Ophthalmological manifestations in segmental neurofibromatosis type 1


Aims: To study the ophthalmological manifestations in individuals with the typical features of neurofibromatosis type 1 (NF1) circumscribed to one or more body segments, usually referred to as segmental NF1.

Methods: Visual acuity and colour tests, visual field examination, slit lamp biomicroscopy of the anterior segment, and a detailed examination of the retina by indirect ophthalmoscopy were performed at diagnosis and follow up in 72 consecutive subjects (29 males, 43 females; aged 1–64 years; mean age 14.6 years) seen at the university departments of paediatrics in Catania and Rome, Italy, during years 1990–2003, who had in restricted body areas: (1) typical pigmented manifestations of NF1 (café au lait spots and freckling) only (n = 48); (2) NF1 pigmented manifestations and neurofibromas alone (n = 2); (3) neurofibromas only (n = 15); and (4) plexiform neurofibromas only (n = 7).

Results: None of the 72 patients had Lisch nodules in the iris irrespective of age at eye examination or hypertelorism (a “minor” NF1 feature) and none developed typical associated ophthalmological NF1 complications. An additional child had an isolated optic pathways glioma (OPG), which behaved both biologically and radiographically as an NF1 associated OPG.

Conclusions: This represents the first systematic study reporting on eye involvement in the largest series of individuals at different ages having segmental NF1. As one of the postulated mechanisms to explain segmental NF1 is somatic mosaicism for the NF1 gene (so far demonstrated only in two patients) the present findings could be explained either by the fact that the eye is too far from the mutated area with NF1 lesions in most cases or by the NF1 (or other “predisposing” or “cooperating”) gene mutation restricted to too few cellular clones or to tissues embryologically different from the eye.

It is increasingly recognised that the clinical features of many genetic conditions may sometimes become manifest in a mosaic (segmental) form, involving the body in a linear, patchy or otherwise circumscribed arrangement or in localised regions or organs.1,4

In the most common form of neurofibromatosis, neurofibromatosis type 1 (NF1), patients with the typical disease features limited to one or more body segments are usually referred to as having segmental (localised) NF1 as opposed to the full blown (generalised) phenotype.3,4 Likewise, patients with unilateral features of neurofibromatosis type 2 (NF2) (for example, unilateral vestibular schwannoma accompanied by other ipsilateral tumours) have been reported as having segmental NF2.7,8

Segmental NF1 has been widely reported with increasing frequency5–14 and is probably underdiagnosed because the clinical picture, as a result of limited signs or symptoms in most of the affected individuals, can be neglected by the patient himself and passes unnoticed by the physician.

From a genetic viewpoint, the so far demonstrated mechanism to explain the localised manifestations of the neurofibromatoses is somatic mosaicism for the NF117–18 or NF2 genes.7,8 Putatively, the clinical presentation depends on the timing of the mutational event in development. When the mutation occurs very early—before tissue differentiation—the clinical phenotype would be generalised; the later a mutation occurs in development the more the phenotype will be confined to a single region or organ.3,14,20

In order to better define the clinical phenotype of individuals having localised manifestations of NF1 and to determine if the eye or limited regions of the eye are involved we studied the ophthalmological manifestations in a cohort of 72 consecutive individuals with segmental NF1 ascertained through the neurofibromatoses clinics in Catania and Rome, Italy followed up from 1990 to 2003.

SUBJECTS AND METHODS

The neurofibromatoses clinics at the departments of paediatrics of the universities of Catania (southern Italy) and Rome (central Italy) were established in 1990 and 1998, respectively, as consultation services primarily to assist in the diagnosis and management of the different forms of neurofibromatosis in children. Children (and also adults), have been referred to the clinic by paediatricians and adult physicians, geneticists, dermatologists, ophthalmologists, neurologists, general practitioners, and through the local and national neurofibromatosis associations because of: (1) a form of neurofibromatosis suspected as a result of presence of pigmentary lesions, cutaneous or subcutaneous nodules, or specific problems related to neurofibromatosis; (2) a previous diagnosis of NF1, NF2 or other forms of neurofibromatosis; (3) a first degree relative affected by neurofibromatosis. The clinics cater for families with neurofibromatosis primarily from the eastern provinces of Sicily (population of approximately 2.6 million inhabitants out of the six million inhabitants of the region Sicily) and the region of Rome (populations of approximately 2.9 million inhabitants), with additional referrals from other Italian regions.

From January 1990 to December 2003, 730 individuals from 412 families were evaluated at these clinics, of whom 600 had been referred and fully assessed for specific concerns regarding a suspect NF1. Overall, 388 out of the 600 had NF1 according to the NIH criteria19 revised25 (218 males, 170 females).
In the clinics from January 1990. Patients referred and/or seen or already being followed up before 1990 were enrolled according to the criteria reported elsewhere (see also listed features under Results and table 1). Patients referred and/or seen or already being followed up before 1990 were enrolled in the study formal consent was obtained by parents or legal tutors of children and/or by patients themselves.

The following features were specifically searched for at clinical and/or ophthalmological examination: congenital small orbit, plexiform neurofibromas of the orbit, hypertelorism, eyelid and/or periorbital café au lait spots or freckling, eyelid cutaneous, nodular or plexiform neurofibromas, congenital ptosis, exophthalmos or buphthalmos, prominent corneal nerves, Lisch nodules in the iris, congenital or acquired glaucoma, choroidal hamartomas, dilated vessels and any retinal anomaly suggestive of optic nerve pathology.

**DNA analysis**

DNA from all the segmental NF1 subjects was extracted from peripheral blood leucocytes. Genomic DNA was isolated from total blood samples using standard protocols. For polymerase chain reaction amplification of the 60 exons of the NF1 gene published primers were used and analysed by means of DHPLC analysis and DNA sequencing by AG.

**RESULTS**

The localised NF1 manifestations in our study group fell into three main clinical subgroups: (1) pigmentation anomalies (café au lait spots and freckling) with (fig 1A) or without neurofibromas (n = 50); (2) (dermal and/or nodular) neurofibromas only (n = 15) (fig 1B); and (3) plexiform neurofibromas only (n = 7).

Clinical and ophthalmological examination of the probands revealed no NF1 pigmentary lesions (café au lait spots and/or freckling) or neurofibromas in the periorbital region or the eyelids. In the 15 patients who had neurofibromas only these were restricted to specific body areas (see table 1). Seven patients had plexiform neurofibromas as their only NF1 manifestations localised either under the scalp of the temporal or occipital regions (n = 3) sparing the skull bone including the orbit as revealed by computed tomography (CT) and magnetic resonance imaging (MRI) of the head or the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical features and inclusion criteria for the study</th>
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<tr>
<td>Inclusion criteria</td>
<td>No of cases</td>
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<tr>
<td>Café au lait spots and freckling only</td>
<td>48</td>
</tr>
<tr>
<td>Café au lait spots and freckling only (+ hyperpigmented background in involved area)</td>
<td>15</td>
</tr>
<tr>
<td>Café au lait spots and freckling only (Chest region (skin))</td>
<td>5/15</td>
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<tr>
<td>Café au lait spots and freckling only (Chest region (major thoracic nerves))</td>
<td>3/15</td>
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<tr>
<td>Café au lait spots and freckling only (Abdominal region (skin))</td>
<td>4/15</td>
</tr>
<tr>
<td>Café au lait spots and freckling only (Limbs (skin + major nerves))</td>
<td>3/15</td>
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<tr>
<td>Café au lait spots and freckling only (Café au lait spots and freckling only + neurofibromas)</td>
<td>2</td>
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<tr>
<td>Café au lait spots and freckling only (+ hyperpigmented background in involved area)</td>
<td>7</td>
</tr>
<tr>
<td>Café au lait spots and freckling only (Plexiform neurofibromas only)</td>
<td>7</td>
</tr>
<tr>
<td>Café au lait spots and freckling only (Scalp temporal/occipital region)</td>
<td>3/7</td>
</tr>
<tr>
<td>Café au lait spots and freckling only (Abdominal region)</td>
<td>2/7</td>
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<tr>
<td>Café au lait spots and freckling only (Pelvic region)</td>
<td>2/7</td>
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*1 woman also had an NF1 complication (that is, plexiform neurofibroma) (see fig 1A).
NF1 features in a restricted area varying from one segment to one half of the body or more than one involved segment of the body on both sides of the midline either in a symmetrical or asymmetrical arrangement. What is important to understand is that segmental NF1 should not be regarded as a separate form of neurofibromatosis but as a localised phenotype of NF1.

Age at presentation of NF1 lesions in this series varied according to the presence of pigmentation anomalies only (birth to 2 years of age) or neurofibromas alone (from around puberty to young adulthood). Affected individuals manifested their NF1 features in exactly the same way as when they occur in the full blown disease. Despite that, none of the patients in this study group had typical NF1 ophthalmological manifestations, including eye complications, regardless of age at examination. It was of interest that the age spanning of this series included the ages most at risk for manifesting the typical NF1 ophthalmological features (for example, Lisch nodules) or NF1 ophthalmological complications (for example, orbital or intracranial plexiform neurofibromas associated or not with dysplasia of greater wing of sphenoid (1–2 years of age) and optic pathway gliomas (4–9 years of age)). Despite this age span and the relatively long follow up in this group and the full screening protocol by means of eye ultrasound and head MRI performed in some children in this group, we could not find any typical NF1 ophthalmological complications. Furthermore, most of these patients were at the age of having already developed the major pigmentary lesions of the disease and therefore the lack of café au lait spots and/or Freckling in (restricted areas of) the eyelid and the orbit were also significant.

Lisch nodules were not encountered in the present series regardless of age at eye examination. Lisch nodules have been reported in isolated cases—when the eye was specifically searched for—in previous segmental NF1 series and were not always unilateral or ipsilateral to the side of NF1 manifestations (reviewed in Huson and Ruggieri and Ruggieri and Huson). Although it is difficult to find a reasonable explanation for these phenomena it can be postulated that this probably occurs because the eye is too far from the mutated area with NF1 lesions in most cases or because the NF1 (or other “predisposing” or “cooperating” gene) mutation affects tissues or clones different from the eye. Notably, however, patients with manifestations of NF1 restricted to the face only reported in previous studies (for example, patients having either plexiform neurofibromas or cutaneous and/or nodular neurofibromas of the orbital region or the face as their only NF1 manifestations) had no Lisch nodules regardless of age at eye examination. There are also two families (Tenconi R, personal communication, 1996 and Riccardi and Lewis) with parents having unilateral or bilateral Lisch nodules (that is, only one major diagnostic criterion for NF1) whose sons had generalised NF1. One may question the specificity of iris nodules in NF1 as these may be seen in the full blown disease. Despite that, none of the patients in this study group had typical NF1 ophthalmological features limited to restricted body areas or specific organs or parts of organs (including, or not, the gonads).

Previous cases of typical NF1 ophthalmological complications in the setting of segmental NF1 have been reported in the literature—optic pathway gliomas or orbital plexiform

**DISCUSSION**

The calculated prevalence of segmental NF1 in the general population is one in 36 000–40 000 individuals, or 0.0027%. Clinically, affected patients manifest their NF1 features in a restricted area varying from one segment to one half of the body or more than one involved segment of the body on both sides of the midline either in a symmetrical or asymmetrical arrangement. What is important to understand is that segmental NF1 should not be regarded as a separate form of neurofibromatosis but as a localised phenotype of NF1.

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**Figure 2**  Brain axial T1 weighted (TR, 450; TE, 40) magnetic resonance images shows distortion of the normal architecture and enlargement of both optic nerves and the chiasm with enlarged periopitic spaces in this 9 year old boy who had no other NF1 stigmata.
neurofibromas (reviewed in Huson and Ruggieri1 and Ruggieri and Huson11). Segmental NF1 cases with plexiform neurofibromas of the orbit or the eyelid as their only NF1 manifestations have been also reported.3 14 Whatever figures we take for prevalence of NF1 complications in segmental NF1—including eye involvement—this is certainly much lower (around 7% in the literature)13 than in the generalised disease. A possible explanation for this phenomenon could be that the NF1 gene mutation is restricted to too few cellular clones in most of these patients.12 20

In this study one additional child had an isolated optic pathway tumour, which behaved both biologically and radiographically as a typical NF1 associated tumour. Other authors15 20 have recorded similar findings. Even though there has been a considerable debate on whether the clinical and radiological manifestations and natural history of OPGs associated with NF1 differ from those of sporadic tumours there are some distinguishing characteristics of NF1 OPGs compared to non-OPGs15 16 26 27: (1) initial signs in NF1 OPGs are usually proptosis, precocious puberty, and decreased visual acuity (the latter as in the present case) vs increased intracranial pressure/ hydrocephalus, nystagmus, and strabismus in non-NF1 OPGs; (2) in NF1 OPGs the tumour location is common in the intraorbital optic nerve (as in the present case), multicentric, and usually chiasmatic vs a rarer location in the intraorbital optic nerve, a unicentric origin usually confined to the optic tract and/or chiasmat in the non-NF1 OPGs; and (3) tumour growth during follow up is uncommon in NF1 associated OPGs (like in this child) vs a common (and often rapid) growth during follow up in non-NF1 OPGs. Thus, even though we did not include this child in the series of segmental NF1 patients we reported it in the study as one might theoretically postulate that the isolated OPG (behaving as the typical NF1 tumour) could be a localised form of NF1.13 14 Other authors (RJ Packer, personal communication, November 2003 and Listernick et al28) have drawn similar conclusions. Notably, cases of isolated long bone dysplasia behaving clinically and radiographically as a typical NF1 associated dysplasia have been reported in association with localised pigmentary features of NF1.14 18

What is important to understand is that all the clinical and molecular data in this study seem to be compatible with a pathogenic mechanism different from the most commonly postulated explanation for segmental NF1: mosaicism for a NF1 gene mutation.14 15 17 18 We could find no NF1 gene mutation in blood DNA in the 72 cases analysed and no ocular NF1 abnormalities were seen. Many laboratories have analysed peripheral blood samples and biopsy specimens taken from affected and unaffected skin areas in a large number of cases with segmental NF1 so far14 15 20 and only two reports have shown NF1 gene mutations in a mosaic pattern.17 18 By taking together these data we might hypothesise that segmental NF1 could be a heterogeneous condition in which only in very exceptional cases mosaicism for a NF1 gene mutation has been found. Thus, the mechanism in the majority of cases might be different. Similar findings have been shown in another localised form (likely a third major form)19 20 of neurofibromatosis—multiple schwannomatosis (a recently recognised disorder defined as the occurrence of multiple pathologically proved schwannomas without vestibular tumours diagnostic of NF2); only in a minority of cases does multiple schwannomatosis result from mosaicism of a NF2 gene mutation; in the majority of cases the primary genetic defect is linked to a region on chromosome 22 different from NF2, that predisposes or cooperates with somatic (acquired) mutations in the NF2 gene in Schwann cells.10 13 15

From a genetic counselling viewpoint is of interest that there are a handful of familial cases in the literature where parents with localised manifestations of NF1 had children either with full blown5 14 15 37 or with localised disease.15 34 At present there are no means to exclude, in a given individual with localised manifestations of NF1, involvement of both somatic and gonadal tissue29 and, therefore, the exact level of risk is not definable with current knowledge. Studies of pigmentary anomalies in chimeric mice suggest the degree of gonadal involvement might be proportional to the area of skin involved.4 14 40 However, even though the segment of the body affected is distant from the gonads, there can be gonadal involvement with the chance of transmitting the full blown or segmental disease to offspring. Therefore, the presence or lack of Lisch nodules in the setting of segmental NF1 (and we would add in any case)20 should not be considered a predictor for transmission of NF1 to offspring.

In conclusion, even though ocular manifestations of NF1, including Lisch nodules and NF1 ophthalmological complications, have been reported in previous isolated cases of segmental NF1 we could not confirm these findings in the present systematic study. Whatever figures we take, this means that eye involvement is much less frequent than expected in patients with generalised disease and, therefore, close ophthalmological monitoring in the setting of segmental NF1 could be unnecessary. Furthermore, as the risk of typical NF1 eye complications in segmental NF1 is extremely low the use of neuroimaging screening may no longer be warranted.

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