skeleton			
Increased carpal bone age	95	+	(-)
Flared metaphyses	88	-	?
Advanced general osseous maturation	82	+	?
Others			
Umbilical hernia	84	-	+
Excessive and loose skin	94	-	?
Inguinal hernias	90	-	-

The slightly raised fasting prolactin response found in case 1 may have been induced by stress, but may also be because of TRH testing or hypothalamic dysfunction.

In our opinion, Weaver syndrome is a possible diagnosis in case 1, although it cannot be excluded that several features, such as the macrocephaly and hypertelorism,²⁸ are part of the spectrum of NF1, and in the absence of a diagnostic marker the diagnosis of Weaver syndrome remains a tentative one.

The cause of Weaver syndrome is unclear. Males are reported to be affected twice as frequently as females. Affected males with mild expression of the syndrome in their mothers have been described repeatedly.^{23,27,29,30} This is most compatible with autosomal dominant inheritance with sex limited expression or X linked recessive inheritance. Male to male transmission has not been reported so far. However, most cases have been sporadic.

Autosomal recessive inheritance has also been suggested,³¹⁻³³ but the patients reported by Teebi *et al*³³ almost certainly do not have Weaver syndrome,²¹ the patient reported by Roussounis and Crawford³¹ has been shown to have a chromosome anomaly (46,XX,5p-), and the data in the paper by Jalaquier *et al*³² are insufficient to allow a conclusion of autosomal recessive inheritance.

The combination of NF1 with Weaver-like syndrome in two related patients may be a chance finding without a causal relationship. Another, admittedly speculative, explanation may be that the deletion at 17q11.2 has influenced the functional activity of an unknown growth factor. In this respect it should be noted that a de novo nonsense mutation in the NF1 gene was found in a patient with another entity showing overgrowth features, that is, encephalocraniocutaneous lipomatosis.³⁴ Furthermore, other overgrowth syndromes, such as Simpson-Golabi-Behmel syndrome and Beckwith-Wiedeman syndrome

involving different genes on Xq26 and 11p15 respectively, both followed the same (IGF2) pathway.³⁵ Hence further studies of the IGF2 pathway in the present patients may be useful.

A third explanation is the potential disruption of another gene close to the NF1 gene causing the overgrowth. In combination with NF1, this would then constitute a contiguous gene syndrome. It remains difficult to explain why other reported patients with a deletion of similar magnitude have not shown symptoms of an overgrowth syndrome, although Wu *et al*³⁶ reported a father and son both carrying an entire NF1 gene deletion who had, apart from earlier reported clinical characteristics of this large NF1 deletion, large hands and feet. The epigenetic influence(s) of modifying genes³⁷ or exogenous factors may be important to both explanations. Besides this, the genomic rearrangements could have caused position effect phenomena.³⁸ The observations do suggest the existence of a relationship between NF1 with an extraordinarily large deletion and Weaver syndrome, which warrants investigation for deletions in the 17q11.2 region in Weaver syndrome patients.

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