A Review: Symptoms, Gene Analysis, Diagnosis and Treatment of Neurofibromatosis type 1 (NF1) syndrome

Aqsa javed[1], Muzdalfa Zulfiqar[1], Muhammad Mubeen Sajid[2], Zeshan Haider[2*]

1. Department of Bioinformatics and Biotechnology, GC University Faisalabad, Allama Iqbal Road Faisalabad, Pakistan, Punjab-38000
2. Department of Centre for Agricultural Biochemistry and Biotechnology, University of Agriculture Faisalabad, University main Road, Faisalabad, Punjab – 38000

***Corresponding Author's Emails:** zhaider310@gmail.com , 2018ag4459@uaf.edu.pk

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Abstract

Neurofibromatosis type 1 (NF1) is an autosomal predominant, mucocutaneous and inclination disorder. They include it in the development of benign and malignant tumors. Hereditary change in NF1 prompts changes in the outflow of cytoplasmic protein. 90% of all cases represent NF1 in neurofibromatosis. children tainted with NF1, they distinguish them inside a year.NF1 Patients ordinarily experience the ill effects of the café au laitt, freckling, and skeletal dysplasia. The GTPase actuating protein goes about as the principal job in NF1 quality, which fills in as a negative controlled by authoritative with the RAS protein. The neurofibromatosis type 1 quality is a 287-kilo premise of chromosome 17q11.2. In NF1 patients, the dermatologists distinguished the basic cutaneous highlights. Cutaneous neurofibroma has a variable pace of development during life expectancy. The threatening fringe nerve sheath tumor is plexiform neurofibromas. Palpebral plexiform neurofibroma is mono-sidelong. We have analyzed inherent dysplasia real criteria for NF1. The more exact technique to analyze NF1 in the patient is radiological indicative. An entire body MRI can test the interior nerve sheath tumor. They have announced that the research center analytic is extremely troublesome; However , it has done the RNA and ELISA tests somewhat. The treatment of NF1 patients is exceptionally troublesome because of the adequacy of the organ of the body. There is a biopsy, medical procedure, and radiotherapy performed for NF1 patients.

Keywords: Neurofibromatosis type 1 (NF1) , Frequency, Symtoms, Gene Analysis, NF1 types, Diagnosis, Treatment

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant, multisystemic and mucocutaneous disorder. Its protein neurofibroma function as a tumor suppressor, one of the main function of protein is to reduce cell proliferation by the inactivation of proto-oncogene *p21ras.* Proto-oncogene *p21ras* play important role in mitogenic intracellular signaling pathway (Ferner and Gutmann 2002).NFI is a predisposition syndrome.it is involving the growth of the benign and malignant tumor. Which include both peripheral and central nervous systems.NF1 is associated with the malignant peripheral nerve sheath. NF1 disorder is characterized by the pigmentary change of the skin and hamartomas nodules ("Institute of Medical Genetics, Cardiff University, Heath Park Campus, Cardiff, CF14 4XN, United Kingdom" 2011).

Moreover, recent finding shows that extracellular signal-regulated kinase is the subfamily of the mitogen-activated protein kinases of the signaling protein. These mutated pathways act as hyperactivated in human genetic syndrome.NF1 in neural stem cell increase the number of linage cell but these distinct mechanisms depend upon the region of the brain(Plotkin et al. 2015).

Genetic modification in NF1 leads to a change in the expression of cytoplasmic protein. Cell regulated protein RAS-GTP to RAS-GDP. Which is an inactive form of protein? If there is a lack of neurofibromin result in excessive cell growth lead to deregulation(Abdolrahimzadeh et al. 2016). Somatic mutations arising early in embryogenesis that cause disease which is indistinguishable from nonmosaic Neurofibromatosis type 1. A localized disease that is restricted to one part of the body results from somatic mutations and occurs in one in 36000 to one in 40000 individuals.

Homozygotes with divergence repair syndromes can be misdiagnosed as having Nf1 as they have a cafe ´ au lait patches and an affected first-degree relative. (Brown, Gianino, and Gutmann 2010).If a clinical and radiographic examination performed then 72% to 92% oral manifestation occurs in this disease. Tongue and buccal mucous are most affected sites. It is observed that cell proliferation with enlarged with sinuous nuclei separated by a slim of collagen fibers. There was a scattered mast cell with connective tissues(Munhoz et al. 2010).

MIA melanoma-inhibitory activity/cd-rap is a potential biomarker for the tumor NF1.MIA are present in large quantity in NF1 patients and the serum level is also higher in these patients. MIA plays an important role in the therapy of NF1 patients(Kolanczyk et al. 2011).

Frequency

Neurofibromatosis type 1 is also known as Recklinghausen's disease.it has been reported that 90% of all cases are accounted for NF1 in neurofibromatosis.NF1 is the biggest human mutation in human beings. It has been reported that 50% of the patient's family contains a positive history and 50% contain the mutation about these diseases. The characteristics of NF1 contain Café-au-lait spots, axillary and inguinal freckling, optic glioma, Lich nodules, and specific bone lesions are some common clinical features of Neurofibromatosis type 1, an Oral manifestation is common 72% are present in NF1 patient's(Cunha et al. 2004).

There is a well-known correlation between the GIST (Gastrointestinal stromal tumors) and NF1 patients. The 7% of patients of GIST are with NF1. The total frequency rate of NF1 patients that relate to GIST is>5%(Malhotra, Wright, and Gajra 2012). Glioma is the second most reason of death between <20 years of age. All cardiovascular death occurs approximately <50 year of age which is approximately 73% of death of all patients (Evans et al. 2011).

Table 1.1 Survival year of patient age NF1 (Neurofibromatosis type 1) in the overall population

Gender	Disease	Normal	Lower level	Upper level
Male	**Healthy**	**78.0**	**78.0**	**78.2**
	Patients	**71.0**	**69.0**	**72.2**
Female	**Healthy**	**82.0**	**81.7**	**82.3**
	Patients	**74.0**	**69.7**	**73.3**

There is shown that the survival rate after the disease of Neurofibromatosis type 1 (NF1) women have more year of age than the men (Evans et al. 2011).

Symptoms

Children that are infected with NF1 are inherited from affected patients they are usually found within the 1 year. We needed just one feature from a family that possesses a positive history. Neurofibromas can occur anywhere in the peripheral nervous system(Jett and Friedman 2010).

Early manifestation includes café au lait spots present at early childhood and followed by axillary freckling(Nickle et al., n.d.). Plexiform neurofibroma of NF1 patients is mostly culprits in morbidity and cosmetic impairment(Sirvaitis et al. 2017).

a Cafe-au-lait muscle>o.5 cm before puberty and 1.5 cm after puberty. Freckling is typically small <93mm in diameter's Nodules are melanocytic that are examined by the slit-lamp and do not affect the vision. Skeletal Dysplasia shows the following symptoms that are small stature, dystrophic scoliosis, tibial pseudoarthrosis, and sphenoid arm dysplasia (Williams et al. 2009).

Table 1.2 Feature of Neurofibromatosis type 1

Features	Evaluation
Café-au-lait	**Hyperpigmented muscle**
Skinfold freckling	**Freckling in the axillary and inguinal area**
Lisch nodules	**Pigmented formation**
Skeletal dysplasia	**Congenital bones defect leads to pseudo arthroses**
Cardiovascular abnormalities	**High blood pressure**

Neurofibromatosis type 1 (NF1) is not limited to clinical features. A first-degree diagnostic by using the above list (Williams et al. 2009).

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Gene Analysis

Neurofibromin, the protein which acts as a tumor suppressor in the NF1 gene product. The GTPase-activating protein act as the key role in the NF1 gene. These proteins consist of 400 amino acid regions of NF1 neurofibroma. These play an important role in the inactivation of protooncogene RAS in various cell types (Pasmant and Vidaud 2016).

GTPase functions as a negative regulator in the NF1 gene. It works as a negative regulator by binding with the RAS protein. which converts it into an inactive form. By promoting the RAS, the GTP convert into inactive GDP bound form. Loss of NF1 expression

results in the hyperactive form of RAS signaling and they cause the RAS resistance in NF1 lacking neuroblastoma cell line (Wimmer et al. 2002).

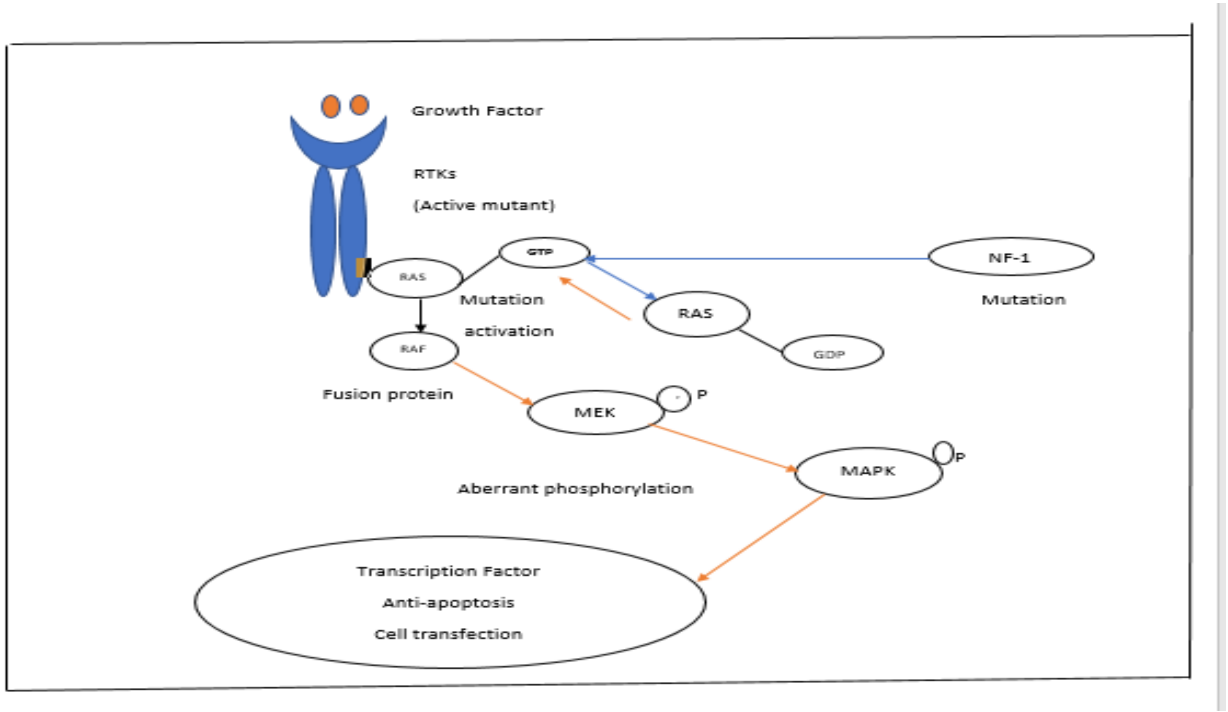

Figure 1.1 Scheme of occurs genomic region of Neurofibromatosis type 1 (NF1) Mutation (Wimmer et al. 2002).

The majority of (Neurofibromatosis type 1) patients that have the genes which are 287 kilobases of chromosome 17q11.2 and consisting of 57 constitutive and 3 alternatively spliced exons. Furthermore, if there are three base pair frameshifts occur at the position of c.2970-2972 delAAT, within exon 17 of the NF1 which may become the reason of loss single amino acid (p. Met992del), which is lead to phenotype of NF1 that is characterized the skinfold freckling (Kehrer-Sawatzki, Mautner, and Cooper 2017).

NF1 implicated the hyperactive RAS in the pathogenesis of JMML. It has been recorded that the RAS signaling gene mutation can be found approximately 90% in JMML patients(Hölzel et al. 2010). Most mutation in the NF1 gene is 85% to 95% small lesions. Such as single-base substitution insertion, deletion. Other multiexon deletion, insertion is 2% and microdeletion that consist of the NF1 gene and neighboring gene are ~5% to ~10%(Chang et al. 2013).

Clinical application has been showed the genotype-phenotype correlations. It has been noticed that NF1 locus missense and deletion is affected the p. ARg 1809. In the frame, deletion affects the p. Met992 gene. Genetic heterogeneity has been finding in NF1 with the identification of Legius syndrome. These produced by a mutation in the SPRED1 gene that encodes a negative regulator in the RAS-MAPK pathway(Valero et al. 2011).

Types of Neurofibromatosis type 1 (NF1)
Cutaneous alterations

In NF1 patient's dermatologists not only find the salient skin feature but also find the common cutaneous. the cutaneous tumor is dome-shaped, fleshy, and soft, but subcutaneous are nodular shaped. cutaneous neurofibromas usually increase in size throughout childhood(Manuscript 2010).Localized cutaneous neurofibroma derived from the peripheral nerves. The major limitation of the age is the 50.5 year. Cutaneous neurofibroma has the variable rate of growth during the lifespan, but it has been demonstrated that the rate of growth could not be captured at the younger age or difference at pregnancy or puberty (Cannon et al. 2018).

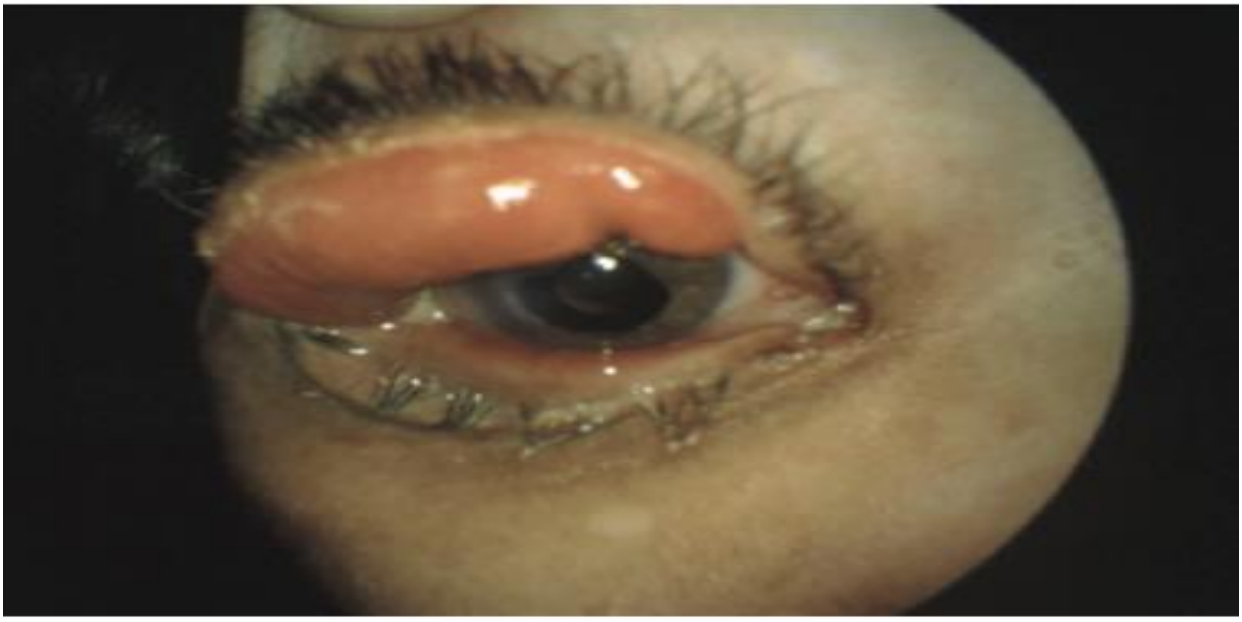

Figure 1.2 Cutaneous neurofibroma at the upper eyelid (Cannon et al. 2018).

whole exons sequence has been done on a DNA sample that was isolated from the cutaneous neurofibroma. Single nucleotide sequence variants and short insertion and deletion were found. After this variant from the whole exon sequences were identified by Sanger sequence(Emmerich et al. 2015). After the analysis of the NF1 cutaneous neurofibroma patient, it has been notifying that independent somatic mutation contributes to tumorigenesis in a second hit model.

Germline mutation appears at distinct loci of the same individual. Both mutation of germline and somatic mutation affect the burden and behavior of the cutaneous neurofibroma. Numerous investigations show that phenotypic behavior affects both germline and outside of the mutant loci. Additional studies of transcriptome and epigenetic modification are needed for the growing and non-growing cutaneous(Faden et al. 2017).

Malignant peripheral nerve sheath:

Malignant peripheral nerve sheath tumor consists of the death of highly antagonistic soft tissue of sarcoma. Malignant peripheral nerve sheath tumor is plexiform neurofibromas and benign peripheral nerve sheath tumor(Kim and Stewart 2017). They are rarely consisting of segmental neurofibroma. they are consisting of the spindle-shaped tumor cell in a peripheral nerve trunk. Low-grade MPNST consists of an unusual spatial and chronological relationship (Li, Won, and Moon 2005).

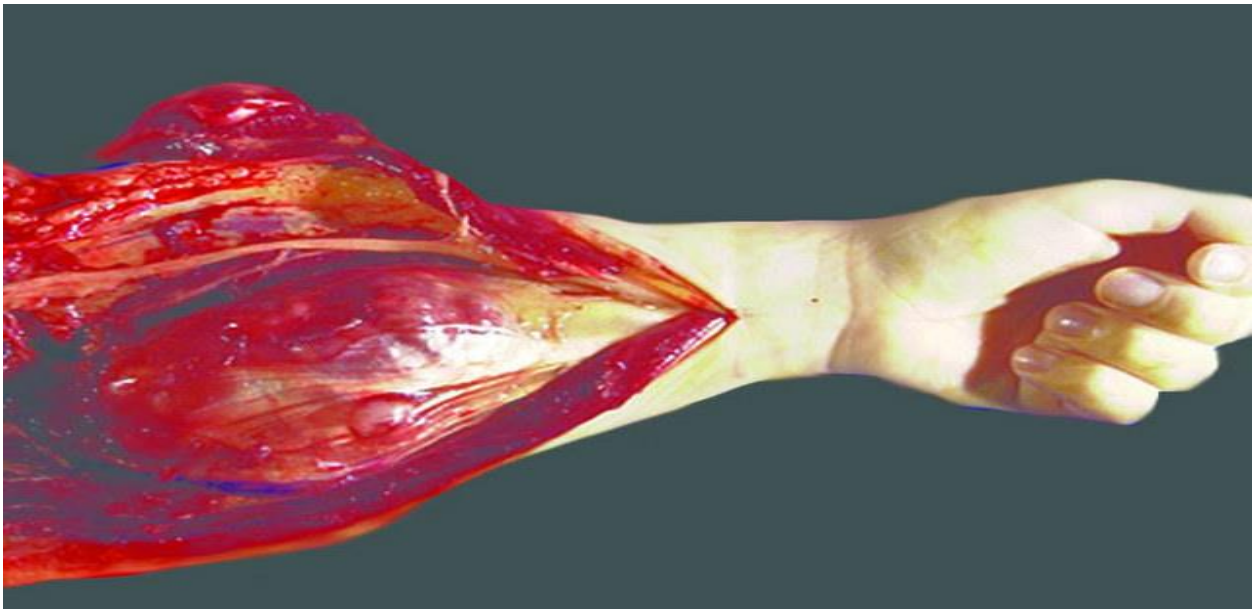

Figure 1.3 Malignant peripheral nerve sheath tumor develops at limb extremities (Li, Won, and Moon 2005).

NF1 associated tumor progression from peripheral nerve to malignant peripheral nerve sheath tumor is usually follow up that it the first formation of primary MPNST and then it converted into MPNST metastasis. These all determined with the help of whole-genome sequencing. These all mutations of primary and metastasis occur at chromosome 17p(TP53). The somatic mutation occurs at the SUZ12 and EED encoding component and at complex 2 PCR2 reported at sporadic MPNST.it play an important role in silencing (Kim et al. 2017).

This is exceedingly difficult to find MPNST from peripheral neurofibroma. There are various monoclonal antibodies used for the detection of MPNST. Neurofibromin specific antibodies used for the differentiation of MPNST from other spindle neoplasms(Balcerzak, Dorobisz, and Czopnik 2016). Classic Ras AND R-Ras both contribute to MPNST proliferation.

The oncogene of MPNST derived from the therapeutic targets. It has been studied that growth factor signaling upstream mediator of RAS activation in MPNST(Carroll 2016). Fluorescence in situ hybridization (FISH) analysis is used more frequently for the analysis of MPNST.it was performed on an unstained, paraffin-embedded tissue segment using the Dual Color, these use the fluorescent probe(Suzuki et al. 2014).

The survival diagnoses of NF1 patients with the MPNST and sporadic MPNST patients. From five years 37 patients have the 42% sporadic MPNST. The five-year survival rate for the male is 32% and for a female is 56% was determined(Article 2002).

Ophthalmic and adnexal manifestations:

Palpebral plexiform neurofibroma is monolateral.it appears on the upper eyelid and it appears after the two years of age. There is facial deformation occurs. There is unusual growth and bleeding started and furthers investigation to rule out the malignant transformation. Iris hamartoma in NF1 formation of Lisch nodules (Abdolrahimzadeh et al. 2016).

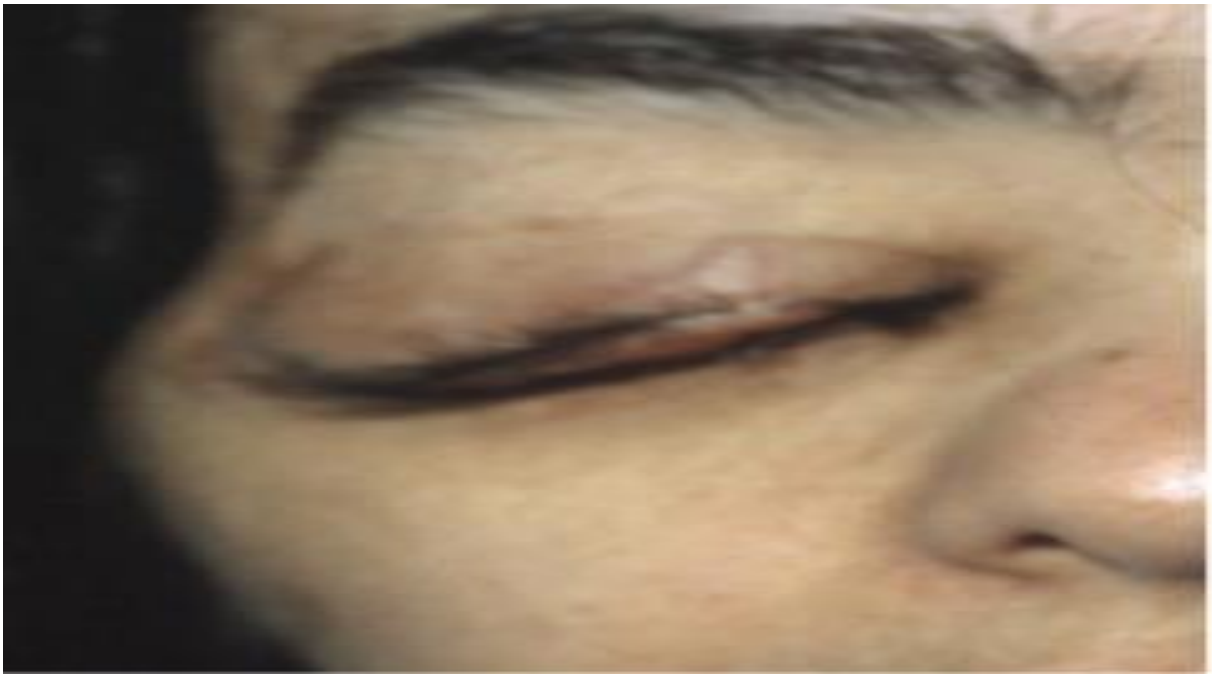

Figure 4: Ophthalmic and adnexal manifestations affect the upper eyelids (Abdolrahimzadeh et al. 2016).

Orbital tumors may be a metastatic extension from adjacent tissues sinuses, lids, Eyeball or manifestation of leukemia. In which inflammatory lesion is most common. Biopsy remains the gold strand for the orbital tumor. If there is no specific treatment held on time then it may be converted into systemic metastasis(Halepota et al. 2014).

Change in intraocular pressure is related to many orbital disorders. these include the congenital disease and disruption of orbital tissues by surgical procedure, arteriovenous malformation and tumor interference in the proper venous, inflammation that change the structure of orbit(Nassr et al. 2009).

These tumors occur in children is about 15% with NF1. They are more show no symptoms and inactive in the population. some tumors produce reduced visual acuity, atypical color vision, visual field damage, squint, pupillary irregularities, proptosis and hypothalamic illness(Ferner et al. 2007).

Systemic and skeletal alterations

NF1 is a genetic disorder that is associated with superficial and deep neurofibroma. It affected cognitive and musculoskeletal performance. Congenital dysplasia has been diagnostic major criteria for NF1 (Sullivan et al. 2014). Approximately 40% of individuals that effected show display skeletal pathologies in NF1.These including non-ossifying bone scratches, pseudointellectual arthrosis, condensed stature, dystrophic scoliosis, irregularity of facial bones, osteosclerosis, tibial prostration, pectus excavatum and low bone mineral density(Karolak, Yang, and Elefteriou 2015).

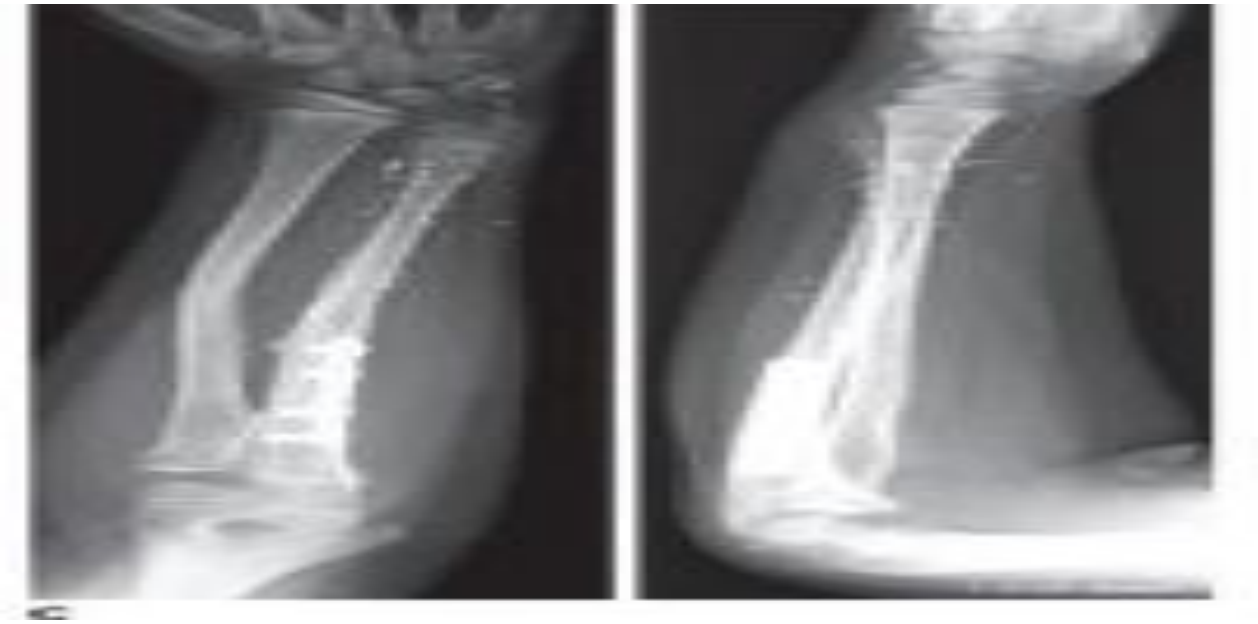

Figure 5: Tinning of the bones due to skeletal alterations (Karolak, Yang, and Elefteriou 2015).

Treatment and management of NF1 dystrophic scoliosis are mostly difficult to destructive surgical stabilization. Bone cysts, spinal canal broadening, vertebral body thinning and rib-penciling(Stevenson et al. 2008).Scoliosis is the most common wide-ranging abnormalities of spinal deformity. In NF1 and 2% of all pediatric scoliosis that have the characteristics of NF1. Non-dystrophic or dystrophic are the subtypes of the scoliosis NF1. These types can be recognized by the radiography(Rhodes et al. 2015).

Many unique functions become more prominent or recognize by the autophagic process (study their molecular delineation). At the same time, they show new approaches to treating the host of diseases that affect the most axial and appendicular skeleton(Karwacki and Wozniak 2011).

Dystrophic scoliosis characterized by the following feature that may consist of the rotation of the ribs. These rotations consist of the apical vertebra, broadening of the spinal canal, widening of neural foramina and paraspinal mass(Ornitz and Marie 2015).

Diagnostic tests

Radiological Diagnostic

Whole-body MRI can evaluate the internal nerve sheath tumor of NF1.MRI scans reviewed by the radiologist the location and appearance of each tumor(Plotkin et al. 2012). There is a various method to determining the NF1 of Whole-body MRI. There is 3D,2D and 1D are used for analyzing of NF1 tumor. But from a recent study, it has been proving that 3D is the most accurate rather than 1D and 2D(Fayad et al. 2016).

Indication for diagnostic MR1 is involved approximately abnormal eye symptoms 44%, asymptomatic patients 43%, headache symptoms (4%), head plexiform neurofibroma (3%), various other indication include 2%, no subject was found due to puberty(Fayad et al. 2016).

RNA testing:

It has been studied that the laboratory diagnostic is exceedingly difficult but there are various approaches used for diagnostic of NF1. In these diagnostics, the RNA of the patient is extracted and then complementary DNA is prepared. which we used for the diagnostic of neurofibromin protein. The neurofibromin protein may be diagnostic by direct DNA sequencing(Fisher et al. 2012).

ELISA

The Elisa determines Ras activation. Elisa was performed according to the manufacturer's protocol. Elisa was performed using the microtiter plate luminometer. After 5 and 60 minutes of addition of substrate WINSLOW software was performed to evaluate the Relative luminescence(Wimmer et al. 2002).

Treatment

NF1 is a targeted treatment. because it affects most of the organs of the body. there is a specific need to monetarizing the individual that treat clinically, radiologically and their specific patient outcomes measured. Now a day there is specific use of novel therapy which helps us for the treatment of NF1 patients. Recently it has been noted that abnormal signaling in the MEK/ERK/RAF pathway sustaining the growth of neurofibroma. A selective MEK inhibitor produced which plays a significant role in the reduction of the neurofibroma size. These all implemented in mice with the presence of MPNST human cell(Karajannis et al. 2016).

Mutation at NF1 is played role in resistant to the BRAF gene, which is recognized as an inhibitor. These are sensitive to MEK and mTOR pathways for collective inhibition. In melanoma cell, loss of NF1 was showed as crucial mediator resistance to BRAF inhibitor. The neuroblastoma model for zinc finger transcription factor encodes resistance in NF1(Ratner and Miller 2016).

At the age of 5 years, a child was diagnosed with the NF1 and optic pathway tumors. The child was started to take a high dose of vitamin c treatment for 30 months. After 30 months there was a reduction of NF1 and left optic nerve according to radiographic imaging (Scimeca 2016).

All the patients that can come for surgery were suffering in the glomus tumor of the finger and toes. glomus tumor cases are mostly found in NF1 patients.in four or five fingers bony involvement occur at the first surgery. Recurrence may occur at the first-time operation(Stewart et al. 2012). Curative surgery was mostly performed for MPNST patients. These were included the pelvic exoneration and limb salvage. But at last, it has been notifying that no patient was suitable for curative surgery. All systemic relapse patients have received palliative surgery(Kar et al. 2006).

palliative surgery was performed to relieve the symptoms of the tumor. A biopsy alone was performed when there are unresectable lesions. Radiotherapy was performed to reduce the symptoms like pain or other neurologic sign after the surgery (Hwang et al. 2017).

Survival Rate

Table 1.3 Surgical Treatment and Outcome of NF1 patients

Surgery	Operation	Results

Curative	**Pancreato-duodenectomy**	**alive 3 years**
	Local excision	**alive 6 months**
Palliative	**Gastroenterostomy**	**alive 9 months**

In neurofibromatosis type 1 Synchronous adenocarcinoma of duodenum and pancreas are present (Costi et al. 2001). The average age of NF1 patients reduced about 15 years of age (Evans et al. 2011).

Conclusion

Neurofibromatosis type 1 (NF1) is not only neurocutaneous but also a multisystem disorder. Patients need to help management and proper treatment for their lives due to multifaceted throughout the whole body. If there is no treatment and management occur, then after a 3-5 year it converted into a malignant form from a benign tumor. Neurofibromatosis type 1 associated with the complications of the central nervous, respiratory, cardiovascular, musculoskeletal, and GI and genitourinary systems. These also implicated on pregnant women. the treatment with the drug is rarer than the surgical procedure. Recent research is concentrating on genotype-phenotype correlations, investigation of the pathobiology for the various clinical appearances of the disease, and the search for treatment options for the unique features of neurofibromatosis type 1.

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