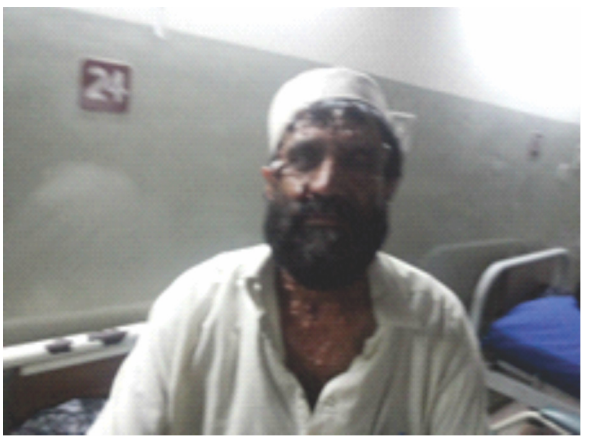
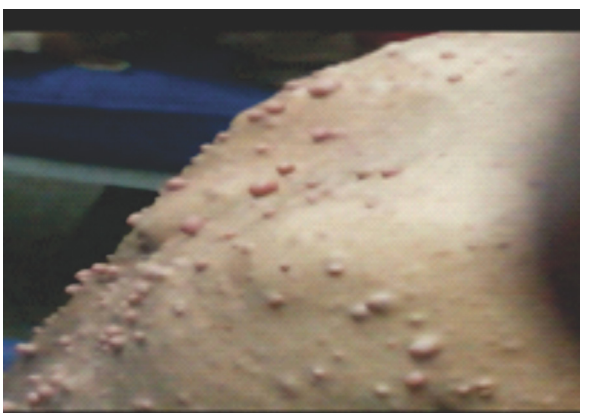
NEUROFIBROMATOSIS

Andleeb

CASE HISTORY

A 45years old married gentleman,Hypertensive since his adulthood presented with a gradual onset history of Soft fleshy multiple nodules over his back,neck,face and lower limbs,associated with Pruritis .There was no family history of hypertention or nodular skin changes.





PHYSICAL EXAMINATION

Conscious and well oriented man,having multiple fleshy cutanous leisions over his back,legs and face. Light coffe coloured 13 macules over his back,trunk and neck greater than 15mm in longest diameter with no freckling in axillary or inguinal regions.B.P:160/100. pulse 89/min.cardiovascular,abdominal and nervous systems were unremarkable.ear and eye examination did not reveal any abnormality.

TESTS

Tests done to rule out hypertention were done.U/s abdomen did not reveal any underlying cause.electrolytes were Na=133 mmol/l,k=4.4mmol/l,cl=109mmol/l.24hrs urinary Vinyl mandelic acid levels were 36mg/24hrs.patient's MIBG SCAN was postponed due to nonavailability of the isotopes.

On the basis of history,physical examination and sky high vinyl mandelic acid levels,diagnosis of spontaneous neurofibromatosi type 1 was made.patient underwent thorough investigations including MRI brain,slit lamp examination to look for other signs of the disease but they were normal.patient was counselled about his disease and advised to screen his children for the disease.

LITERATURE REVIEW

Neourofibromatosis refers to a number of inherited conditions that are clinically and genetically distinct and carry a high risk of tumor formation particularly in the brain.It is an autosomal dominant disorder wich means only one copy of the affected gene is needed for the disorder to develop so if one parent has the disorder ,each child will have 50% chance to have the disease. It has three main types:

-Neurofibromatosis 1(NF1)..most common(95%)

-Neurofibromatosis 2(NF2)..(5%)

-Rare type: shwanomatosis.

CAUSE

In neurofibromatosis type one(nf1)there is loss of NEUROFIBROMIN gene on chr.17 as a result there is no inhibition of the RAS pathway and so cell division is not controlled properly causing overgrowth of all the cell lines derived from neural crest cells.50% of the cases are familial and 50% are spontaneous occurring during conception and so there will be no family history in such cases.Penetrance of the disease is 100%. Neurofibromin is expressed in many tissues including skin, brain, kidney, spleen, and thymus and so they are affected in the disease.[1]

DIAGNOSTIC CRITERIA

Two or more of the following clinical features,present in a patient will make the diagnosis.

1.six or more café-au-lait spots 1.5cm or larger in post pubertal individuals or 0.5 cm or larger in pre pubertal individuals.

2.Two or more neurofibromas of any typeor one or more plexiform neurofibroma.

3.freckling in the axilla or groin

Address for Correspondents:
Dr. Andleeb
Deptt. of Medicine HMC, Peshawar.

4.optic glioma.

5.two or more Lisch nodules(benign iris hamartomas)

6.A distinctive bony lesion(dysplasia of sphenoid bone)

7.A first degree relative with NF1 based on above criteria.[2]

CLINICAL FEATURES

1. Freckling Occurs in axilla and groin ahere skin is apposed and Appear by age 4 or 5.

2.Café-au-lait spots are uniformly hyperpigmented macules.Initially increase in size and no.and then stabilizes overtime.Present in 95% pts.

3.Pseudoarthrosis.

4.Bony dysplasia especially of sphenoid bone causing facial asymmetry.mechanism is not known.

5.Short stature(13%).

6.Scoliosis(10-25%).

7.Osteoporosis(Cause unknown).

8.Benign tumors including neurofibromas.Pregnancy increase their number and size explaining the role of hormone in their growth.

Neurofibromas have four types:

Cutanous:most common,soft,painless,inc.in size and no.with cosmetic concerns,pruritis.

Subcutanous:firm,tender,are present along the course of peripheral nerves.

Nodular plexiform:present in clusters along nerve roots and nerves,can cause spinalcord compression and pain.

Diffuse plexiform:involve multiple nerves,has serpiginous growth,are very vascularand have the potential of malignancy to Peripheral nervesheath tumors.[3]

TUMORS IN NEUROFIBROMATOSIS

OPTIC PATHWAY GLIOMA.It occurs in15% of children with NF1and can arise anywhere along the visual pathway.It is more benign in pt.s with NF1 than in non NF1.signs and symptoms relate to the size and site of tumor and include dec.visual acuity,abnormal pupillary function,proptosis,optic N.atrophy,premature or delayed puberty.

OTHER TUMORS that can occur as complication are astrocytoma and brainstem gliomas,rhabdomyosarcoma, gastrointestinal stromal tumours, CML and pheochromocytoma.[4]

COMPLICATIONS

Those due to tumor over growth are Learning and thinking problems(poor in reading,spelling and mathematics),Seizures(4%), Macrocephaly(25-50% children) and Hydrocephalous.others include Osteoporosis and scoliosis, Optic glioma and visual problems, HTN (renovascular and pheochromocytoma)and Metastasis in 10%(MPNST).[5]

TESTS

- Slitlamp examination for Lisch nodules.
- X.Rays forbone and spinal abnormalities.
- Ultrasound for renal artery stenosis,
- Evaluation of pheochromocytoma.
- MRI brain for early diagnosing and monitoring optic pathway glioma and deep brain tumors.
- Genetic testing which is costly but useful for prenatal diagnosis(in case of spontanous mutations) and counseling.it also helps differentiate Legius syndromefrom NF1.[6]

MONITORING

It is done by Yearly age appropriate checkups to assess for:

- Skin changes.
- B.P
- Growth and development.
- Signs of precocious puberty.
- Skeletal changes.
- Learning and school performance.
- Complete eye examination for visual problems.[7]
- TREATMENT
- There is no cure for the disease and treatment aims at symptomatic relief.
- For diffuse plexiform neurofibromas treatment options aresurgery(debulking),farnesyl transeferase inhibitor,oral tipifarnib,imatinib,pegylated interferon alfa 2-b,antiangiogenic agents.Some of them have completed phase 1 trial while on others still studies are underway.
- nodular neurofibroma carboplatin has been used in some trials but the adverse effects outweight the benefits.
- pseudoarthrosis amputation of the part followed by prosthesis can be done.[8]
- Osteoporosis:Calcium supplements,vit.D have shown no improvement .Bisphosphonates still need further studies.
- For Optic pathway glioma, radiations used caused ischemic stroke,growth hormone deficiency and other malignancies.

- For scoliosis bone surgery may be combined with back braces.[9]
- Regarding Learning disabilities trials on statins are underway.[9]

REFERENCES

1. Costa, R. M.; Silva, A. J. (2002). "Molecular and cellular mechanisms underlying the cognitive deficits associated with neurofibromatosis 1". Journal of child neurology 17 (8): 622–626; discussion 626–9, 626–51. doi:10.1177/088307380201700813. PMID 12403561
2. Tonsgard JH, Short MP, Yamini B, et al: Surgical treatment of neurofibromatosis,inSchmidekHH,RobertsDW(eds):Schmidek and Sweet's.
3. Krab LC, Oostenbrink R, de Goede-Bolder A, et al; Health-Related Quality Of Life in Children with Neurofibromatosis Type 1: Contribution of Demographic Factors, Disease-Related Factors, and Behavior. J Pediatr. 2008 Oct3.
4. Ferner RE, Huson SM, Thomas N, et al; Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet. 2007 Feb;44(2):81-8. Epub 2006 Nov 14.
5. Gandhi V; Plexiform neurofibromatosis. Indian Pediatr. 2004 Jun;41(6):624. BURMAN M. The significance of the café au lait spot. Bull Hosp Joint Dis. 1950 Oct;11(2):140–150.
6. Jack J Kanski, Brad Bowling. Clinical Opthalmology: A systemic approach. 7th ed. Elsevier Saunders; 2011.
7. Listernick R, Charrow J, Greenwald MJ, Esterly NB. Optic gliomas in children with neurofibromatosis type 1. J Pediatr. May 1989;114(5):788-92.
8. Créange A, Zeller J, Rostaing-Rigattieri S, Brugieres P, Degos J D, Revuz J, Wolkenstein P. Neurological complications of neurofibromatosis type 1 in adulthood. Brain 1999. 122473–481.4
9. Operative Neurosurgical Techniques, 5th Edition. Amsterdam, 1:968-974, 2