



## Neurofibromatosis and Retinitis Pigmentosa- Is there a link?

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### ABSTRACT

*Neurofibromatoses are autosomal dominant disorders that cause tumors to grow on nerves and result in other abnormalities such as skin changes and bone deformities. It was believed that there were 2 types of neurofibromatosis (type 1 and type 2), but it is recognized that they are clinically and genetically distinct diseases and should be considered as separate entities: neurofibromatosis type 1 (NF-1) and neurofibromatosis type 2 (NF-2). We present a case of 1.5-year-old girl with NF1. The child was admitted for a simple respiratory infection and child was worked up for NF as child had clinical findings suggestive of Neurofibromatosis. Child's father and paternal uncle were suffering from blindness due to retinitis pigmentosa.*

**Keywords:** Neurofibromatosis, retinitis pigmentosa, NF1.

### INTRODUCTION

Neurofibromatosis (NF) is a term that has been applied to a variety of related syndromes, characterized by neuroectodermal tumors arising within multiple organs and autosomal-dominant inheritance. At least 8 different clinical phenotypes of neurofibromatosis have been identified and are linked to at least two genetic disorders. Neurofibromatosis type I (NF-1) is the most common type of the disease accounting 90% of the cases, and is characterized by multiple café-au-lait spots and the occurrence of neurofibromas along peripheral nerves.

### CASE REPORT

A 1.5 year old girl, born out of non-consanguineous union, was admitted with complaints of respiratory tract infection. On

examination child had multiple café-au-lait spots (>30 in number) whose size has been increasing as per history given by parents. Child also had restriction of movements of the left tibia for which a CT scan was done, Was suggestive of ossifying fibroma (osteo-fibrous dysplasia). The mucous membranes were not affected. Ophthalmological status: No abnormality detected. The child's Father and his brother were blind and were diagnosed as retinitis pigmentosa.

The standard laboratory tests values were in the normal range. MRI brain was done, suggestive of Multiple hamartomas in both cerebellar hemispheres, pons and thalami. Spine was normal.

### DIAGNOSIS

The diagnosis NF-1 was made according to the presence of 2 of the seven diagnostic criteria of

the National Institute of Health Consensus Development Conference: (1) six or more café-au-lait macules larger than 5 mm in greatest diameter in prepubertal individuals and larger than 15 mm in greatest diameter in postpubertal individuals. (2) Axillary or inguinal freckling consisting of multiple hyperpigmented areas 2-3 mm in diameter. (3) Two or more iris Lisch nodules (Benign iris hamartomas) (4) Two or more neurofibromas or 1 plexiform neurofibroma. (5) A distinctive osseous lesion such as sphenoid dysplasia (which may cause pulsating exophthalmos) or cortical thinning of long bones with or without pseudoarthrosis (e.g., tibia). (6) Optic gliomas (7) A 1st-degree relative with NF-1 whose diagnosis was based on the aforementioned criteria.



**Picture1**



**Picture2**



**Picture 3**

Pictures 1 and 3 showing multiple café-au-lait spots; picture 2 showing ilizarov external fixator (images taken after taking consent from the mother of the child)

## DISCUSSION

Manifestations of neurofibromatosis have been observed for a long time before being described by Robert William Smith in 1849. The classic description is by a German pathologist, Friedrich Daniel von Recklinghausen, who accurately described the diverse findings as a single entity in 1882; thus the condition is often referred to as von Recklinghausen's disease. There is no single commonly accepted classification. According to the most widely accepted classification, there are four recognized forms of neurofibromatosis: · von Recklinghausen's neurofibromatosis (or neurofibromatosis type 1 [NF-1] or peripheral neurofibromatosis)· Bilateral acoustic neurofibromatosis (or neurofibromatosis type 2 [NF-2] or central neurofibromatosis)· Segmental neurofibromatosis · Cutaneous neurofibromatosis Riccardi<sup>3</sup> suggested the presence of three additional forms: type 3 (mixed), type 4 (variant) and type 5 (late-onset). However, these may not represent separate conditions. The neurofibromatosis comprise of at least two separate genetic disorders (NF-1 and NF-2) characterized by the formation of tumours surrounding nerves and a variety of other pathological features. The most common type (NF-1) accounting for 90% of cases, is characterized by multiple cafe-au-lait spots and the occurrence of neurofibromas along peripheral nerves. Cutaneous neurofibromas are soft, flesh- or lilac-pink coloured tumours, sessile or dome-shaped, sometimes pedunculated, and

most numerous on the trunk and limbs. Other clinical features include Lisch's nodules (melanocytic pigmented iris hamartomas) and oral lesions. Possible complications in childhood include the development of an optic glioma, endocrine disturbances and involvement of the lower urinary tract. The children may also present with learning disabilities. Von Recklinghausen's neurofibromatosis (NF-1) is inherited in an autosomal-dominant fashion, although 50% are sporadic, with an estimated incidence of 1 in 3000. The penetrance of NF-1, or the proportion of people with the NF1 gene with a clinical presentation of the disorder, is close to 100% but because the mutation rate is so high, about a half of the newly diagnosed cases may represent with new mutations. The gene has been isolated to the proximal long arm of chromosome 17 (17, 11.2) and its abnormal protein product is neurofibromin. This has a high sequence homology with GAP (GTPase) activator protein. These proteins have an important role in growth and differentiation. Approximately 100 mutations have been identified in various regions of the gene. The usual cognitive defect is a learning disability, not mental retardation.

**Diagnostic Criteria** According to the National Institute of Health Consensus Development Conference, at least two of the following criteria must be present to make the diagnosis of NF-1: 1. Five or more cafe-au-lait spots larger than 5 mm in diameter in prepubertal patients; six or more cafe-au-lait spots larger than 15 mm in diameter in postpubertal patients 2. Two or more neurofibromas of any type, or one plexiform neurofibroma 3. Axillary or inguinal freckling 4. Optic glioma 5. Two or more Lisch's nodules 6. A distinctive osseous lesion (pseudoarthrosis of the tibia or sphenoid wing dysplasia) 7. A first-degree relative diagnosed with NF-1 in accordance with the above criteria Plexiform neurofibromas of the orbit tend to originate from the orbital branches of the trigeminal nerve. They often affect the upper eyelid, causing a characteristic sinusoidal deformity of the lid margin.<sup>7</sup> The tumor is soft and feels like a "bag of worms"; the resultant

displacement of the globe or ptosis can result in amblyopia in children. Plexiform neuromas of the orbit are associated with congenital absence of the sphenoid or enlargement of the sella turcica. Peripheral neurofibromas are benign tumors consisting predominately of Schwann's cells and fibroblasts with endothelial, perineural, and mast cells.<sup>8</sup> There is evidence that they have a single-cell origin despite multiple cell types within the tumors.<sup>9</sup> Plexiform neurofibromas occur in about one third of NF-1 cases, most commonly on the trunk and less often on the limbs, head and neck. They are benign and rarely symptomatic, but they can cause significant cosmetic and visual problems if the orbit is involved. Café- au-lait spots are composed of epidermal melanocytes with giant pigment granules (macromelanosomes) within the cytoplasm and are of neural crest origin. They are not pathognomonic of neurofibromatosis, having been reported in association with several other conditions and in patients not affected by the condition.<sup>10</sup> Hamartomas of the iris (melanocytic nevi) can be seen and are called Lisch nodules. They are variable in size and have a smooth, dome-shaped configuration.<sup>11</sup> One study found these nodules in 92% of the affected population over the age of 6 years; this may mean that their absence prior to that age does not rule out their later occurrence. Lisch nodules may also be seen in the trabecular meshwork.<sup>12</sup> In a more recent study, the incidence of Lisch nodules in / JofIMAB 2008, vol. 14, book 1 / 65 patients with neurofibromatosis beyond the second decade of life, was 100%.<sup>13</sup> Lisch nodules, which can be indicative of Neurofibromatosis 1 when multiple, are rarely seen in Neurofibromatosis 2.<sup>14</sup> Although clinical findings are primarily Neurocutaneous in nature, any organ system can be involved. The diagnosis requires six or more cafe au lait cafe-au-lait spots, each larger than 1,5 cm in diameter. Axillary freckling is also highly suggestive of the diagnosis.<sup>15, 16</sup> Areas of hypopigmentation or hyperpigmentation can also be seen.

Management is primarily supportive: anticonvulsant medications for seizures, surgery for accessible tumors and orthopedic procedures for bony deformities.

## CONCLUSION

The patient described here is a very typical case of NF-1, which presents a considerable interest because of the hamartomas in brain. In such cases, a detailed patient investigation is required, because of the possibility for generalized involvement of other organs. This patient in particular, who was worked up after general physical examination, emphasizes the need for a proper physical examination whatsoever the complaints of the patient be. The proper clinical and genealogic analysis is important for the determination of the genetic risk and prognosis for the relatives of the proband. A proper followup of the patient is required as they have greater risk of having precocious puberty, short stature and learning disabilities. The association of neurofibromatosis with retinitis pigmentosa could not be confirmed as there was no literature indicating the association of the two, though there are case reports of Neurofibromatosis and retinitis occurring in the same patient or in first degree relatives, which emphasizes the need for further research and understanding about their association.

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