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Neurofibromatosis 1 with Variable Expression in a Family.

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Abstrct

Neurofibromatosis is a autosomally dominant disorder. It has been classified as Neurofibromatosis 1 and Neurofibromatosis 2. Neurofibromatosis 1 is caused due to the mutation in the NF1 gene which is located in the pericentromeric region of the chromosome 17. Expression of the Neurofibromatosis 1 might range from subcutaneous nodules of neurofibromas to skeletal deformities. We are reporting a family with variable expression of Neurofibromatosis 1. The Index case is showing skeletal deformities. Father of the index case have multiple subcutaneous nodules of neurofibrobas all over the body, his elder brother is affected with plexifprm neurofibroma on the face and the younger sister is mildly affected and showing only few of the subcutaneous nodules on the limbs.

Key words: Neurofibromatosis, Neurofibroma, Chromosome, Gene.

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Introduction

Neurofibromatosis is a autosomally dominant disorder [1,2]. It has been classified as Neurofibromatosis 1and Neurofibromatosis 2 [3]. Neurofibromatosis1 is caused due to mutation in the chromosome 17 and commonly known as Von Recklinghausen neurofibromatosis or peripheral neurofibromatosis [4]. It characterized by cafe-au-lait macules, neurofibromas and osseus manifestations[3]. Neurofibromas are commonly seen along the peripheral nerves and may assume one of the three growth patterns: localized, diffuse or plexiform [5]. Neurofibromatosis 2 is characterized by bilateral acoustic nerve tumors and is caused due to mutation in the chromosome 22 [6].

Clinical report

We are reporting four subjects from same family with variable expression of Neurofibromatosis 1 (Fig.1A).

Patient 1*:*
The index case, a 17 yrs old boy was referred to our cytogenetic lab from Orthopedics OPD for karyotyping. He had a complaint of pain in the right hip joint and difficulty in walking. On physical examination it was found that he had swelling on the right hip, a few multiple subcutaneous nodules allover the body and pseudo gynaecomastia i.e. areolae of the mammary glands were swollen (fig.1B). He was thoroughly investigated i) Radiological: The X-ray pelvis was showing lengthening of the neck of right femur as compared to the left side. Findings of the X-ray were confirmed by the MRI , on MRI it was also found that the subject also had scoliosis and sacral bone dystrophy (Fig. 2 A). ii) Histopathological examination confirmed that the peripheral subcutaneous nodules are neurofibromas (Fig. 2 B). (iii)Hematological: Reports of sickling and C-reactive protein were normal. iv) Genetic: Karyotype of the patient was normal (46, XY). No structural aberration was seen on chromosome 17 (Fig. 3).

Patient 2
He is father of the index case, 56 years old. He had multiple subcutaneous nodules of neurofibromas and café au lait spots on his body (Fig. 4 A).

Patient 3
He is elder brother of the index case, 20 years old . He was severely suffering from plexiform Neurofibroma on the face. He was even unable to open his left eye (Fig. 4B).

Patient 4
She is younger sister of the index case, 15 yrs old. She had very few subcutaneous nodules on her body.

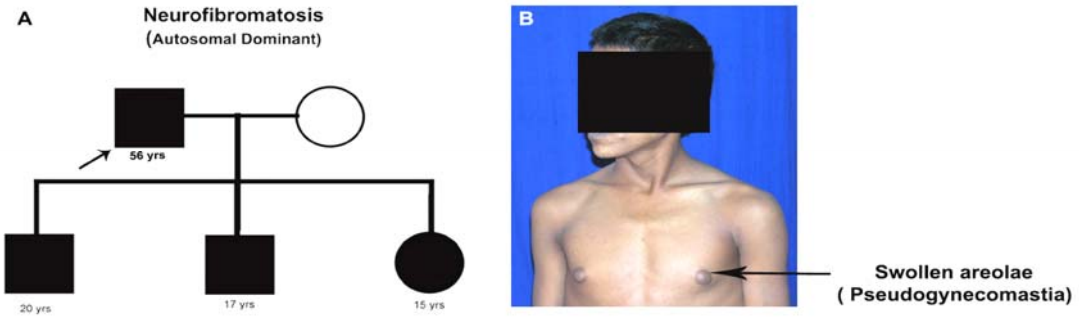

Figure 1A. *Pedigree chart of the family with variable expression of Neurofibromatosis 1.*
Figure 1B. *Patient 1(Index case) showing pseudogynecomastia.*

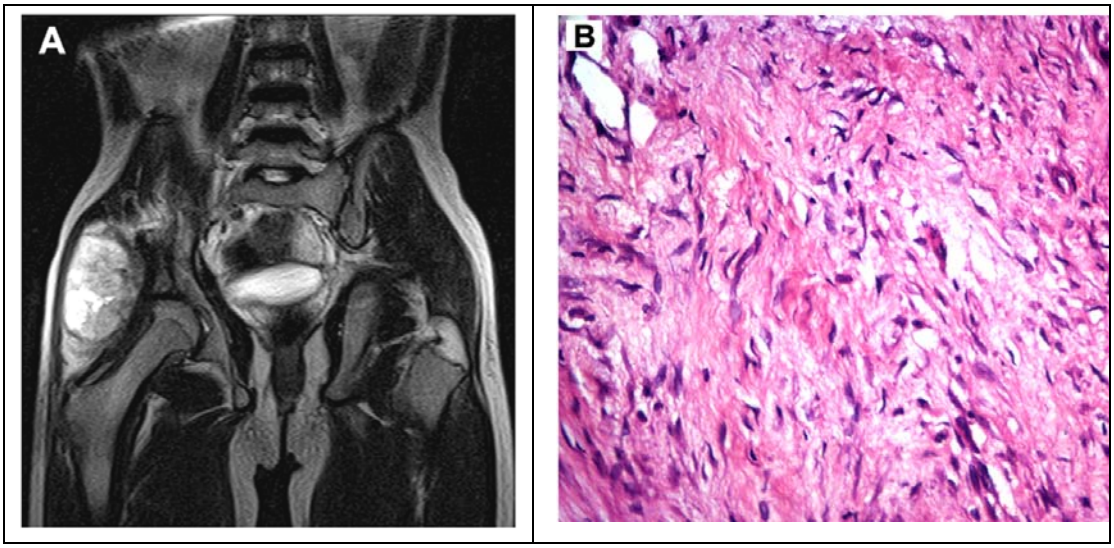

Figure 2A. *MRI of the index case showing lengthening of the neck of right femur.*
Figure 2B. *Neurofibroma with myxoid matrix.*

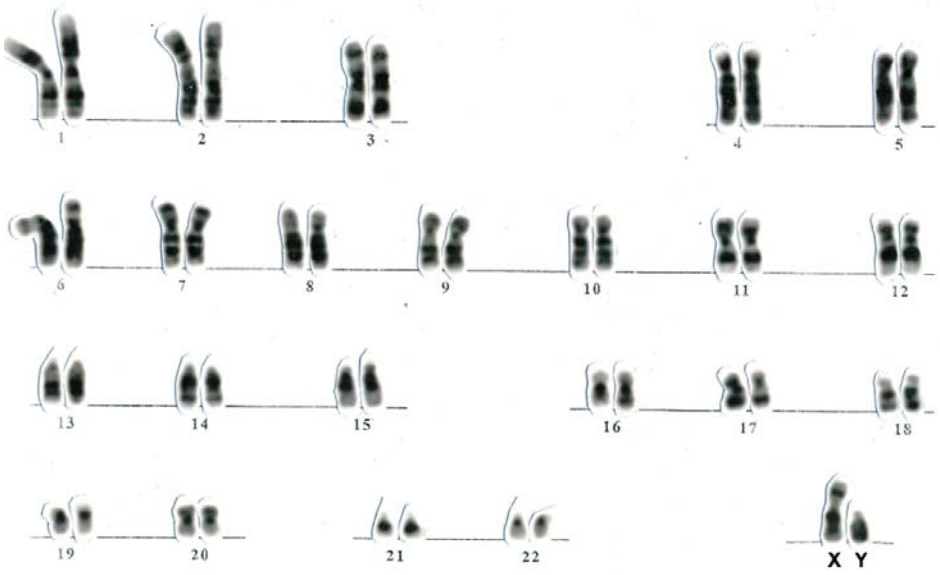

Figure 3. *Karyotype of the Index case: 48, XY.*

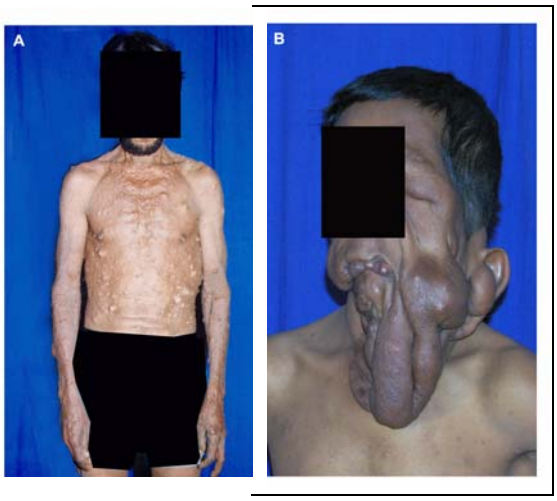

Figure 4 A. *Father of the index case with multiple subcutaneous nodules of neurofibroma on the body.*
Figure 4B*. Elder brother of the index case with plexiform neurofibroma.*

Discussoin

Neurofibromatosis 1 is a autosomally dominant disorder affects the peripheral tissues of the body and commonly seen 1 in every 2500 to 3000 live births[5]. It is associated with deletions ,insertions or mutations in the tumor suppressor gene (NF1) which is located in the pericentromeric region of chromosome 17 [2,4]. NF1 is one of the largest genes and encodes a protein known as neurofibrin which is located to various portions of the cells of all the tissues in the body [2,7]. The neurofibrin is homologous to the family guanosinetriphosphtase activating protein (GAP) which is important in the control of cell growth through their downregulation of the *ras* gene[7]. Expression of the Neurofibromatosis 1 might range from subcutaneous nodules of neurofibromas to pathological changes in various organs of the body including gastrointestinal tract, appendix, larynx, blood vessels, heart and skeletal deformities [5]. Numerous skeletal defects includes unusually longer and thicker long bones due to the development of tumor which is commonly seen in the tibia, fibula and femur [3]. Other skeletal defects includes spinal deformities like scoliosis, kyphosis or lordosis [3,8,9]. The onset of skeletal deformities has been reported to occur between the ages seven to sixteen years [3]. The skeletal deformities are mild in young age group, severe at puberty and becomes dystrophic with advancement in age causing disabilities in the patients [3]. We have noted skeletal defects in the index case which includes lengthening of the right neck of femur, scoliosis and sacral bone dystrophy.

There are numerous soft tissue effects associated with Neurofibromatosis 1 which includes café-au-lait spots on the skin, subcutaneous nodules on the peripheral and central nerves called neurofibromas, lisch nodules i.e. clumps of dark pigment cells located in the iris of the eyes and pseudogynecomastia [5,10,11]. Pseudogynecomastia was also noted in the index case. The most common tumor associated with Neurofibromatosis 1 is the neurofibroma [5]. In the present clinical report father of the index case had plentiful neurofibromas all over his body as compared to the sibs. Neurofibroma can develop anywhere on the body at any stage of the life and it may assume one of the three growth patterns i.e. localized, diffuse or plexiform [5]. In the report we are presenting the elder brother of the index case was suffering from the plexiform pattern of the neurofibroma. As we have discussed above the degree of expression in the Neurofibromatosis 1 may vary from simple subcutaneous nodules to severe skeletal deformities associated with spinal deformities leading to the dystrophic changes in the patients. These changes are not congenital but rather are developmental with early onset. Hence careful attention should be paid by the physicians to the dystrophic features before the age of ten years as it can be an early indication of chance of deformity which can be prevented by appropriate early surgical intervention and proper counseling can be made to the patients and their families.

Refernces

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