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A Neurocutaneous Syndrome Proceeding with Pigmentation Disorder: Neurofibromatosis Type 1

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Abstract

Neurofibromatosis type 1 is a relatively common inherited disease. The condition may involve frequently difficult to manage benign and malignant tumors in affected patients and can also affect tissues such as bone and skin. Symptoms include large numbers of cafe-au-lait macules, tumoral lesions known as neurofibromas, and scoliosis in the spinal cord. Tumors may also be seen in the brain, the cranial nerves or the spinal cord. This study discusses type 1 neurofibromatosis in the light of the current literature.

Keywords: Café au lait macules; Pigmentation disorder; Neurofibroma; Inherited disease

Introduction

Neurofibromatosis Type 1 (NF1) has been known by this name since it was first described in the medical literature by Friedrich von Recklinghausen in 1882. New diagnostic criteria were published in 1987 [1]. These involved six or more café au lait macules; axillary or inguinal freckling; two or more neurofibromas of any type or plexiform neurofibroma; optic nerve glioma; two or more Lisch nodules; pronounced bone lesions; and presence of a patient with NF1 in the family. Two or more of these seven criteria were reported to be sufficient for diagnosis. The worldwide incidence, irrespective of sex and ethnic origin, is 1/2500-3000. NF1 is a multisystemic disease particularly involving the nervous system and the skin. Individuals with NF1 are disposed to benign and malignant tumor growth in the central and peripheral nervous systems, and malignant diseases affecting other regions of the body can also be seen [2,3].

Etiopathogenesis and Genetics

Although a mutation in the NF1 gene is known as the only factor in the onset of NF1 syndrome that can involve the neurocutaneous and skeletal systems, the etiopathogenesis of multiple systems in various organ systems in this disease is complex. NF1 occurs with mutation in the NF1 gene in which the tumor suppressor protein neurofibromin is coded. The broad spectrum of different clinical phenotypes and their development, severity and prognosis are thought to derive from interactions between a large number of cell types, cell signaling networks and the cell-extracellular matrix. Bi-allelic inactivation in the NF1 gene has been reported to play a very important role in the development of such clinical findings as glomus tumor, cafe-au-lait macules and neurofibromas. The NF1 gene consists of 57 constitutive axons and 4 alternative axons (9a, 10a2, 23a, 48a) comprising approximately 280 kb DNA located in the 17q11.2 chromosome band. NF1 inheritance is autosomal dominant, and it is heterozygous in character in all affected individuals. In utero mortality has been reported in studies of homozygous NF1 in mice. However, neurofibromas have been observed not to develop in mice with the NF genotype. Approximately 50% of human NF1 cases are not familial but occur de novo (spontaneously) as the result of a new sporadic mutation in the NF1 gene. The majority (80%) of sporadic NF1 gene mutations are of paternal origin. Those of maternal origin are known as microdeletion. These are found in the entire NF1 gene and in the contiguous region containing 17 genes [4].

Diagnosis

Diagnosis in NF1 is clinical. The presence of at least 2 of the 7 diagnostic criteria determined at a National Institutes of Health (NIH) conference in 1987 were reported to be sufficient for diagnosis [1]. In 1997, the National Neurofibromatosis Foundation Clinical Care Advisory Board reviewed the existing data and published recommendations regarding the treatment and diagnosis of affected patients. However, it did not alter the diagnostic criteria cited by the NIH and decided that these were still valid and sufficient [5]. These diagnostic criteria are shown in Table 1 [6].

Two or more criteria are needed for diagnosis
Six or more cafe aula it patches >15 mm in adultsand > 5 mm in children.
Two or more neurofibromas or one plexiform neurofibroma.
Axillary or groin freckling.
Lischnodules (iris hamatomas).

Optic pathway glioma.
A first degree relative with NF1.
A distinctive osseous lesion such as sphenoid wing dysplasia orthinning of the long bone cortex with or without pseudoarthrosis.

Table 1: Diagnostic criteria for neurofibromatosis 1.

Clinical Characteristics

Skin findings

Cafe-au-lait macules and freckling: Cafe-au-lait spots (CLS) are seen in 95% of cases of NF1, and generally until the age of 3 years. Freckling and concomitant hypopigmented macules occur in intertriginous areas. Transient orange papules and xanthogranulomas associated with chronic myeloid leukemia are observed in 102% of patients in early childhood [6]. CLS in patients with NF1 are typically oval with distinct margins. They are uniform in color (slightly darker than the individual's own skin color) and approximately 1-3 cm in size. They may also sometimes be smaller or larger and irregular in shape. Pigmentation is darker in darker, typical lesions, while dark pigmented small CLS or freckles may be more irregular. CLS may be less evident in individuals with very pale or very dark complexions in whom the lesions resemble the rest of the skin in color. A Wood's lamp may be useful in showing pigmented macules in these cases. CLS may be seen anywhere on the body in patients with NF1, apart from the palms of the hands and soles of the feet. Freckling is widely seen in areas exposed to the sun and also on the proximal extremities and trunk. Similar freckling is widespread in individuals without NF1 with pale complexions. Additionally, freckling may also occur in places such as the axillary and inguinal regions and beneath the breast in women [7].

Neurofibromas: Large numbers of benign cutaneous neurofibromas are generally observed in adult patients with NF1. Different cutaneous and subcutaneous neurofibromas are rare before childhood. Total neurofibroma numbers in adults range from a few to hundreds or even thousands. Although the incidence varies from year to year, cutaneous and subcutaneous neurofibromas may continue to develop throughout life. There have been reports of a rapid increase in neurofibroma numbers and dimensions in pregnant women [8].

Plexiform neurofibromas are present in approximately half of patients with NF1, but these may be internal and not suspected clinically [9]. The majority of these tumors, especially in early childhood, exhibit gradual growth over the years, but rapid growth may be observed in benign lesions. When plexiform neurofibromas are symptomatic, they may be life-threatening in addition to involving function and form disorder [10].

Other skin findings: Juvenile xanthogranuloma and nevus anemicus are more common than thought in cases of NF1, and it may be useful to support diagnosis in children not meeting standard diagnostic criteria. Juvenile xanthogranulomas are accumulations of small, orange papules. Nevus amicus describes a macule that is irregular in shape, lighter in color than the surrounding skin and that, in contrast to the surrounding skin, does not redden when rubbed [11].

Ocular findings

Optical findings in NF1 include optic glioma that may lead to blindness and Lisch nodules (harmless hematomas of the iris). Symptomatic optic pathway glioma in individuals with NF1 generally takes the form of loss of visual acuity or proptosis before the age of 6. However, these tumors may sometimes not be symptomatic until late childhood or adulthood. They may also remain stable for years or progress very slowly. Some of these tumors may contract spontaneously [12]. Less common ocular findings in NF1 include retinal vasoproliferative tumors and neovascular glaucoma [13].

Neurological findings

Most patients with NF1 are of normal intelligence. However, learning problems and difficulty may occur in 50-70%. Mental disability is seen in 6-7% of patients, double the level in the general population. Autism findings have been reported in more than 30% of patients. The most common disorders involve visual performance, social sufficiency and attention deficit. Motor function, executive function, memory and speech problems may also be seen [14].

Multiple nerve root tumors capable of causing diffuse polyneuropathy may develop in some patients with NF1. Affected patients are at high risk of malign peripheral nerve sheath tumors [15]. Seizures are more common in patients with NF1 of any age compared to the general population. These seizures are generally focal and associated with areas of infarction or brain tumor. Focal seizures in NF1 can be controlled with concomitant use of more than one anti-epileptic drugs or surgical procedures involving the affected region of the brain [16].

Sleep disorder is frequently seen in patients with NF1. Headache, including migraine, is more widespread than expected in patients with NF1. Pain associated with plexiform neurofibroma is more common, and must be differentiated from pain representing the first symptom of malign peripheral nerve root tumor [17,18].

Musculoskeletal findings

Generalized osteopenia is more common than thought in patients with NF1. Osteoporosis is twice as prevalent as in the general population and is seen at earlier ages. The pathogenesis of changes in bone structure is not yet fully understood. However, low 25-hydroxy vitamin D concentrations indicating increased bone destruction and higher than normal serum parathyroid hormone levels have been reported in patients with NF1. Abnormal osteoblast and osteoclast functions have been reported in patients with NF1 [19,20]. Dysplasia is uncommon, especially in long bones such as the tibia and fibula, but is a characteristic finding of NF1. These lesions are congenital and always unilateral. They are generally seen in the anterolateral part of the lower extremities in infants. Early diagnosis of tibial dysplasia can prevent fractures. The first radiographic changes are cortical thickening in the bone and narrowing in the medullary canal [21,22]. Long bone dysplasia reflects bone anomaly itself but is not usually associated with neighboring neurofibromas. In contrast, sphenoid and vertebral dysplasia, two other lesions characteristic of NF1, are associated with neighboring plexiform neurofibroma [23,24].

Sphenoid dysplasia proceeds with clinical strabismus and orbital asymmetry. It is determined coincidentally at cranial imaging. It is generally stable but may sometimes lead to progressive enophthalmos [25]. Scoliosis in NF1 may be dystrophic or non-dystrophic. It also resembles adult scoliosis and is associated with vertebral anomalies. Dystrophic scoliosis occurs at younger ages (6-8 years). It is characterized by a narrow angle in a short segment of the spinal cord, and rapid growth may be observed. Bone defect or fracture healing are unsatisfactory and generally difficult [26]. Decreased muscle strength has been determined in children with NF1 compared with normal individuals of the same age, sex and weight [27].

Vascular findings

Hypertension is widespread in NF1 and may be seen at any age. Hypertension is essential in most cases. However, hypertension associated with characteristic vasculopathy with renal artery stenosis, aortic coarctation or other vascular lesions may also be seen [28]. NF1 vasculopathy may be severe, and even fatal, when it involves the arteries of the brain or heart or large vascular vessels [29]. Anatomic variants in the cerebral arteries, enlarged vessels and intracranial aneurysms are more common in patients with NF1 compared to the general population [30].

Tumors

Neurofibromas are a benign Schwann cell tumor capable of involving any nerve in the body. Cutaneous neurofibromas are seen in almost all patients with NF1. Size and number increase gradually with age. Plexiform neurofibromas may occur in approximately half of patients. However, most are internal and may not be observed at clinical examination. Size of plexiforms on the surface of the body may not be ascertainable through visual observation alone. Magnetic resonance is the best option for visualizing plexiform neurofibromas. Plexiform neurofibromas begin growing in childhood and adolescence and remain stable in adulthood. Although most are asymptomatic they may sometimes be painful and may compromise surrounding tissue functions when they attain large size [31].

Malign peripheral nerve root tumors are the most common malign neoplasm seen in 10% of patients with NF1. Compared with the general population, they are seen more in adolescence or early childhood in patients with NF1 [32].

The most common tumors in children with NF1 apart from benign neurofibromas are optic nerve gliomas and brain tumors. Optic gliomas are generally asymptomatic and remain stable throughout life. Secondary central nervous system gliomas are subsequently seen in at least 20% of patients with NF1 with optic pathway gliomas identified in childhood [33].

Leukemias (especially juvenile chronic myeloid leukemia and myelodysplastic syndromes) are rare. However, they are still more prevalent than in children without NF1. Other tumors, such as gastrointestinal stromal and retinal vasoproliferative tumors, may also be seen in NF1 [34]. The risk of breast cancer and mortality therefrom is high in women with NF1 aged over 50 [35].

Life expectancy and quality

Mean life expectancy in patients with NF1 is 8 years lower than that in the general population. Malignancy (particularly malign peripheral nerve root tumors) and vasculopathy are the most common causes of early death in NF1 [35,36]. Lower quality of life has been reported in both children and adults with NF1 compared to normal control groups [37].

Treatment of clinical symptoms

Involvement of the eyes, central or peripheral nervous system or those of the cardiovascular system must be evaluated by specialists in the fields. Impaired appearance or cutaneous or subcutaneous neurofibromas can be treated surgically, or with laser or electrocautery if small in size [7].

Surgical treatment of plexiform neurofibromas is unsatisfactory due to proximity to nerve areas and recurrence [38]. Radiotherapy is contraindicated in individuals with genetic predisposition as it may induce peripheral nerve root tumors. Chemotherapeutics such as carboplatin or imatinib van also be used [7].

Although the only preferred treatment in malignant peripheral nerve root tumors is complete surgical excision, studies have reported that adjuvant chemotherapy or radiotherapy can also be used when this is not possible [39].

Since many optic pathway gliomas are asymptomatic they may be coincidentally identified at MRI and require no treatment. Chemotherapy can be administered if they are progressive. Surgical treatment is not preferred for cosmetic reasons and due to the risk of blindness. Radiotherapy must be avoided due to the risk of malignancy [40].

Despite being complex and difficult, surgical treatment is required for dystrophic scoliosis. If scoliosis is non-dystrophic it can be treated like idiopathic scoliosis [41]. Surgical treatment of tibial pseudoarthritis is difficult and frequently unsatisfactory [42].

Monitoring

Recommended monitoring includes:

- Annual physical examination by the monitoring physician
- Annual ophthalmological examination in childhood, or less frequently in later childhood and adulthood
- Regular development assessment in childhood
- Regular blood pressure checks
- Other evaluations (MRI etc.) need be performed only on the basis of clinical symptoms and findings
- Evaluation must be performed by appropriate specialists in the case of skeletal, cardiovascular or central nervous system involvement

Conclusion

NF1 is a genetic disease capable of involving systems and causing serious complications. It is therefore important to identify and diagnose cases early. Early diagnosis is therefore important in terms of informing the families about the disease and of regular clinical monitoring of these children. We think it is also important in terms of averting treatable complications. In addition, we wish to emphasis that diagnosed cases should not be considered in isolation and that family members should also be assessed.

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