



Neurofibromatosis, Type I

Alternative Names

NF1
Neurofibromatosis
von Recklinghausen Disease
Neurofibromin
Neurofibromatosis, Type I with Leukemia
Neurofibromatosis, Type I with Glioma
NF1 Microdeletion Syndrome
NF1 Microduplication Syndrome

Record Category

Disease phenotype

WHO-ICD

Congenital malformations, deformations and chromosomal abnormalities > Other congenital malformations

Incidence per 100,000 Live Births

11-50

OMIM Number

162200

Mode of Inheritance

Autosomal dominant

Gene Map Locus

17q11.2

Description

Neurofibromatosis type 1 (NF1) is one of the most common autosomal dominant disorders in man, affecting 1 in 3500 people. NF1 is a complex neurocutaneous disorder with an increased susceptibility to develop both benign and malignant tumors but with a wide spectrum of inter and intrafamilial clinical variability. The most prominent clinical hallmarks of the disorder are café-au-lait macules, neurofibromas, Lisch nodules of the iris, and axillary freckling. Other clinical manifestations are abnormalities of the cardiovascular, gastrointestinal, renal, and endocrine systems, facial and body disfigurement, cognitive deficit, and malignancies of the peripheral nerve sheath and central nervous system. About

25% of people with neurofibromatosis type 1 develop one or more of these clinical complications, which together cause significant morbidity and mortality. The tumors that occur in neurofibromatosis type 1 are dermal and plexiform neurofibromas, optic gliomas, malignant peripheral nerve sheath tumors, pheochromocytomas, and rhabdomyosarcomas. Children with neurofibromatosis type 1 have an increased risk of developing myeloid disease, particularly juvenile chronic myeloid leukemia.

Molecular Genetics

Neurofibromatosis type I is caused by mutation in the neurofibromin gene, NF1. The NF1 gene on chromosome 17q11.2 spans more than 350 kb of genomic DNA and contains 60 exons. The 8,457 bp open reading frame predicts a protein of 2,818 amino acids with an estimated mass of 327 kDa. The NF1 gene product, neurofibromin, contains a 360 amino acid region with homology to the catalytic domain of the mammalian guanosine triphosphatase activating protein. Over 70% of NF1 germline mutations cause truncation or loss of the encoded protein.

Approximately 5-20% of all NF1 patients carry a heterozygous deletion of usually 1.5 Mb involving the NF1 gene and contiguous genes lying in its flanking regions, which is caused by unequal homologous recombination of NF1 repeats. To date, several children with some features of neurofibromatosis type 1 and hematologic malignancies have been identified with homozygous mutations in the mismatch repair genes MLH1 and MSH2. The establishment of genotype-phenotype associations in NF1 is potentially useful for targeted therapeutic intervention but has generally been unsuccessful, apart from small subsets of molecularly defined patients.

Epidemiology in the Arab World

Arab

Mandani et al. (1996) reported the case of a boy aged just over five years with neurofibromatosis



type 1, who developed precocious puberty at the age of four years. The latter disorder appeared to have a CNS origin.

Iraq

Al-Gazali et al. (2010) reported an Iraqi child, living in the United Arab Emirates, with Neurofibromatosis type 1. A novel frameshift deletion was identified in NF1 gene.

Kuwait

Nanda (2008) described two patients of neurofibromatosis type 1 having an association with vitiligo in one, and alopecia areata and autoimmune thyroiditis in another.

Morocco

Tarrass (2008) described a patient with an association of Neurofibromatosis Type I with Focal and Segmental Glomerulosclerosis. The 58-year-old male patient with known NF1 presented with deteriorating renal function. He had no family history of NF or kidney disease. Upon examination, he was found to be hypertensive, and had café au lait spots and multiple neurofibromas scattered all across his chest, back, and arms. Serum creatinine was high at 6.5 mg/dl, and urinalysis showed proteinuria of 4 g/day, with microscopic hematuria. Renal biopsy revealed FSGS with severe interstitial fibrosis and tubular atrophy. Tarrass (2008) suggested linkage investigation to assess whether the co-occurrence of these two evidences was coincidental or linked to the same gene defect.

Oman

Jacob and Chand (1995) reported massive cerebral infarction in an Omani man aged 32-years with neurofibromatosis type 1. This patient was not known to be hypertensive or diabetic and was not a smoker. He was brought to the emergency with one day history of altered consciousness and left sided weakness. Clinically, he was found to have high blood pressure of 170/125 mmHg, although his cardiovascular system was normal. He was noticed to have multiple skin lesions (measured 2cm by 3cm) of café au lait spots and freckles all over his chest, abdomen and hips, as well as soft subcutaneous neurofibromas on the extremities and trunk, and osteoma on the sternum. Neurologically, he was drowsy, inattentive, obeying simple commands, had dense left hemiplegia and hemianesthesia, but there were no signs of meningeal irritation. Investigations revealed evidence of renal failure with elevation of blood urea and serum creatinine, normal blood counts, and normal blood biochemistry. Chest x-ray was normal, but abdominal ultrasound revealed a small right kidney (hypoplastic or ischemic). CT scan of

the brain showed extensive infarction due to internal carotid artery occlusion which manifested as large non-enhancing hypodense areas on the right frontal, temporal and occipital lobes. Other investigations were planned (carotid Doppler studies, echocardiogram and carotid angiogram) but the patient's condition deteriorated and he became unresponsive and then died. The patient's family refused autopsy. Jacob and Chand (1995) concluded by mentioning that neurofibromatosis could cause cerebral infarction in the young.

Koul et al. (2000) reported the diagnosis of neurofibromatosis type 1 in monozygotic twins with Dandy-Walker syndrome. The twins, both males, were born at term vaginally to non-consanguineous parents and at delivery they were noted to be monozygotic twins as there was a single placenta. There were no antenatal or perinatal complications. As motor and mental developmental delay was noticed by the parents, these children at the age of 32-months were referred to the authors' care for neurological evaluation, which revealed marked motor delay (head control at nine months, sitting at one year, and just standing with support when seen) and no speech development. Examination revealed head circumference at the 50th percentile but both weight and height were below the third percentile. Both children had dysmorphic features which were not descriptive of any syndrome, including prominent forehead, hypotelorism, low set ears and prominent occiput. In addition to these features, they had café-au-lait spots seen more on their trunks with few of 5 cm² in size, along with few depigmented spots. A diagnosis of neurofibromatosis type 1 was made on the basis of the presence of the features of café-au-lait, microcephaly and short stature. Routine investigations, including blood count, liver and renal function tests, nerve conduction studies and brainstem auditory evoked potential, and karyotyping were normal. In both children, CT scan of the brain revealed typical features of Dandy-Walker syndrome which were cerebellar aplasia, cystic dilatation of the fourth ventricle and enlarged posterior fossa. In addition, one twin had hydrocephalus as well. Koul et al. (2000) suggested an underlying genetic basis for this unique association of neurofibromatosis type 1 with Dandy-Walker syndrome in monozygotic twins.

Alkindy et al. (2012) evaluated the clinical phenotype associated with the specific types of NF1 mutation in a retrospectively recorded clinical dataset comprising 149 NF1 mutation-known individuals from unrelated families. Each patient was assessed for 10 NF1-related clinical features, including the number of café-au-lait spots, cutaneous and subcutaneous neurofibromas and the



presence/absence of intertriginous skin freckling, Lisch nodules, plexiform and spinal neurofibromas, optic gliomas, other neoplasms (in particular CNS gliomas, malignant peripheral nerve sheath tumors (MPNSTs), juvenile myelomonocytic leukemia, rhabdomyosarcoma, pheochromocytoma, gastrointestinal stromal tumors, juvenile xanthogranuloma, and lipoma) and evidence of learning difficulties. Patients were subcategorized according to their associated NF1 germ line mutations: frame shift deletions (52), splice-site mutations (23), nonsense mutations (36), missense mutations (32) and other types of mutation (6). A significant association was apparent between possession of a splice-site mutation and the presence of brain gliomas and MPNSTs ($p = 0.006$).

Saudi Arabia

Bin Amer and Al-Khenaizan (2007) described a patient with Neurofibromatosis in association with malignant melanoma. The 21-month old Saudi boy presented with fever, cough, respiratory distress, and progressive bone pain in the right leg. He was found to have hepatosplenomegaly, and decreased air entry with coarse crepitations. CT chest showed large opacities in both lungs. There was severe tenderness over the right femur, and CT showed bone destruction in the proximal right femur. The patient had major pigmentary changes on the skin; multiple café-au-lait macules on the trunk and extremities, skin-colored firm neurofibromas on the back, and a giant speckled lentiginous nevus extending from the waist to mid-thighs studded with multiple hairy giant congenital melanocytic nevi. Biopsy results of the skin and bone were consistent with a diagnosis of invasive malignant melanoma. A week after the diagnosis, the patient died of respiratory failure.

Tunisia

Gouider et al. (1994) conducted a multidisciplinary transversal descriptive study (June-October 1992) to determine the clinical manifestations and laboratory findings observed in 66 patients from Tunisia with type 1 neurofibromatosis. All patients over the age of 25 had café-au-lait spots, neurofibromas, lentiginos and nodules. Occurrence of lesions of the central nervous system was significantly earlier than peripheral nervous manifestations. The optic glioma was the most frequent lesion of the central nervous system. Complications were observed during the first twenty years of the disease.

United Arab Emirates

Hamza et al. (1996) reported a 45-year old woman with neurofibromatosis type 1 presented with the third largest plexiform neuroma described and the first from the Middle East of such dimension. The

woman consulted for massive swelling of both buttocks almost reaching to the mid thighs, increasing in size steadily since birth. Clinical examination revealed café-au-lait spots, neurofibromas, plexiform neuromas, axillary and inguinal freckling. Two of her children showed signs of the disease including skin freckling and café-au-lait spots. Genetic studied revealed all the family members carrying the NF1 gene on chromosome 17.

[See also: Iraq > Al-Gazali et al., 2010].

References

- Al-Gazali L, Ali BR. Mutations of a country: a mutation review of single gene disorders in the United Arab Emirates (UAE). *Hum Mutat.* 2010; 31(5):505-20. PMID: 20437613
- Alkindy A, Chuzhanova N, Kini U, Cooper DN, Upadhyaya M. Genotype-phenotype associations in neurofibromatosis type 1 (NF1): an increased risk of tumor complications in patients with NF1 splice-site mutations? *Hum Genomics.* 2012; 6:12. PMID: 23244495
- Bin Amer Y, Al-Khenaizan S. Fatal malignant melanoma in a child with neurofibromatosis type 1. *Int J Dermatol.* 2007; 46(9):967-70. PMID: 17822504
- Gouider R, Azaiz MI, Kchouk M, Lasram L, Ben Osman A, Mrabet A. [Type 1 neurofibromatosis in Tunisia: 66 cases] *Ann Dermatol Venereol.* 1994; 121(2):185-9. PMID: 7979037
- Hamza H, Hussein Y, Salih AJM. Giant plexiform neuroma of the buttocks (Hippopotamus bottom woman). *Emirates Med J* 1996; 14:184-6.
- Koul RL, Chacko A, Leven HO. Dandy-Walker syndrome in association with neurofibromatosis in monozygotic twins. *Saudi Med J.* 2000; 21(4):390-2. PMID: 11533827
- Mandani F, Al Tawari A, Al Mazidi Z. Precocious puberty in a child with neurofibromatosis. *Kuwait Med J.* 1996; 28(2):209-11.
- Nanda A. Autoimmune diseases associated with neurofibromatosis type 1. *Pediatr Dermatol.* 2008; 25(3):392-3. PMID: 18577055
- Poovathoor C, Pratap C. Fatal cerebral infarction in Neurofibromatosis type 1. *Oman Med J.* 1995; 12(1):48-9.
- Tarrass F. Focal and segmental glomerulosclerosis and von Recklinghausen's neurofibromatosis: coincidental or associated? *Saudi J Kidney Dis Transpl.* 2008; 19(3):453-4. PMID: 18445911

Related CTGA Records

Alopecia Areata 1
 Dandy-Walker Syndrome
 Neurofibromin 1
 Vitiligo



External Links

<http://www.genetests.org/profiles/nf1>
<http://www.nlm.nih.gov/medlineplus/neurofibromatosis.html>
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=636

Contributors

Pratibha Nair: 20.10.2014
Pratibha Nair: 13.10.2014

Ghazi O. Tadmouri: 25.6.2013
Nada Assaf: 27.5.2013
Abdul R Hamzeh: 8.1.2013
Ghazi O. Tadmouri: 16.9.2009
Eiman Ibrahim: 15.7.2007
Eiman Ibrahim: 22.6.2007
Ghazi O. Tadmouri: 11.10.2005
Ghazi O. Tadmouri: 22.2.2005
Sarah Al-Haj Ali: 25.1.2005

