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Case Report

Neurofibromatosis with Severe Facial Hemihypertrophy

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Abstract:

Neurofibromatosis, though not discussed in depth, is not at all a clinical rarity. The condition has been reported in all races and does not exhibit specific clinical manifestations and features for the occurrence. The hereditary nature has been recognized for long though the depth of mutations is still a long way in short of understanding. It has got a chance occurrence of 50% mutation rate. It occurs with a frequency of one case in approximately 3000 births. Malignant transformation has been reported in a few cases, which underlines the importance of in-depth analysis of this condition. In the present world of molecular studies, pathogenesis of this condition should be discussed and evaluated to decrease the mortality rates and the aim of our case discussion is mainly to highlight the importance of this condition, which needs immediate focus for further enhancements in treatment protocols.

Key Words: Café au lait spots, freckles, neurocutaneous

Introduction

Neurofibromatosis (NF) is one of the most common hereditary neurocutaneous disorders with an incidence of 1:3000. It is autosomal dominant and shows no race or sex predilection.[1] 30-50% are *de-novo* cases occurring due to spontaneous mutations.[2] The condition first documented in 1882 by the German pathologist Von Recklinghausen presents with protean clinical manifestations.[3] This case is reported due to the severe facial hemihypertrophy associated with NF.

Case Report

A 12-year-old female patient presented with swelling of left side of the face since infancy. Swelling was first noted at 1-year of age after which it increased steadily and reached the present size. The speech was slurred. No family history of such a condition was observed. On extraoral examination severe hemihypertrophy of the maxilla was noted with subsequent disfigurement of the face on account of deviation of the nose and mouth to the right (Figure 1). There was a soft painless mass on the left forehead measuring 4 cm in length and 2 cm in breadth. There was an overgrowth of coarse, stiff hair on the mass. The skin showed patchy pigmentation. A left eye is pushed downward and remained closed due to the pressure exerted by the mass. On palpation, the mass was soft to firm with diffuse borders. No fixity to underlying tissue was noted. There was no associated regional lymphadenopathy. Café au lait spots (CALS) of size 1-2 cm and blue-black in color were distributed over the trunk and palms of hands. There was a large CALS of size 10 cm × 15 cm in the back of trunk, which was irregular with diffuse borders (Figure 2).

Intraoral examination showed a firm mass extending from right maxillary lateral incisor to left maxillary first premolar. The mass measured 3 cm × 2 cm in size and was firm and non-tender on palpation. Maxillary left central incisor was found embedded, and the lateral incisor and canine were partially exposed. CALS were noted on the mass. Nodular masses were seen on the palate adjacent to right maxillary premolars, on the mass adjacent to right central incisor and on the left upper lip. There was hemihypertrophy of the tongue and spacing of teeth on the left side resulting in malocclusion (Figure 3).

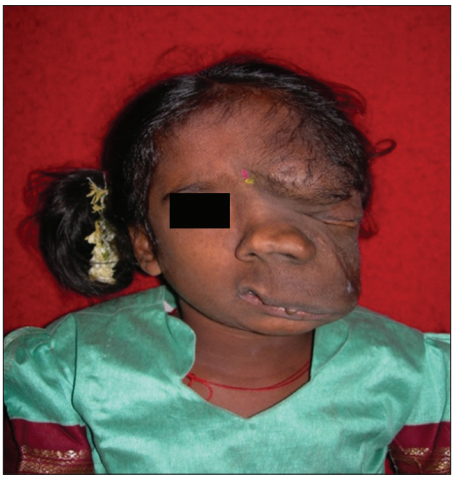

Figure 1: Extra oral photograph showing severe hemihypertrophy of left side face.

Computed tomography scan shows the lesion extended well in to the brain - cerebrum, frontal sinus, and eye, nasal and maxillary sinus (Figure 4). Preliminary hematological investigations including serum calcium and alkaline phosphatase were carried out and values were found within normal limits.

An incisional biopsy was performed from the anterior palate. Histopathological examination of H and E stained sections showed cells with elongated, bent nuclei separated by abundant, fine, and sinuous collagen fibers. There is the presence of nerve bundles, mild vascularity and areas of hemorrhage. The overlying epithelium is orthokeratinized stratified squamous epithelium of normal thickness (Figure 5). A panel of immunohistochemistry markers were done and positive staining was seen with S-100 marker (Figure 6). Since S-100 is a neural tissue marker, other markers were excluded from the diagnostic panel. Thus, by correlating clinically, a diagnosis of NF was made. The patient was referred to the department of oral surgery for further treatment.

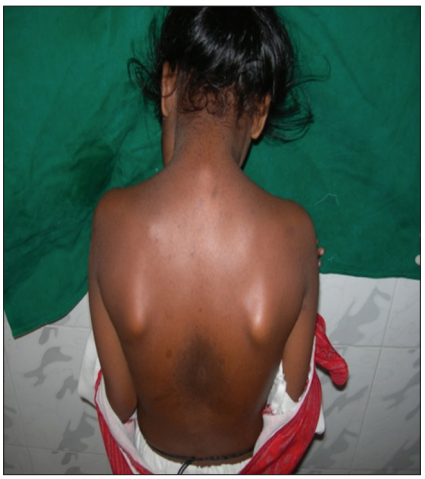

Figure 2: Café au lait spots seen below the scapula on the midline.

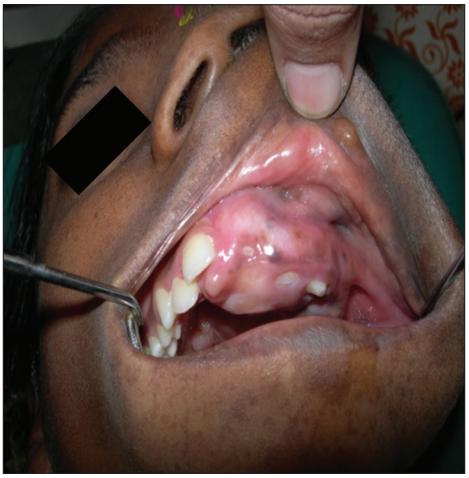

Figure 3: Hemihypertrophy and malocclusion seen in maxilla.

Discussion

Present knowledge shows that NF consists of at least two diseases, which show distinct clinical and genetic features, the peripheral form or NF1, and the central form or NF2. The more common one is the NF1.[4] This is autosomal dominant and 50% of cases are new mutations, 80% of which are of paternal origin. The NF1 gene, one of the largest in the human genome is a tumor suppressor gene located in the pericentromeric region of chromosome 17. It encodes the NF protein, which consists of 2800 amino acids. Due to the large size of the gene

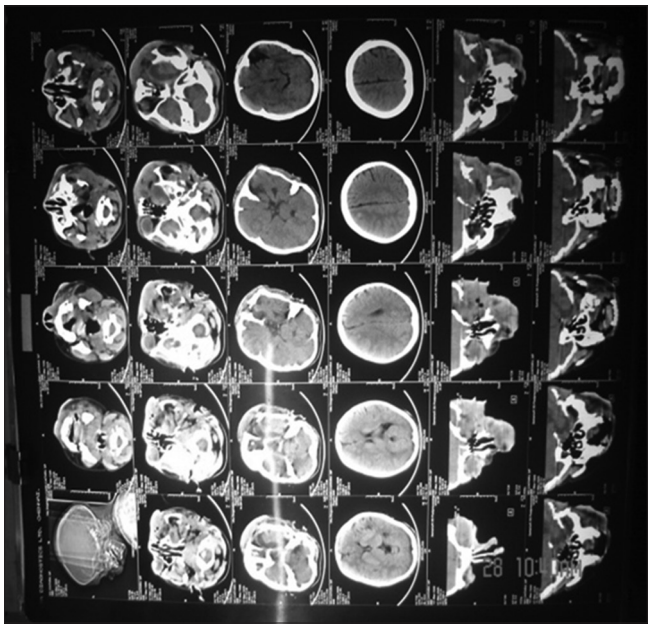

Figure 4: Computed tomography scan shows the lesion extended well in to the brain - cerebrum, frontal sinus, and eye, nasal, and maxillary sinus. The extension of the lesion well into the zygomatic region is also evident.

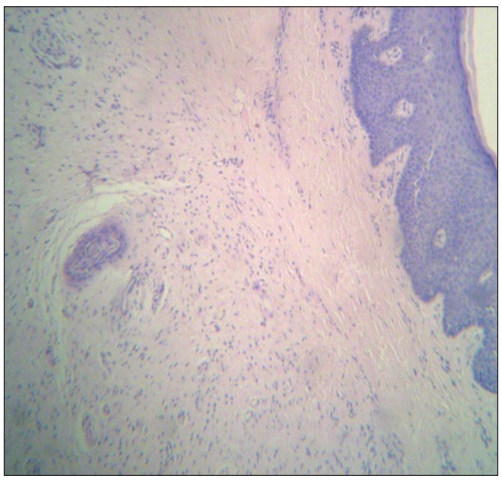

Figure 5: Histopathological examination of H and E stained sections showed cells with elongated, bent nuclei separated by abundant, fine and sinuous collagen fibers. There is presence of nerve bundles, mild vascularity and areas of hemorrhage. Overlying epithelium is orthokeratinized stratified squamous epithelium of normal thickness (H and E, ×10).

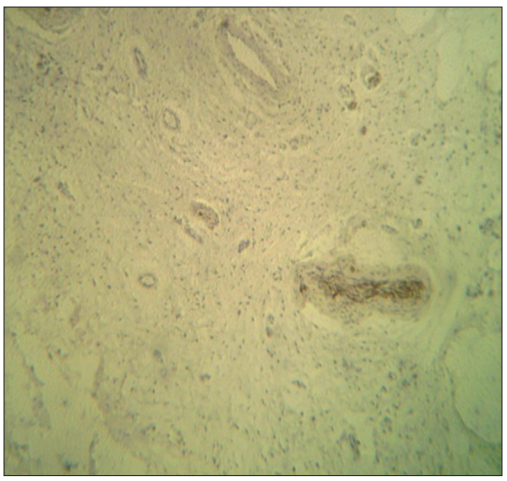

Figure 6: Positive reaction present with immunohistochemical (IHC) marker S-100. The neural cells have taken up brown color which signifies adequate staining; it represents strong reactivity. (IHC, ×40).

and numerous mutations that may occur genetic testing is not a viable option in diagnosis. A protein truncation assay is used to detect stop mutations, but this confirms the disease only in two-thirds of cases and cannot predict the severity.[5,6] Diagnosis is confirmed if two or more of the diagnostic criteria are present (Table 1). Hence, clinical findings are imperative.

Accurate correlations between the genotype and phenotype have not been possible because of the large size of the gene. Still, it has been found that the severity of the condition increases with complete gene deletions with the occurrence of large numbers of NF and a significantly higher lifetime risk for malignant peripheral nerve sheath tumors (MPNST). Familial spinal NF corresponds with mutations at the 3' end of the gene. Somatic mosaicism may account for the segmental forms of NF.[5]

The clinical manifestations are first seen in childhood as small macules resembling freckles, which slowly increase in size and deepen in color. Microscopically melanin pigment is seen in macromelanosomes. The number of CALS indicates the severity of the disease. In mild forms with fewer spots the NF occur late in life and may also be restricted to one part of the body. Secondary symptoms may arise due to the occurrence of NF. An abrupt increase in size may indicate malignancy or may be due to pregnancy or onset of puberty.[7] The central nervous system may be affected with NF for example the optic nerve glioma.[8] The skeleton may be affected due to primary defects and also pressure effect from the tumors. Cystic lesions are noted within the bones histologically resembling non-ossifying fibroma.[9] Renovascular hypertension occurs due to vascular stenosis. The varied symptoms of NF include growth disorders, abnormal sexual development, and lung abnormalities. Certain forms of NF shows atypical or incomplete features compared to the classic form. These

Table 1: Diagnostic criteria for NF.

1	Six or more café au Lait macules >5 mm in greatest diameter in prepubertal individuals and >15 mm in greatest diameter in postpubertal individuals
2	Two or more NF of any type or one plexiform NF
3	Freckling in axillary or inguinal region
4	Optic glioma
5	Two or more Lisch nodules (iris hamartomas)
6	A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudo arthrosis
7	First degree relative (parent, sibling, off spring) with NF1 by the above criteria

NF: Neurofibromatosis

variants are segmental NF, gastrointestinal NF, familial spinal NF, and familial CALS.[8]

NF is a disease with diverse characteristics. Early diagnosis aids in proper monitoring of the patient. Genetic counseling is also required in familial cases. Frequent reviews are needed as there is possibility of development of MPNST in a subset of NF1. Proper histologic evaluation is essential as it is difficult to differentiate an NF with atypical histologic features from a low-grade MPNST.

Germ-line mutations in genes encoding RAS-ERK signaling pathway components cause a set of related, autosomal dominant developmental disorders, termed "RASopathies," which include Noonan syndrome. Noonan syndrome with multiple lentigines (NS-ML; formerly known as Leopard syndrome), cardio-facio-cutaneous syndrome, Costello syndrome, and NF1. RASopathy patients typically display short stature, facial dysmorphia, cardiac defects, developmental delay, and other variably penetrant features.[10]

Conclusion

NF and concomitant symptoms are always associated with numerous manifestations. The condition including von Recklinghausen disease has to be understood in depth for proper diagnostic criteria and treatment protocols. Though, significant steps has been taken for analyzing the molecular pathway and genetic mutations involving the conditions, the finer details are still out of light as far as the molecular origin and pathway is concerned. Extensive discussion and deliberation are necessary in this regard so that debility and mortality rate occurring concomitantly with the condition can be reduced to a larger extent.

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