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A Rare Case of Neurofibromatosis Type I with Heterozygous Exon 31 to 36 Deletion, Diagnostic Challenges in Resource-limited Settings

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Abstract

Neurofibromatosis type I (NF1) is an autosomal dominant genetic condition caused by germline and sometimes somatic NF1 gene mutations. Skin lesions, skeletal deformities, peripheral neurofibromas, central nervous system tumors, and behavioral abnormalities are some of the phenotypic manifestations of the condition.

We present a case of a child diagnosed with NF1 who had cutaneous lesions from birth and plexiform neurofibromas for a year, as well as a newly reported variant of the NF1 gene mutation.

A three-year-old female infant appeared with generalized hyperpigmented skin lesions that had been present since birth, as well as a one-year history of right facial edema. Physical and radiological examination revealed café-au-lait macules on the face, trunk, and lower limbs; right facial edema with ipsilateral ptosis and proptosis; plexiform neurofibromas involving the right cranial nerves III, IV, and V. As a result, the clinical criteria for NF1 diagnosis were met. In our context, the right face plexiform neurofibroma was inoperable, thus the patient was scheduled for palliative treatment and observation. Again, genetic testing to add to the diagnostic criteria for NF and determine the type of NF1 gene took months because the sample had to be sent abroad (Germany) for the confirmatory gene type test.

The discovery of an NF1 gene mutation with heterozygous exon 31-36 deletion is highly unusual. The dearth of experienced people and diagnostic facilities at primary and secondary health care delivery and initial care centers resulted in a lack of anticipatory screening and timely intervention, resulting in delayed suspicion and diagnosis of NF1. Furthermore, the complex and costly logistics of coordinating and performing confirmatory genetic analysis abroad is a major barrier to the diagnosis and comprehensive care of this and other genetic-linked illnesses in developing nations.

Keywords: *Neurofibromatosis Type 1, NF1 Mutations, Exon 31-36 Deletion, Plexiform Neurofibromas.*

Introduction

Neurofibromatosis type I (NF1) is an autosomal dominant genetic disorder caused by inherited or spontaneous mutations in the NF1 gene (1). Diagnosis of NF1 follows the Revised National Institute of Health Consensus Development Conference criteria, which helps healthcare professionals identify the characteristic features of the disorder. The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present:

i. Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in post pubertal individuals.
ii. Freckling in the axillary or inguinal region.
iii. Two or more neurofibromas of any type or one plexiform neurofibroma.
iv. Optic pathway glioma.
v. Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (Cas)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging
vi. A distinctive osseous lesion such as sphenoid dysplasia anterolateral bowing of the tibia, or pseudarthrosis of a long bone
vii. A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells (1).

The global prevalence of NF1 is approximately 1 case for every 3000 individuals, with a variable range depending on geographical and demographic factors, ranging from 1 in 960 to 7812 individuals (2). NF1 is caused by mutations in the NF1 gene, a tumor suppressor gene located on the long arm of chromosome 17 gene. The NF1 gene encodes the neurofibromin protein, which plays a crucial role in regulating several molecular pathways (3). The resulting phenotypic manifestations of NF1 involve various systemic pathologies, including skin lesions, skeletal deformities, peripheral neurofibromas, central nervous system tumors, and behavioral abnormalities. The severity and manifestation of these symptoms can vary greatly between individuals. Although there is currently no definitive treatment for NF1, early diagnosis and genetic testing are essential to confirm the condition and rule out other differential diagnoses. Close follow-up, observation, and timely intervention for associated multisystemic lesions, comprehensive family counseling and screening, as well as the prescription of approved or experimental interventions, are crucial. Additionally, improving diagnostic and interventional skills and experience at both the individual and institutional levels is important. In this report, we present a case of NF1 in a child from Dar es Salaam, Tanzania, who was diagnosed late with inoperable plexiform neurofibromas.

Case Report

A 3-year-old female child was admitted in our pediatric oncology unit, she presented with generalized hyperpigmented skin lesions since birth, lesions were increasing on size. They were on the face, trunk, buttocks, and lower limbs. She also had a one-year history of increasing right facial swelling that began as a reddish enlargement near the outer angle of the right eye and eventually evolved to a black swelling. The bulge grew to around 6 by 8 centimeters in size over time. It affects the cheek and above the eye on the ipsilateral side. Later, followed by eye protrusion that alters facial symmetry with protrusion of the entire right side with lip deviation to the left. It was observed to be uncomfortable since birth, which resulted in poor feeding habits and insufficient nutrition due to limited amount of intake. There was no history of seizures or behavioral changes on the patient or related lesions on the parents or siblings.

Physical examination revealed several hyperpigmented patches with uneven margins (café au lait spots) over the face, trunk, buttocks, and limbs, totaling 8 Café au lait spots greater than 5 mm and multiple Café au lait spots smaller than 5 mm. She displayed right-sided facial edema with hyperpigmented overlaying skin, as well as ipsilateral ptosis and proptosis and mouth deviation to the contralateral side (fig. 1). Ophthalmoscopic examination revealed a very pale right optic nerve with cupping of the optic disc.

Radiographic investigations included computed tomography (CT) and magnetic resonance imaging (MRI). The CT scan revealed a dysplastic right sphenoid wing with a gaping bony defect on the posterior orbit (emptying orbit sign) and congestive prominence and enlargement of the extraocular muscles and the globe (fig. 2). Magnetic resonance imaging revealed heterogeneously enhancing numerous lesions of varying sizes surrounding the right extraconal and conal spaces, right cavernous sinus, and ipsilateral cranial nerves III, IV, and VI. Furthermore, bilateral thalamic enlargement was found in T2/FLAIR (Fluid-attenuated inversion recovery) images (fig. 2). These findings suggest multiple right intra-orbital and right cavernous sinus plexiform neurofibromas, right sphenoid wing dysplasia, and thalamic vacuolization. Conversely, a biopsy of the swelling was performed and the results were inconclusive.

Accounting to these findings, criteria for the diagnosis of NF1 was therefore met and considered as the final diagnosis after clinically ruling out the differential diagnoses of Legius syndrome, Noonan syndrome or Neurofibromatosis type 2.

In our settings, the multidisciplinary team determined that the right face plexiform neurofibroma was inoperable, so the patient was scheduled for palliative care, pain management with oral analgesics, vitamin and mineral supplements, and growth monitoring.

Genetic testing was recommended to confirm and determine the type of NF1 gene mutation, which took months to complete due to the requirement to coordinate and send the samples abroad (Germany) for the test. Cento gene testing is performed using genomic DNA that has been enzymatically fragmented, and target regions are enhanced using DNA capture probes before being sequenced on an Illumina platform. To evaluate variations with pathogenicity and disease causality, a bioinformatics pipeline, variant calling, annotation, and comprehensive variant filtering are used. The findings revealed that the NF1 gene had one copy lost (heterozygous deletion) spanning exons 31-36. The discovery was made at seq [GRCh37] del(chr17) (q11.2q11.2) chr17: g.29579927_29592361x1 genomic coordinates at transcript NM_00104249.3. As an internal control, this deletion was validated using multiplex ligation-dependent probe amplification (MLPA). Due to existing constraints to undertake genetic testing locally, as well as economic and logistical challenges of performing the test abroad, family screening involving parents and siblings to determine whether the mutation is inherited or de novo, has not been done.

Figure 1: Physical examination findings.
The figures show the right sides facial swelling with hyperpigmented overlying skin with ipsilateral proptosis and ptosis with mouth deviation towards contralateral side.

Figure 2: Radiological features.

Figure 1A: CT scan of the head at the level of the orbits bone window showing a dysplastic right sphenoid wing with a bone defect at the posterior aspect of the orbit and proptosis.

Figure 2b: Axial TI-weighted image of the brain at the level of orbit, it reveals lesion that is isointense to the muscle involving the right extraconal and conal space extending to the ipsilateral cavernous sinus and temporalis muscles.

Figure 2C: On Axial T2-weighted image of the brain at the level of the orbit the lesion appear slightly hyperintense compared to the surrounding mass.

Figure 2D: T1 post contrast coronal MRI image of the brain at the level of cavernous carotid showing extensive heterogeneous enhancing soft tissue mass, involving the right temporalis muscle extending to the ipsilateral cavernous sinus, encase the inferior, medial and lateral aspect of the right cavernous carotid artery.

Figure 2E:T2 weighted coronal image at level of orbit showing extensive heterogeneous hyperintense lesion involving the right temporalis muscles with infiltration to adjacent extraocular muscles which appeared to be enlarged.

Figure 2G and 2H show the axial T2-weighed and FLAIR images respectively showing bilateral enlargement of thalami with slightly hyperintensity on T2/FLAIR images.

Figure 1

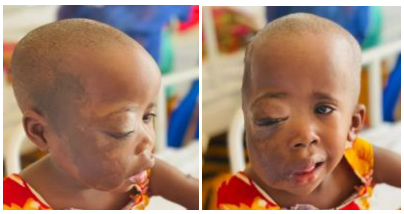
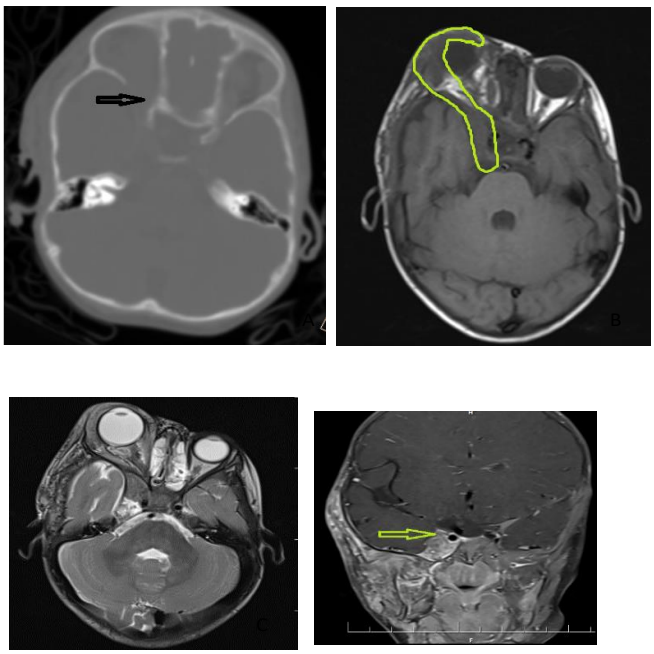


Figure 2



Discussion

Autosomal dominant neurofibromatosis, type 1 (NF1, OMIM:162200) has been associated with pathogenic variants of NF1 gene mutation. The disorder has multisystemic phenotypic manifestation characterized by café-au-lait macules, intertriginous freckling, behavioral changes such as Attention Deficit Hyperactive Disorder (ADHD) and Autism Spectrum

Disorder (ASD) in children, neurofibromas, plexiform neurofibromas, skeletal deformities, and internal lesions mostly involving the central nervous system as well as any other system. Serious lesions could include optic nerve, CNS gliomas, spine and tibial (scoliosis and dysplasia), malignant peripheral nerve sheath tumors (MPNST), endocrine, gastrointestinal, and pulmonary pathologies. Our patient under discussion has numerous multisystemic lesions including the café-au-lait macules, plexiform neurofibromas and intracranial lesions including neurofibromas, thalamic vacuolization and optic nerve lesion which was not involving optic nerve. Presence of these lesions meets the clinical criteria neurofibromatosis type 1, a diagnosis also confirmed by gene testing. The plexiform neurofibromas are usually congenital, rare, and with slow growth with exception in early children and during pregnancy (4). They originate from either internal nerve plexus, cranial nerves, or large peripheral nerve sheaths (5). Although the most common cranial nerve to be affected is trigeminal nerve (CN V) (6), our patient presented with cranial nerve III, IV and VI plexiform neurofibromas. Sphenoid wing dysplasia is a common manifestation of NF1 which can be seen as a bony defect, decalcification or remodelling of the greater wing of the sphenoid bone (7). In our case, right sphenoid wing dysplasia was noted which allowed the plexiform neurofibromas to extend into the middle cranial fossa (cavernous sinus). This resulted into involvement of ipsilateral cranial nerves that traverse the cavernous sinus.

The most common malignancy in optic in NF1 in children is Optic glioma but, in this case, Optic nerve was spared and thus less likely. Neurofibroma plexiform have been described to be painful which was seen in this patient since birth thus interfere with eating habits which likely deprive the nutritional status of this child. Neurofibroma Plexiform have high risk of bleeding due to extensive blood supply thus being inoperable tumour.

Furthermore, the likelihood of progressing to malignancy is high, thus a skin biopsy was performed with inconsistent findings. The inconclusive pathology results for the tumour kind present diagnostic problems in the current situation. It should be noted that the presence of a specific tumour type is not required for the diagnosis of NF1. Neurofibromas, especially plexiform neurofibromas, are common in NF1 but vary in appearance and behaviour. As a result, depending simply on histology to determine tumour type may not always yield definitive results.

Pathogenic variants of the NF1 gene mutations are usually heterozygous and can range from gross gene deletion, single or multiple exons deletions, to small base changes in the exons (8). There are currently more than 2,600 inherited gene mutations recorded in the human

gene mutation database (HGMD®) (9). However, the variant of NF1 gene mutation discovered in our patient which involved heterozygous exon 31-36 deletion is rare and we could not find any other report in literatures, experimental data, or HGMD®. It therefore suffices to infer that, the deletion of exon 31-36 of NF1 gene is most likely a pathogenic variant that led to emergency of the pathological lesions observed in our patient and this report is novel.

When screening patients with skin pigmentation comparable to that found in neurofibromatosis type 1 (NF1), differential diagnoses such as McCune-Albright syndrome and Watson syndrome should be investigated. McCune-Albright syndrome is an uncommon genetic condition with café-au-lait macules, polyostotic fibrous dysplasia, and endocrine abnormalities. Watson syndrome, on the other hand, is distinguished by the presence of café-au-lait macules, pulmonic stenosis, and intellectual impairment. These disorders have some similarities with NF1, making them essential distinctions to examine. Despite the fact that the patient in this case had normal cognition, normal pulmonary results, and no endocrine problems.

The point of care for this patient is a tertiary hospital located in Dar es Salaam, Tanzania, which offer multidisciplinary care to patients from different areas of Tanzania and neighbouring countries. Like many developing countries, specialized care including diagnosis or high suspicion index of “silent” genetic disorders is rarely available in most primary and secondary health facilities at which majority of the population are served first. Moreover, genetic test for confirmation of genetic-linked disorders including NF1 is done in the country instead, it depends on arrangements made with partner- or donor-institutions abroad. In this case, although the patient was born with multiple dermatological lesions followed by progressive facial lesions, probably no suspicion was made for NF1 or there was no readily available means for the patient to be tested until when attended at the tertiary hospital at a late stage. Again, although specific gene mutation has been confirmed in this patient, there is no locally available means yet to confirm whether this mutation is de novo or inherited and the initial collaboration with external diagnostic centres is temporarily inaccessible. This circumstance renders the family counselling and care to be based merely on circumstantial or deductive facts. Even though currently there no curative interventions for neurofibromatosis type 1, there are still promising results from clinical trials such as that using Selumetinib for treatments of inoperable plexiform neurofibromas even in children (10), however, the current patient’s settings do not warrant the availability of such medications.

Conclusion

This case report described a rare manifestation of Neurofibromatosis Type 1 in a 3 years old child, whose diagnosis was hindered by a lack of awareness among healthcare providers and diagnostic facilities in resource-limited settings. Overall, this case study emphasizes the importance of raising awareness about NF1 and other genetic disorders, improving access to genetic testing and specialized care, and fostering collaborations between resource-limited healthcare institutions and external diagnostic centers to improve the diagnosis and comprehensive care of patients with genetic-linked illnesses. This patient's heterozygous deletion of exons 31-36 of the NF1 gene is quite uncommon.

Declarations

Data Availability Statement

The authors declare any required additional data is available on request from the corresponding author.

Conflict of Interest

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics Statement

This report was reviewed and approved by Ethics Committee of Muhimbili University of Health and Allied Sciences and Muhimbili National Hospital. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for Publication

Patient privacy and confidentiality have been prioritized throughout the study, and any identifiable information has been redacted or altered to ensure anonymity. Written informed consent for the participation of the minor patient in this study has been obtained from their biological parent, in accordance with national legislation and institutional requirements. This revised statement explicitly addresses the mention of efforts to conceal the patient's identity and emphasizes that complete anonymity cannot be guaranteed.

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Authors' Contribution

AUL as a corresponding author involved in identification of the case, analysing the history, managing the case and writing the manuscript. AMKN interpreted the patient data regarding type of the tumour involved the head and analyse the findings with relevancy to the patient's history, provide the management plan of the patient on aspect of neurosurgery. DM examined the patient and analyse examination findings and interpretation of examination findings. KCM assisted in genetic testing and interpretation of genetic test results. LC was involved in formulation of appropriate diagnosis, management of the patient. AFM was involved in editing of manuscript and analysing of haematological findings and other blood workout results. VK was involved in interpretation of radiographic findings and analysing them. All authors participated in assisting and review of manuscript writing.

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