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Neurofibromatosis type 1 – A clinical case report and management review

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ABSTRACT

INTRODUCTION: Neurofibromatosis Type 1 (NF1) or Von Recklinghausen's disease, is a rare genetic disease characterized by multiple benign tumors of nerves and skin (neurofibromas), and skin decorations. However, it is multisystem and can affect each organ in the body, leading to debilitating effects.

CLINICAL CASE: We present a case of an 18-year-old girl with NF1. The disease onset started in childhood at the age of 3 years with the appearance of hyperpigmented skin macules. Her mother also presented with multiple nodules on the face and trunk, and her little brother was reported to have disseminated macules. She had poor performance at school and delayed menses. The diagnosis of NF-1 was made, and a multidisciplinary team was involved in management of the patient

CONCLUSION: Although genetic testing and confirmation are available, NF1 remains a clinical diagnosis and requires management by multidisciplinary team

Keywords: Neurofibromatosis Type 1, Von Recklinghausen's Disease, Chromosome, Autosomal

INTRODUCTION

Neurofibromatosis Type 1 (NF1) or Von Recklinghausen's disease, is a rare autosomal dominant genetic disease with an incidence of 1:3000 [1]. NF1 is benign and familial and inherited in half of the affected individuals. This condition is characterized by the development of multiple benign tumors from peripheral nerve sheaths which also comprises a mixture of variable cells such as Schwan cells, perineurial-like cells, and fibroblasts. Neurofibromatosis type I (NF-1) is the most common type of disease accounting for 90% of cases [2].

Although it is mainly located on the skin, neurofibromatosis Type 1 oral manifestations have been reported in 4- 7% of the affected persons. In addition, the most common diagnostic criteria in

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NF1 patients are ophthalmological manifestations mainly including Lisch nodules, which appear smooth and elevated with a clear to brownish-yellow coloration on slit lamp examination.

There are three main distinct clinical and genetic forms of neurofibromatosis: neurofibromatosis type 1 and type 2 (NF1 and NF2) and schwannomatosis [3]. The pathogenesis of NF1 is associated with a pathogenic variant in the NF1 gene that has a locus at chromosome 17q11.2 coding for a protein known as neurofibrin [1]. This variant results in loss of production and decreased function of the later protein. This pathogenic gene is at complete penetrance for affected individuals carrying the variant to express the disorder. However, this is associated with variable expressions in the severity among affected individuals [4].

CLINICAL CASE

An 18-year-girl consulted with her 64-year-old mother. She came complaining of multiple nodules on the head and back associated with macules, and non-itchy skin lesions. Symptoms became visible in childhood around the 7 years of age, with the appearance of multiple hyperpigmented skin macules. Her mother had the same complains but with variable severity, as she had multiple nodules on the face and the trunk (Figure 1), and her young brother had disseminated macules as well.

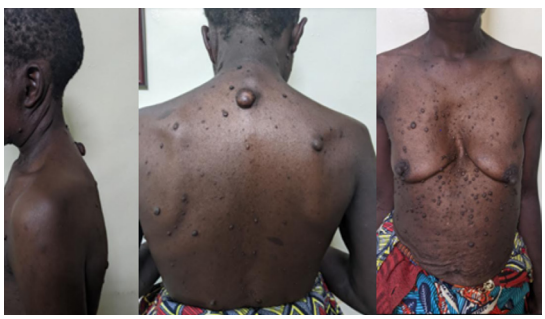

Figure 1: Patient's mother with multiple nodules

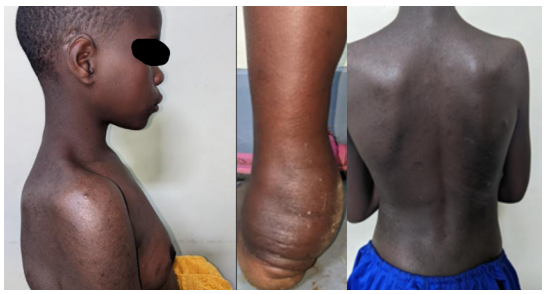

Figure 2: Patient's skin lesions and maleolar mass

Their past medical history was unremarkable. The girl was still in level 5 primary school due to learning difficulties and had her first menses when she was 15.

Physical examination revealed hyperpigmented skin lesions on the back, axillar and inguinal freckling; skin nodules at the back and posterior aspect of the head, with a medial malleolus mass measuring >6cm non-tender and hard to palpation (Figure 2). Her visual acuity was normal in both eyes (6/6), no proptosis (the iris surface was normal), the optic nerve head was normal (cup disc ratio = 0.3), and the retina and peripheral visual fields were normal as well.

The diagnosis of NF-1 was made due to the presence of two or more diagnostic criteria developed by the United States National Institutes of Health Consensus development conference (Table 1) [5]. Since our patient demonstrated the following diagnostic criteria: she had six or more café-au-lait spots measuring 15 mm or more, axillary freckling and the first degree relative with NF1 disease symptoms as well.

The patient was referred to psychology, ophthalmology, medical and surgical departments for further management and screening of NF1 complications.

DISCUSSION

NF1 is a common neurocutaneous condition with genetic inheritance associated with many clinical complications characterized by variability of expression within the same family members and complete or incomplete penetrance mechanisms. The development of molecular biology and neuroimaging has helped diagnose and manage the condition. NF1 is a multisystem condition with debilitating effects on patients' lives through psychological, socio-economic, and systemic impacts.

Our patient had many psychological difficulties related to the disease's complexity and nature, including a lack of self-esteem, social interaction, and learning difficulties that prevented her from achieving his full educational potential. Most children with neurofibromatosis demonstrate cognitive problems, as the main neurological complications with low average range IQ raise the need for educational support in most cases. Studies have revealed that over one-third

Table 1: Diagnostic criteria of Neurofibromatosis type 1

1) Six or more café-au-lait macules are>5mm in diameter in pre-pubertal individuals and >15mm in diameter in post-pubertal individuals. For each lesion, the longest diameter is measured. Ordinary room light (no wood's lamp) is used.
2) Two or more neurofibromas of any type or one plexiform neurofibroma
3) Freckling in the axillary or inguinal region
4) Optic pathway glioma (OPG)
5) Two or more Lisch nodules (iris harmatomas) or two or more choroidal abnomalities.
6) A distinctive bony lesion, such as sphenoid dysplasia, anterolateral bowing of tibia, or long bone pseudoarthrosis.
7) The first degree relative with NF1 diagnosis.

of children with NF1 who followed a regular education required extracurricular educational support, language therapy, and psychological support [2]. Unfortunately, most of our patients cannot afford additional educational care leading to a tremendous negative impact on their development.

Since some GI tumors have been recently observed to be associated with NF1 such as gastro intestinal stromal tumors though they carry a good prognosis, patients with NF1 who present with unexplained anemia with gastrointestinal bleeding, chronic constipation, and abdominal bloating should be evaluated for gastrointestinal tumors [6]. Therefore, educating patients to look out for symptoms and consult is imperative.

Some cardiac conditions, such as congenital heart diseases, pulmonary stenosis, and hypertension, are associated with NF1 [7]. This requires a careful and thorough physical examination of the heart, and it is recommended to do a blood pressure checkup annually. If there are abnormal records, they should be checked three times a month to confirm findings. Additionally, patients with NF1 with hypertension should be screened for renal artery stenosis [8].

NF1 has also been linked to different orthopedic problems resulting from bones abnormalities ranging from mild to severe [9]. Two percent of people with this condition develop bowing of long bones and pseudoarthrosis, which is among the diagnostic criteria for NF1. These bone abnormalities sometimes result in short stature, scoliosis, and osteoporosis [9,10].

Optic Pathway Gliomas (OPG) are low-grade astrocytic tumors, and they occur in about 15% of children with NF1, mostly those less than six years, and rarely occur in adults and older children [11]. These tumors can rise anywhere from optic pathways, optic chiasma or both. Most children with NF1 and OPGs are asymptomatic though the minority develops visual loss. Clinical presentations of OPG include decreased visual acuity, proptosis, optic nerve atrophy, squint, pupillary abnormalities, and hypothalamic dysfunction. The diagnosis is made by Magnetic Resonance Imaging (MRI) which allows better visualization of the tumor and hypothalamic involvement [11,12].

As NF1 has an autosomal dominant pattern of inheritance, there is a 50% risk of passing the condition to offspring, but due to variability of expression, it is difficult to predict clinical presentations and their onset even within the same family members. The family has to be educated about the risks of transmission and the need for annual clinical consultation to evaluate the symptoms and their progression as most neurofibromas grow in the post-adolescent period and mid-twenties [13]. Molecular genetic testing can be performed to confirm the diagnosis in case of diagnosis discrepancy in addition to family members screening. A negative test cannot exclude the diagnosis since molecular testing, including sequencing of the entire coding region, and tests for deletions or rearrangements of a portion or entire genes, all are 95% sensitive, indicating 5% false negative rate. A negative test can also represent mosaicism for a pathogenic variant [14].

CONCLUSION

NF1 is a multisystemic disorder that requires a multidisciplinary team. A successful and comprehensive NF1 management requires collaboration among disciplines of neurology, soft tissue surgery, psychiatry, dermatology, orthopedics, dermatology, pediatrics, radiology, and pathology to diagnose and support the patient as well as family members. Since genetic diseases can be transmitted from one generation to another, clinicians are urged to fully evaluate and take a full history, especially family history. Some genetic conditions diagnoses are based on the clinical background before confirmation by genetic testing. Therefore, careful clinical evaluation is crucial, especially in resource-limited settings with the lack and unaffordability of molecular genetic testing.

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