

Lisch and the Importance of His Nodules

A Maharaj¹, VRS Singh¹, SA Lalchan²

ABSTRACT

Neurofibromatosis 1 is the commonest neurocutaneous autosomal dominant disorder with full penetrance, although expression may not be complete by the age of five years. Lisch nodules, however, are predominantly visible in children usually after the age of six years. Therefore, it is important to appreciate that their absence before this age does not pre-empt the diagnosis. A child being treated for hypertension of unknown aetiology with café au lait lesions presented to the ophthalmologist with blurred vision. Clinical examination revealed Lisch nodules which confirmed the suspicion of neurofibromatosis 1 as per National Institutes of Health criteria. The aim of this report is to highlight the importance of regular ophthalmic screening, both in suspected and confirmed cases, as these patients have long-term sequelae.

Keywords: Lisch nodules, neurofibromatosis-1, optic nerve glioma, sphenoid wing dysplasia

Lisch y la Importancia de Sus Nódulos

A Maharaj¹, VRS Singh¹, SA Lalchan²

RESUMEN

La neurofibromatosis 1 es el trastorno neurocutáneo autosómico dominante más frecuente con penetrancia completa, aunque su expresión puede no ser completa todavía a los cinco años de edad. Sin embargo, los nódulos de Lisch, son predominantemente visibles en los niños, generalmente después de los seis años de edad. Por lo tanto, es importante señalar que su ausencia antes de esta edad no anula la posibilidad del diagnóstico. Un niño que recibía tratamiento para la hipertensión de etiología desconocida, con manchas de color café con leche, y aquejado de visión borrosa, acudió al oftalmólogo. El examen clínico reveló la presencia de nódulos de Lisch, que confirmaban la sospecha de la neurofibromatosis 1, según los criterios de los Institutos Nacionales de Salud. El objetivo de este reporte es resaltar la importancia de practicar regularmente el tamizaje oftalmológico, tanto en los casos sospechosos como en los confirmados, ya que estos pacientes tienen secuelas a largo plazo.

Palabras claves: Nódulos de Lisch, neurofibromatosis-1, glioma del nervio óptico, displasia del ala del esfenoides

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INTRODUCTION

Karl Lisch, an Austrian ophthalmologist (1907–1999), first described the iris hamartomas in 1937 and the association with neurofibromatosis Type 1 (NF1). Friedrich Daniel von Recklinghausen, a German pathologist, identified it as a genetic disease (1, 2). Neurofibromatosis 1 is the commonest neurocutaneous autosomal dominant disorder with full

penetrance, although expression may not be complete by the age of five years. Lisch nodules, however, are predominantly visible in children usually after the age of six years. Therefore, it is important to appreciate that the absence of them before this age does not pre-empt the diagnosis. The aim of this report is to highlight the importance of regular ophthalmic screening both in suspected and confirmed cases as these patients have long-term sequelae.

CASE REPORT

A 14-year old boy was referred by the optician for 'iris nodules'. The Snellen visual acuity was 6/6 (+0.50 DS) in both eyes. The medical history included treatment for hypertension (enalapril, atenolol). Notably, there was normal

From: ¹Faculty of Medical Sciences, The University of the West Indies, St Augustine, Trinidad and Tobago and ²Lily – The Eye Specialist Limited, Ankavilla Building, #8 Endeavour Road, Chaguanas, Trinidad and Tobago.

Correspondence: Ms SA Lalchan, Ankavilla Building, #8 Endeavour Road, Chaguanas, Trinidad and Tobago. Fax: 868-671-7211, e-mail: mslalchan@gmail.com

renal function, negative 24-hour catecholamine levels and vanillylmandelic acid (VMA) results were outstanding; other clinicians included a paediatric nephrologist and cardiologist. The patient’s father reported no proven diagnosis of neurofibromatosis. There was no family history.

Clinical examination revealed multiple café au lait spots (Fig. 1) and Lisch nodules (Fig. 2). The colour vision (Ishihara plates), pupil responses, dilated optic nerve and fundus examination and orbital examination were normal. He was reviewed by his paediatrician with a targeted screen for life-threatening secondary hypertension, in addition to neuroimaging.



Fig. 1: Multiple café au lait macules on the patient.

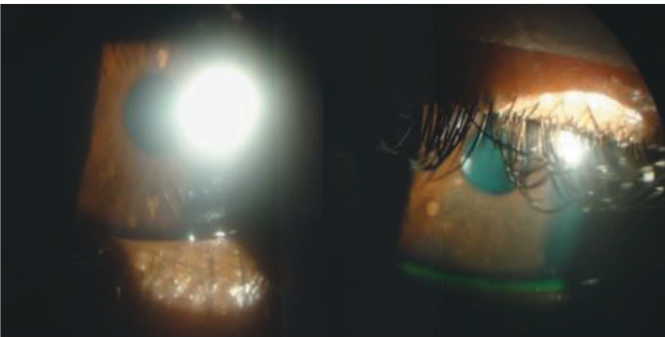


Fig. 2: Multiple Lisch nodules in the patient’s eyes.

DISCUSSION

Neurofibromatosis 1 is an autosomal dominant inherited condition with complete penetrance but has variable phenotypic expressivity caused by mutation in the *NF1* gene on 17q11.2e (3). It has a worldwide incidence of one in 2500–3000 live births (4). Neurofibromatosis 1 is clinically defined by its cutaneous and neural clinical features. The diagnostic criteria for NF1, developed by the National Institutes of Health, are a useful tool for the clinical diagnosis of NF1 (Table). Notably, there are three ophthalmic features: Lisch nodules, optic nerve glioma and sphenoidal wing hypoplasia,

Table: National Institutes of Health diagnostic criteria for neurofibromatosis 1 (NF1)

Two or more of the following clinical features signify the presence of NF1 in a patient

- Six or more café au lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis
- A first-degree relative (parent, sibling, or offspring) with NF1 as defined by the above criteria

hence the importance of ophthalmic screening in suspected and/or proven cases (2).

The clinical manifestations of NF1 are highly variable. Multiple café au lait spots, which occur in nearly all affected individuals, manifest due to pathogenic melanocytes that carry somatic or a second hit mutation in the *NF1* gene (5). Intertriginous freckling develops in almost 90% of patients with NF1 (6).

Neurofibromas are amongst one of the most distinguishing features of NF1 resulting from *NF1* Schwann cell mutation. They can affect any organ of the body and can vary in adults from few to hundreds or thousands (7, 8). Plexiform neurofibromas are a frequent complication of NF1. They can impair function, produce disfigurement, and be the site for the development of malignant nerve-sheath tumours. The paraspinal, sacral plexus, sciatic notch and perirectal regions are the most commonly affected sites. While most plexiform neurofibromas are asymptomatic, rapid growth of benign lesions, especially in early childhood, can cause disfigurement and may compromise function and, rarely, be life-threatening (9).

In 2005, Kordić *et al* reported Lisch nodules had an incidence of 78% in a sample size of 132 patients ranging in age from 0–16 years (10). Lisch nodules represent one of the most common ocular pathognomonic markers for NF1. It is composed of three cytotypes: pigmented cells, fibroblast-like cells and mast cells showing a similar pattern to neurofibromas (11). Although the iris nodules are perhaps not visible at birth, their prevalence in patients with NF1 gradually increases from birth to 50% at five years of age, 75% at 15 years of age and 90–95% over the age of thirty (12). Lisch nodules, therefore, may facilitate early, non-invasive diagnosis in children, as highlighted in our case report. Ophthalmologic examinations and pedigree analysis should be compulsory, both in patients and their immediate relatives (13).

Optic pathway tumours (OPT) occur in about 15% of individuals with NF1 and can result in visual loss and even morbidity in young children (14, 15). They are usually found

along the course of the anatomic optic nerve [Fig. 3] (16). Symptomatic OPT in individuals with NF1 usually manifest before age six years with loss of visual acuity and/or proptosis. This, of course, can be challenging in preverbal children, hence screening is pivotal to early detection and intervention. Some, however, may not become symptomatic until later in childhood or even adulthood. Since the management guidelines for optic nerve gliomas are limited and treatment may itself result in neuro-ophthalmic complications, therapeutic strategy is best guided by a multi-disciplinary team that includes ophthalmology, neurosurgery, radiation, oncology and neuroradiology (17).

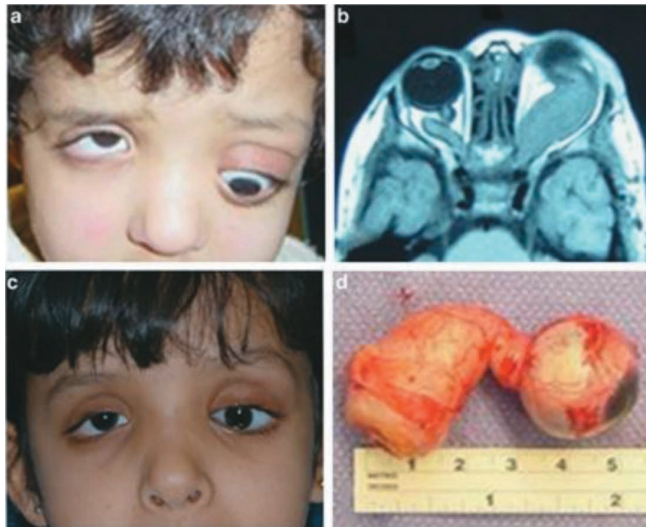


Fig. 3: A two-year old girl (not the patient discussed in this case report) presenting with decreased bilateral vision, proptosis and orbital dystopia. Note the very thick segment of optic nerve glioma after left-sided enucleation and tumour resection on the patient. Source: (16)

Sphenoid dysplasia is a prominent but not entirely pathognomonic facial feature which occurs in 3–7% of all patients with NF1 [Fig. 4] (18). Slow and progressive decal-

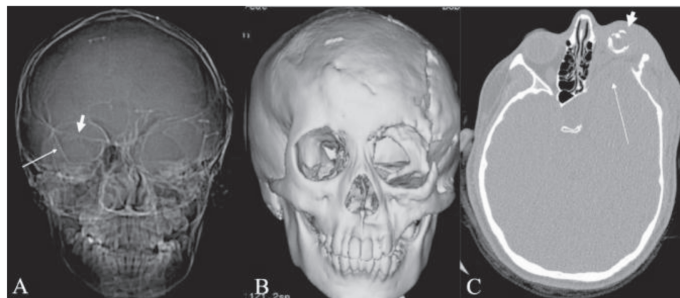


Fig. 4: An example of a frontal computed tomography (CT) scanogram (not that of the patient in our case report) showing the bare orbit sign. (A) A bare and large orbit on the left, with absence of the greater wing of the left sphenoid bone, in this patient with neurofibromatosis type 1. Axial CT scan image (C) shows anterior herniation of the left temporal lobe (thin long arrow) because of the dysplastic sphenoid bone. Source: (18)

cification and remodelling of the sphenoid wing with resultant enlargement of the orbital fossa can result in temporal lobe herniation into the orbital cavity, producing pulsating exophthalmos and gross facial deformity requiring surgical intervention. The typical radiological features are partial or complete absence of the greater wing of the sphenoid (19).

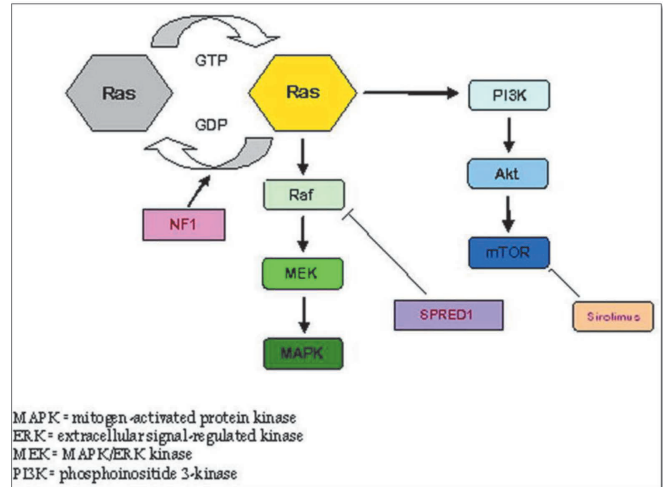


Fig. 5: Schematic of interactions of key proteins and genes involved in the pathogenesis of neurofibromatosis type 1. Source: (24)

Physicians need to be cautious when establishing the exact cause of secondary hypertension in patients with NF1 in an effort to deter life-threatening organ damage and increased mortality. Although in the majority of cases, essential hypertension coincidentally coexists with the condition (20), six per cent of patients with NF1 develop hypertension as a consequence of renovascular disease, mid-aortic syndrome or pheochromocytoma (7, 21). Annual blood pressure monitoring is therefore imperative in the patient with NF1 and, if hypertension is found, further investigation and treatment or referral to an appropriate specialist for management is indicated (22).

Genetic confirmation of neurofibromatosis is now a possibility. Neurofibromatosis 1 results due to a germline mutation of the *NF1* gene (350 kb) on chromosome 17q11.2 (23). The *NF1* gene product, neurofibromin, is a large (2818 amino acids), ubiquitously expressed protein present at low levels in most tissues, with the highest concentration found in the central nervous system (CNS). Neurofibromin is a GTPase activating protein for members of the p21 Ras protein family and serves as a negative regulator for the Ras oncogene pathway by accelerating the conversion of active Ras-GTP to inactive Ras-GDP. Loss of neurofibromin function leads to downstream cell growth activation and an increased risk of neoplasia [Fig. 5] (24). The overall risk of malignancy in patients with NF1 is 5–15% greater when compared to the general population (25).

Genotype-phenotype association for targeted therapeutic options has not been successful. Genetic counselling is problematic in NF1 owing to the marked inter- and intra-familial variation in NF1 expression. The exploration of genotype-phenotype correlations in NF1 is still in its infancy due to the extensive mutational heterogeneity of the gene, and because large-scale mutation screening is laborious owing to the size and complexity of the gene. There have been 1347 mutations identified, of which only fewer than 20% are recurrent (25). This poses a challenge, not surprisingly, for therapeutic success. Until such time, diagnostic accuracy is imperative as these patients are at risk of neurological, ophthalmologic, cardiovascular, gastrointestinal, endocrine and orthopaedic complications.

In conclusion, we report a case of a 14-year old hypertensive male who presented with various stigmata of NF1. This multidisciplinary disorder requires a multidisciplinary team, inclusive of ophthalmologists, to effectively screen and conduct management protocol in a timely manner to reduce both morbidity and mortality.

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