## 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 pigmentary manifestations of NF1 (cafe au lait spots and freckling) only \(n=48\); (2) NF1 pigmentary 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.

**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 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.

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.

**Abbreviations:** NF1, neurofibromatosis type 1; OPG, optic pathways glioma
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). These were screened at first referral, including all their available first degree relatives, by skin, Wood’s lamp, full ophthalmological evaluation, and general and neurological examination. Diagnosis of segmental NF1 was made with Humphrey perimeter were performed. The full protocol 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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<tbody>
<tr>
<td>Inclusion criteria</td>
<td>No of cases</td>
</tr>
<tr>
<td>Cafe au lait spots and freckling only</td>
<td>48</td>
</tr>
<tr>
<td>Neurofibromas only</td>
<td>15</td>
</tr>
<tr>
<td>Chest region (skin)</td>
<td>5/15</td>
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<tr>
<td>Chest region (major thoracic nerves)</td>
<td>3/15</td>
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<tr>
<td>Abdominal region (skin)</td>
<td>4/15</td>
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<tr>
<td>Limbs (skin + major nerves)</td>
<td>3/15</td>
</tr>
<tr>
<td>Cafe au lait spots and freckling + neurofibromas</td>
<td>2*</td>
</tr>
<tr>
<td>Plexiform neurofibromas only</td>
<td>7</td>
</tr>
<tr>
<td>Scalp temporal/occipital region</td>
<td>3/7</td>
</tr>
<tr>
<td>Abdominal region</td>
<td>2/7</td>
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<tr>
<td>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). |

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 (cafe 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 participants revealed no NF1 pigmentary lesions (cafe 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
abdominal (n = 2) and pelvic regions (n = 2). We did not observe ptosis, exophthalmos, or buphthalmos at any stage of our diagnostic examination and at follow up. Lisch nodules were absent in probands and their relatives. Five parents (two fathers, three mothers) had dark brown naevi localised in the iris.

Funduscopy revealed no anomalies in the probands examined. Notably, out of the 72 patients 15 children (aged 3–11 years, average 7 years 4 months) and five adults (aged 35 and 67 years) with localised manifestations of NF1 were initially suspected—elsewhere in Italy—as having full blown NF1 and were enrolled in the full NF1 screening protocol used before 1995 in Italy which included, besides clinical and ophthalmological examination, heart and abdominal ultrasound, electroencephalographic examination (EEG), and brain MRI. These investigations all gave normal results. Three further children in this series after being diagnosed as having segmental NF1 had either episodes of waxing and waning vertigo or acute headache and were admitted to wards where a brain MRI scan was performed yielding normal results.

A 9 year old child was referred to the department in Catania at age 4 for progressive visual acuity deficits. Upon general examination at first referral he had no pigmented or nodular lesions and his general examination was normal. Weight, length and head circumference were at the 50th percentile. Neurological examination revealed an alert boy of normal intelligence. Visual acuity was 6/10 in the right eye and 8/10 in the left eye. The Farnsworth 100 colour test and the computerised visual field evaluation with Humphrey perimeter revealed a yellow-blue defect in both eyes. Funduscopy showed enlarged retinal vessels with a grade 1 papilloedema. T1 weighted images at MRI of the 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 peri optic spaces in this 9 year old boy who had no other NF1 stigmata.

The eye in segmental NF1

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 peri optic spaces in this 9 year old boy who had no other NF1 stigmata.

In the last MRI control (at age 9 years). and the MRI lesions remained stable with mild involution at his last MRI control (at age 9 years).

No NF1 gene deletions, mutations, or microlesions have been detected so far.

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.

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 both optic 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 (even though rarely) occur in individuals who do not have neurofibromatosis (or at least do not have additional evidence of neurofibromatosis). However, though not pathognomonic for neurofibromatosis, iris nodules occur predominantly in individuals with NF1 (90–100% of adults with NF1). Therefore, it might be assumed that individuals with isolated iris nodules and offspring with NF1 (or people with localised features of NF1 and Lisch nodules) may have NF1 (or other “predisposing” or “cooperating”) gene mutations 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
neurofibromas (reviewed in Huson and Ruggieri1 and Ruggieri and Huson4). Segmental NF1 cases with plexiform neurofibromas of the orbit or the eyelid as their only NF1 manifestations have been also reported.3 4 Whatever figures we take for prevalence of NF1 complications in segmental NF1—including eye involvement—which is certainly much lower (around 7% in the literature)14 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.17 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 authors16 17 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-OPGs: (1) initial signs in NF1 OPGs are usually proptosis, precocious puberty, and decreased visual acuity (the latter as in the present case)17 v 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 v a rarer location in the intraorbital optic nerve, a unicentric origin usually confined to the optic tract and/or chiasmatic in the non-NF1 OPGs; and (3) tumour growth during follow up is uncommon in NF1 associated OPGs (like in this child) v 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 NF1.1 14 Other authors (RJ Packer, personal communication, November 2003 and Listernick et al20) have drawn similar conclusions. Notably, cases of isolated bone dysplasia behaving clinically and radiographically as a typical NF1 associated dysplasia have been reported in association with localised pigmented features of NF1.14 15

What is important to understand is that all the clinical and molecular data in this study seem to be compatible with a pathogenetic mechanism different from the most commonly postulated explanation for segmental NF1: mosaicism for a NF1 gene mutation.1 14 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 17 20 and only two reports have shown NF1 gene mutations in a mosaic pattern.17 20 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 pattern.17 20 The diagnostic evaluation and management of neurofibromatosis 1 and neurofibromatosis 2. Am J Med Genet 1999;86:351–4.


