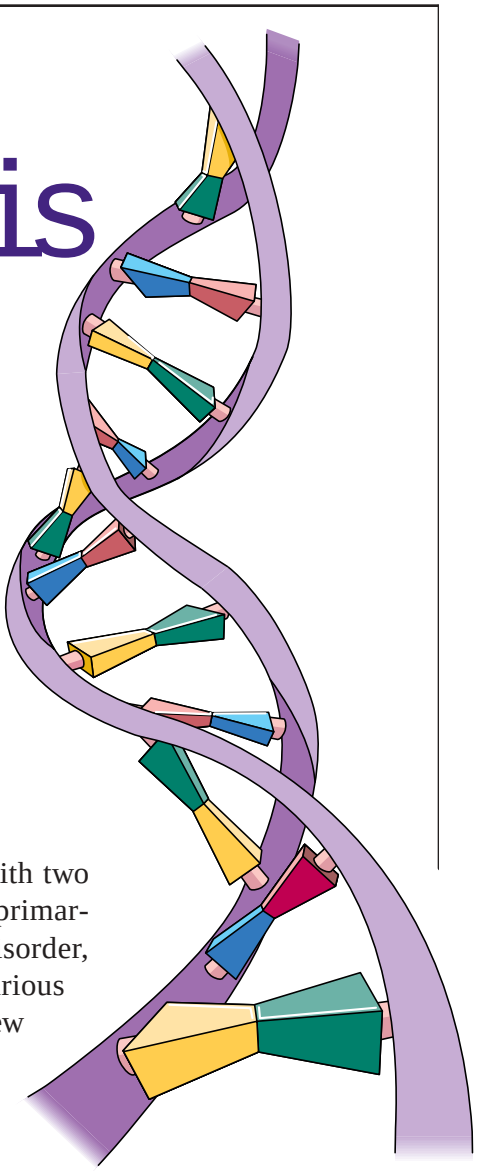
Neurofibromatosis Type I in Childhood



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There are two types of neurofibromatosis (NF) which represent with two distinct disorders housed on separate chromosomes. This article primarily reviews the childhood perspective on NF Type I, a multisystem disorder, and addresses the genetics, diagnosis and clinical spectrum in various stages of childhood. Also featured in this article is a review of the new basic science research that is leading us closer to an understanding of this rather mysterious genetic disorder.

How do you distinguish NF I from NF II and can they ever overlap?

Gene cloning and recent mutation analysis have clarified the classification of the "neurofibromatoses" significantly. All the clinical subtypes of NF proposed over the years ultimately map to either the NF I or NF II regions, and are variants of the same two basic genetic entities.[1] Both are autosomal dominant disorders with very high penetrance, *i.e.*, the gene almost always expresses itself once present. NF II gives quite a constant clinical picture, while NF I has extremely variable expressivity, even among members of the same family. NF I is by far more common, with a disease prevalence of approximately one in 3,700 as compared to one in 20,000 for NF II. A multisystem disorder, affecting primarily the skin, nervous and musculoskeletal systems, NF I maps to chromosome 17. NF II, on chromosome 21, is generally limited to the nervous system (acoustic neuromas, other central nervous system(CNS) tumors). NF I manifestations begin in childhood while NF II

Table 1

NIH Diagnostic Criteria (1984)

% Adults	Two or more of the following
98%	• CAL macules (≥ 0.5 mm prepubertal, ≤ 15 mm post pubertal)
88%/ 40%	• Axillary/Inguinal freckling
95%	• ≥ 2 neurofibromas (any type) or 1 plexiform
20%	• Optic chiasma glioma
≤ 100%	• ≥ 2 Lisch nodules •Distinctive osseous lesion (sphenoid dysplasia or thinning of long bone cortex ± bowing/pseudoarthrosis) • Positive family history in first degree relative (parent, sibling, offspring)

affects primarily adults and rarely adolescents. The only clinical overlap of NF I and NF II is their shared propensity for tumor formation in the nervous system. Apart from this similarity, they are two very different clinical entities which breed true within a family pedigree.

What is known about the NF I gene product, and its role in creating the clinical expression of NF I?

The large NF I gene (335 kb genomic DNA) encodes neurofibromin, which is a guanosine triphosphate (GTP) activating protein (GAP) for members of the Ras oncogene family. Neurofibromin essentially plays a tumor suppressor role. It down regulates Ras activity by promoting the removal of a phosphate group, favoring the conversion of active Ras GTP to inactive Ras guanosine diphosphate (GDP).[2] The highest levels of neurofibromin in body tissues are found in nervous system cells, explaining their propensity for tumor formation in NF I. Neurofibromin also seems to have other regulatory functions guiding the development of normal structure and function in CNS cells (especially Schwann cells). Elucidation of errors in these regulatory functions may ultimately explain much of the dysplastic development and disordered architecture that occurs in NF I.

What is the most reliable way to diagnose NF I at the present time? Is there a simple blood test now that the gene is known?

The gold standard for diagnosis remains clinical – the NIH criteria established in 1984. Two or more of these criteria are necessary for confirmation of NF I. (Table 1). Café au lait (CAL) spots are the most frequent and the ear-

liest findings, appearing generally by age one to two years. A Wood's Lamp Exam is essential in their identification, as they may be unapparent to the naked eye. Up to three CAL macules of any size fall within the range of normal, while six or more are diagnostic of NF I, with a "gray zone" in between. Both skinfold freckling and neurofibromas are rarely apparent before early school age. Lisch nodules are asymptomatic iris hamartomas diagnosed by slit lamp, and require a certain expertise to distinguish them from simple iris freckles. They appear gradually with time to achieve a frequency of roughly 99% of NF patients by age 20 years. As such, Lisch nodules are an invaluable tool in

parental screening for recurrence risk counseling, but not a very useful criterion for diagnosis in childhood.

Active collaborative research worldwide over the past ten years has led to major advances in DNA testing for NF I. Unfortunately, for the most part, mutation analysis is still a costly and cumbersome test, due to the large size of the NF gene and lack of mutation clustering ("hot spots"). Half of NF I cases are attributed to new, spontaneous mutations. Over 100 mutations have been characterized, but genotype – phenotype correlations remain unclear. In most centres, mutation screening is still not routine, but reserved for situations of atypical presentation or planned prenatal diagnosis.

The protein truncation test (PTT)[3] is a more rapid and simple assay, dependent on the principle that 75% of NF mutations lead to a truncated (shortened) protein product. This test is useful as an initial screen in situations where time is crucial (*i.e.*, "rush" prenatal diagnosis) since its specificity is excellent. The combination of PTT and DNA sequencing identifies roughly 95% of NF mutations. The ultimate goal is further simplification of DNA sequencing so it can serve as an accessible screening test on a more routine basis.

Since many young children will not satisfy the NIH criteria in the strictest sense, what can parents be told about diagnosis?

Practically speaking, the higher the number of classic CAL macules over six, the more likely the diagnosis of NF I, as the differential diagnosis of multiple CAL spots is narrow. Generally, parents can be told that NF I is most likely to be the diagnosis, and the child should be managed as if NF I had been confirmed. There are certain additional minor features which are reliable predictors of future diagnostic confirmation of NF I.[4] These features include macrocephaly, hypertelorism (widely-spaced eyes), short stature and thoracic deformity (pectus excavatum or carinatum). The latter two features are especially suggestive of NF I, but any of these four findings would highly increase one's index of suspicion.

Why is the preschool period so critical for patients with NF I?

Many of the important childhood complications of NF I can be picked up in the preschool years by a watchful well-trained eye. Furthermore, if a child with NF “escapes” this period without the onset of these complications, the child is less likely to present serious morbidity through the rest of childhood. Most of the serious childhood sequelae are felt to be congenital in origin. As such, lesions with aggressive growth potential will generally be clinically evident by age five to six years. Those with a slower growth potential grow more indolently, if at all, and pose much less of a

Table 2

Neurofibromatosis Organizations

The National Neurofibromatosis Foundation, Inc.
95 Pine Street, 16th Floor, New York, NY 10005
www.nf.org
E-mail: nnff@nf.org
Toll free 800-323-7938

Association de Neurofibromatose du Québec (ANQ)
9206, rue Joseph-Mélançon
Montréal, Québec H2M 2H8
Tel. (514) 385-6702

Neurofibromatosis Society of Ontario (NFSO)
923 Annes St.
Whitby, Ontario L3V 5K7
E-mail: nfso@direct.com

British Columbia NF (BCNF)
1562 Fort St.
Victoria, B.C. V8S 5J2
Tel. 1-800-385-2263
FAX: 250-370-7598
E-mail: bcnf.@pacificoast.net

Contact person in Saskatchewan:
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threat of long-term morbidity. During the preschool period, efforts should be made to screen for the following complications: Plexiform neurofibromas (PN); optic gliomas; tibial dysplasia/pseudoarthrosis; and developmental delay.

PN are congenital lesions involving multiple branches of a large nerve and occur in 20% to 25% of patients. These lesions may begin as simply a very large area of hyperpigmentation/hypertrichosis/portwine stain or a subtle soft tissue asymmetry.[5] Gradually, thickening/swelling of the area becomes apparent. Despite their benign histology, they can be very locally invasive and difficult to resect — recurrence rates postoperatively are in the range of 50%. Fortunately, not all PN have such an aggressive growth pattern. PN may be associated with deep organ penetration or underlying bony dysplasia, especially when located over the spine or on the face. A 5% to 10% chance of malignant degeneration exists, primarily in the teenage/young adult years.

Similarly, optic gliomas are quite common (15% to 20%) but only a minority will grow aggressively and invariably do so by the age of six. The mean age of clinical presentation is 4.2 years. These are tumors of the optic pathway, most commonly involving the optic nerves and/or optic chiasm. Clinical presentation depends on location: proptosis, pupillary defect, optic nerve atrophy,

strabismus, defects in color vision (optic nerves), and endocrinopathy (chiasm). Visual decline occurs in roughly 1/3 of all optic gliomas but fortunately, is only ongoing and serious in 5% to 7% of all cases.[6] Visual decline often occurs undetected in toddlers, in whom accurate assessment of visual acuity is difficult. As such, routine eye exams are key, at intervals of at least a year. Exams every six months would be ideal in the toddler years. Any change in growth velocity on the curves should raise the suspicion of chiasmal glioma with hypothalamic involvement. Many centres will perform routine neuroimaging of brain and orbits between the ages of three and five, although it is presently not a strict recommendation of the Optic Glioma Task Force.[7]

Tibial dysplasia/pseudoarthrosis generally manifests by age 12 to 18 months as an unusual anterior bowing. This bowing may rarely be seen in other long bones, such as the radius. Immediate bracing maintained throughout childhood is essential. Pathologic fracture must be avoided at all costs. The dysplastic nature of the bone leads to poor fusion post fracture resulting in a false joint/pseudoarthrosis. Once a pseudoarthrosis is present, multiple bone grafts and other orthopedic procedures over several years may be required.[8] Unbroken, the tibia will remodel and eventually strengthen enough to allow removal of the brace after adolescence.

Up to 70% of children with NF I have some degree of developmental lag. Poor general co-ordination and slow language development are common. Most children eventually catch up into the normal range, yet some will require speech/occupational therapy or physiotherapy.

In school age children with NF I, what problems or complications could be anticipated?

As previously mentioned, aggressive optic gliomas are unlikely to declare themselves in school age children if they have not already done so. Plexiform neurofibromas may still develop but, in general, their nature will be less aggressive than those which start in the preschool years. The most frequent (40% to 60%) complication in this age group is learning disability of variable

severity. There is no classic NF I profile, but language-based and visuospatial problems are common as are attention deficits. IQ falls within the normal range, but there is a small general downshift in total scores compared to sibling controls. Frank intellectual handicap is rare — 5% or less.

Parents and teachers must be sensitized from kindergarten. Most learning disabilities will become evident by the third grade level. Neuropsychologic testing is indicated at, or beyond, grade one if concerns arise. Attention should also be paid to potential psychosocial consequences of academic difficulties, such as poor self-esteem, social skill difficulties and isolation.

At any age, surveillance of the child should also include careful monitoring of head circumference. Although macrocrania is frequent, any upward trend can suggest intracranial tumor or aqueductal stenosis from neurofibromatous infiltration. Likewise, a complete neurologic exam is warranted at every age. Lastly, scoliosis checks are important in this age group. The earlier the appearance prior to puberty, the higher the likelihood of underlying vertebral dysplasia which can occur at any level of the spine.

Is adolescence a particularly dangerous period for NF I patients?

There is a popular concern among NF families when children hit adolescence, but this concern is largely unfounded. Certainly, new crops of neurofibromas often herald the onset of puberty and plexiform neurofibromas may grow more rapidly during this time. This is also the beginning of the risk period for malignant degeneration within a pre-existing plexiform neurofibroma. Either an area of rapid local growth within the tumor, or new onset of pain would warrant an immediate biopsy.

Precocious or delayed puberty is not uncommon even in the absence of any detectable CNS tumor. Scoliosis may declare itself and, or accelerate during the growth spurt. Most importantly, self image and peer issues are paramount in this age group. Depression and even suicidal ideation are important concerns when dealing with teenagers with NF I. Lastly, it is essential that they be gently introduced to the notion of dominant inheritance, with its inherent 50% risk of transmission in any given pregnancy. They should be aware of the existence and limitations of prenatal diagnosis, although detailed descriptions are generally unnecessary at this point.

Is there any treatment for NF I presently?

Currently, there is no global treatment to prevent the inevitable but variable progression of NF I throughout the lifespan. However, recent advances have occurred in the management of specific complications. Optic gliomas tend to respond very favorably to specific chemotherapeutic protocols, often with long-term stabilization of the disease. The most exciting area of progress is in the treatment of plexiform neurofibromas. Their previous management has been primarily surgical and largely suboptimal due to their infiltrative/invasive nature. Now that the function of neurofibromin is known, specific therapies aimed at inhibiting Ras activity have been developed and are currently in early clinical trials.

What kind of general outlook is honest and suitable to relay to our NF patients?

Many studies have tried to address the long-term outlook for the NF population. Most agree that the incidence of one or more serious complications is somewhere between 30% to 40%.[9] The corollary is that the majority of individuals with NF I can lead healthy productive lives. They must be encouraged to have a positive attitude. At the same time, they must understand the necessity of regular medical followups to minimize morbidity from any complications that may arise.

What are the resources available to NF families and their treating physicians?

There is a worldwide network for NF I at the research and clinical levels. Resources are easily accessible. Much of this extensive network is linked via a large computer database. There are local and national associations in many countries, one of the largest being the American National Neurofibromatosis Foundation (NNFF), in New York City. There are various provincial associations in Canada, including Québec, Ontario and British Columbia (Table 2). CME

Neurofibromatosis

References

1. Viskochil D: Seminars in Medical Genetics: Neurofibromatosis I. Am. J. Med Genet 1999; 89(1)v-viii.
2. Chichowski K, Jacks, T: NF I Tumour Suppressor Gene Function. Narrowing the GAP Cell. 2001; 104: 593-604.
3. Park V, Pivnick EK: Neurofibromatosis Type I: A protein truncation assay J Med Genet 1998; 35:813-20.
4. Cnossen MH, Moons KG, Garssen MP, et al: Minor Disease Features in Neurofibromatosis Type I. J Med Genet 35(8):624-27.
5. Korf B: Plexiform Neurofibromas. Am J Med Genet 1999; 89(1):31-7.
6. Listernick R, Charrow J, Gutmann D: Intracranial Gliomas in Neurofibromatosis Type I. Am J Med Genet 1999; 89(1): 38-44.
7. Listernick R, Louis DN, Packer RI, et al: Consensus statement from the NF I Optic Pathway Glioma Task Force. Ann Neurol 1997; 41(2): 143-9.
8. Stevenson DA: Descriptive analysis of tibial pseudoarthrosis in patients with Neurofibromatosis I. Am J Med Gen 1999; 84(5):413-9.
9. Cnossen et al. A Prospective 10 year follow-up study of patients with Neurofibromatosis Type I. Arch. Dis. Child. 1998; 78(5):408-12.