Neurofibromatosis – Imaging Spectrum

Subbarao Kakarla

Padmasri Awardee Prof. Dr. Kakarla Subbarao, Hyderabad, India

Neurofibromatosis is a congenital neuroectodermal disorder belonging to the group of Phakomatoses. The following disorders share characteristics central nervous system and skin tumors.

Table I:

Common	**Neurofibromatosis**
	Tuberous Sclerosis
	Von Hippel – Lindau disease
	Sturge – Weber syndrome
Less Common	**Basal cell nevus syndrome**
	Osler – Weber Rendu disease
	Ataxia – Telangiectasia
	Klippel – Trenauny syndrome

Frederick Von Recklinghausen credited Tiresius (1793) with the 1st clinical description of fibroma molluscum, named the disease Neurofibromatosis (1882). This is a congenital hereditary dysplasia involving all three germ layers and involving every organ system of the body. Joseph Merrick was called the "Elephant Man", who exhibited severe disfiguring, cutaneous and skeletal manifestations of Neurofibromatosis (1884). Radiography of his skeleton at London Hospital suggested other osseous dysplasias such as Paget's, Fibrous Dysplasia and Melorheostosis. Neurocutaneous disorders known as phacomatosis are inherited as autosomal dominant entities with variable penetrance. NF1 is characterized by benign tumours of the peripheral nerves known as neurofibromas. The pigmented lesions of the skin are called café – aulait spots. The NF1 gene on chromosome 17 encodes the protein neurofibromin which is GTPasses that modulates signal transduction through the ras path way.

At least eight separate forms of neurofibromatosis (NF1-NF8) have been described although two types, Von Recklinghausen's disease (NF-1) and neurofibromatosis with bilateral acoustic schwannomas (NF-2) are generally agreed upon. The terms "central" and "peripheral" neurofibromatosis are inaccurate; both NF -1 and NF-2 show central nervous system involvement. More than 90% of all NF cases are NF1. These disorders represent dyshistogenesis of neuroectodermal and mesodermal tissue. Autosomal dominant with chromosomal 17 locus for NF1 and chromosome 22 for NF2.

Clinical features of NF1 include Family history in 52 to 60% is elicited. It is autosomal dominant with strong penetrance. The incidence is 1 in 3000 / 4000. 50% of patients show manifestations at birth. By age one, 75%. Café – aulait spots occur > 90%. Smooth edges like the coast of California. 6 or more of these. 1.5cm or greater in diameter (fig.1ab). Molluscum fibrosum – soft, sessile or pedunculated, single or multiple lesions. No sex predilection exists.

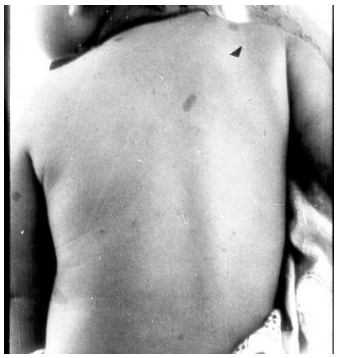


Fig 1a : Café au lait spots in a 2yr old child.

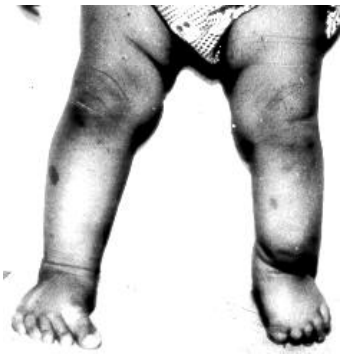


Fig 1b: NF-1 Café au lait spots. Note pseudoarthrosis in left leg.

Fig 1c: Neurofibromata on the Face & Neck in a 21 yr old female

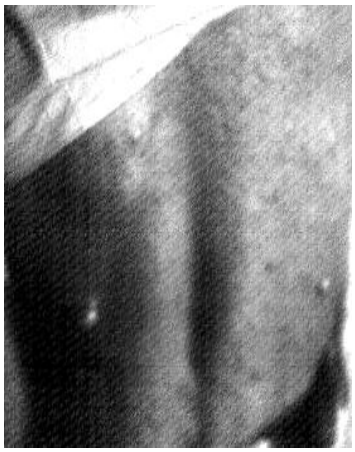


Fig 1d: Molluscum fibrosum

NEUROFIBROMATOSIS -1

Familial autosomal dominant hamartomatous disorder

Table II:

Diagnostic criteria include >2 of these findings	**Six or more 5 mm or larger café – au – lait spots.**
	Either one plexiform neurofibroma or two or more neurofibromas of any type (figs. 1cd)
	Two or more pigmented iris hamartomas (so-called "Lisch nodules")
	Axillary / inguinal freckling
	Optic nerve glioma
	First degree relative with NF – 1
	Presence of characteristic bone lesion (e.g., dysplasia of greater sphenoid wing)

NF1 involves multiple organs and systems from head to toe. These include brain & spinal cord, musculoskeletal system, cardiovascular system, respiratory tract, mediastinum, genitourinary tract, liver & biliary tract, gastrointestinal tract, retroperitoneum and endocrine glands.

Central Nervous System (CNS) manifestations occur in 15 - 20% of patients with NF – 1. The Skull lesions are mentioned in Table III.

Table III:

- **Macrocrania due to macroencephaly**
- **Intracranial calcifications – bilateral psammomatous calcifications in the temporal horns**
- **Hypoplasia of greater wing of sphenoid with temporal lobe herniation into orbit, pulsatile exophthalmus (fig. 2ab)**
- **Calvarial defects (e.g., lambdoid suture) more on left (fig.3ab)**
  Can have enlarged internal auditory canals without facial or acoustic nerve masses (dural ectasia)

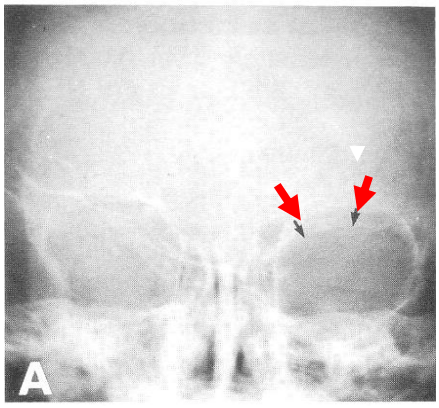


Fig 2a: NF1. absent left greater wing of sphenoid and sutural defects (Empty orbit).

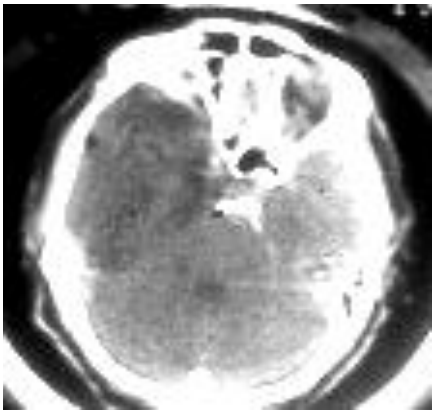
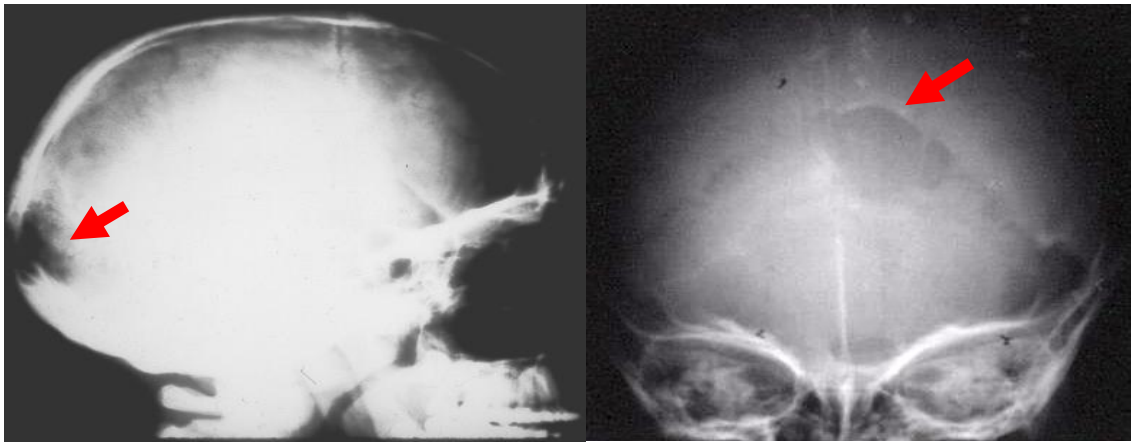


Fig 2b: CT enlarged middle cranial fossa due to absence of greater wing of sphenoid on right.



a. Lateral skull **b. AP view**

Fig. 3ab: NF1 defect in lambdoid suture

Internal auditory canal enlargement can also occur due to dural ectasia and not necessarily from schwannoma (fig. 4ab).

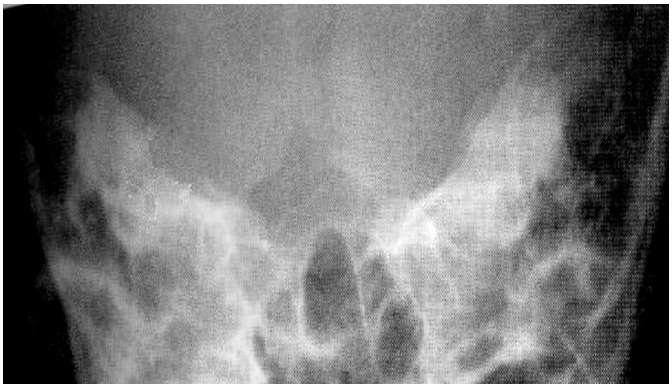


Fig 4a: Towne's projection, showing the internal auditory canals. The right canal is widened.

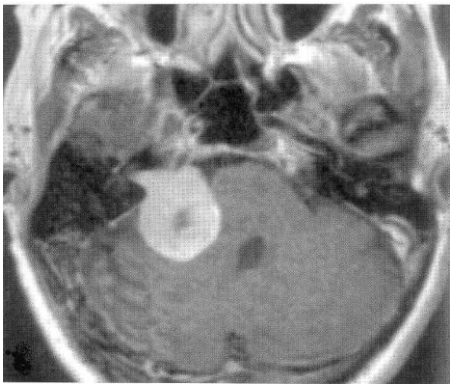


Fig 4b: CT of same Patient - Acoustic Schwannoma.

A comparison of NF1 & NF2 is shown in Table IV.

Table IV:

NF1	NF2
1. Von Recklinghausen's disease	1. Bilateral acoustic schwannomas
2. 1/4000 (represents 90% of NF cases)	2. 1/150,000 (<10% of NF cases)
3. Chromosome 17	3. Chromosome 22
4. Prominent skin manifestations	4. Minimal skin changes
5.Associated with tumors of neurons (hamartomas) and astrocytes (gliomas), plexiform neurofibromas, malignant nerve sheath tumors; dural ecstasia	5.Associated with tumors of meninges (meningiomas) and schwann cells (cranial nerve schwannomas)
6. Spinal neurofibromas (usually small, single)	6. Spinal schwannomas (often large, bilateral, multilevel)
7.Questionable whether these patients develop spinal gliomas at all	7. Spinal ependymomas and astrocytomas a prominent feature

Intracranial neurofibromas are rare except in NF1.

Imaging findings in skull: Plain films may show one or both optic canals to be enlarged. In CT enlargement of optic nerve sheath complex is noted. Contrast enhanced CT will display the features in a better way (fig. 5 & 6).

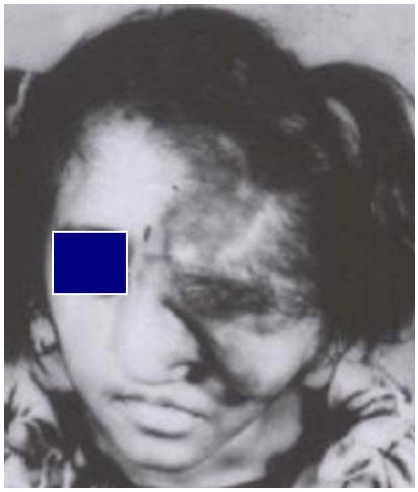


Fig. 5: Plexiform Neurofibroma in 12 yr. old girl

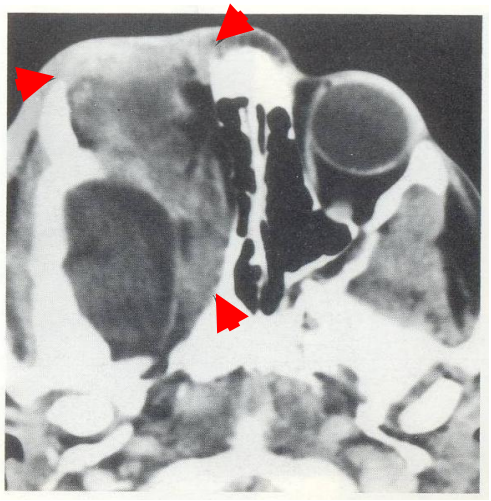


Fig. 6: CECT - A 27 yr. old man with NF1. Hypoplasia of the right greater wing of sphenoid. An extensive cutaneous plexiform neurofibroma is present which involves the orbit and extends into cavernous sinus (arrows)

MR shows lesions of iso / slightly hypointense on T1W1 images mild to strongly Hyperintense. On T2W1 are other high signal areas without mass effect in basal ganglia, internal capsule, pons, cerebral peduncles, cerebellum, etc. These may be slightly hyperintense on T1W1 images also and probably represent hamartomas. Plexiform neurofibroma (diffuse neoplastic involvement of a nerve and its branches) is of exocranial origin but often extend intracranially along natural foramina, fissures (e.g., from orbit, pterygopalatine fossa into cavernous sinus) (Fig. 7).

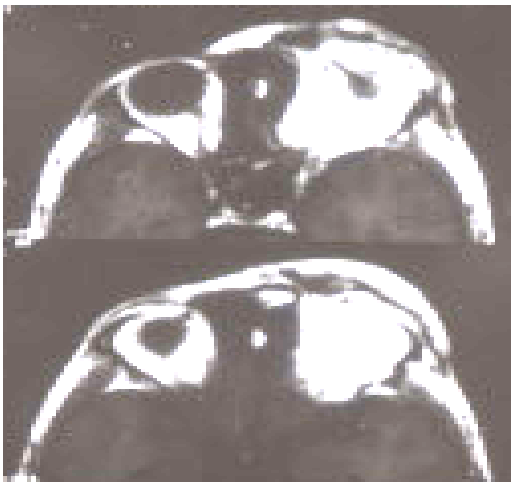


Fig 7: MRI shows diffuse plexiform neurofibroma.

Optic Nerve Glioma

It is most common CNS tumor in NF-1. The lesions can involve one or both optic nerves, chiasm, tracts, lateral geniculate body and optic radiations (fig.8). Mean age of NF-1 patients with ONG is about five years. Optic nerve glioma without NF is twelve years. Histologically it is benign low grade astrocytoma.

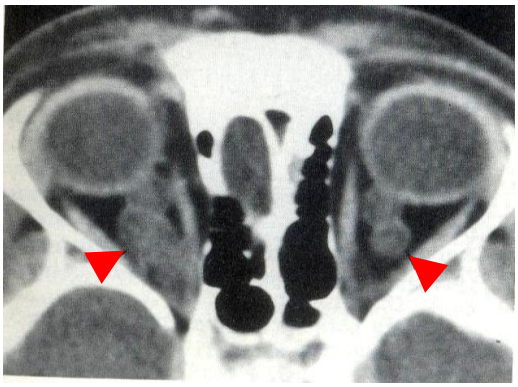


Fig. 8: CT - NF1 Bilateral optic nerve gliomas

MRI shows bright signal in T1 & T2 images (fig. 9)

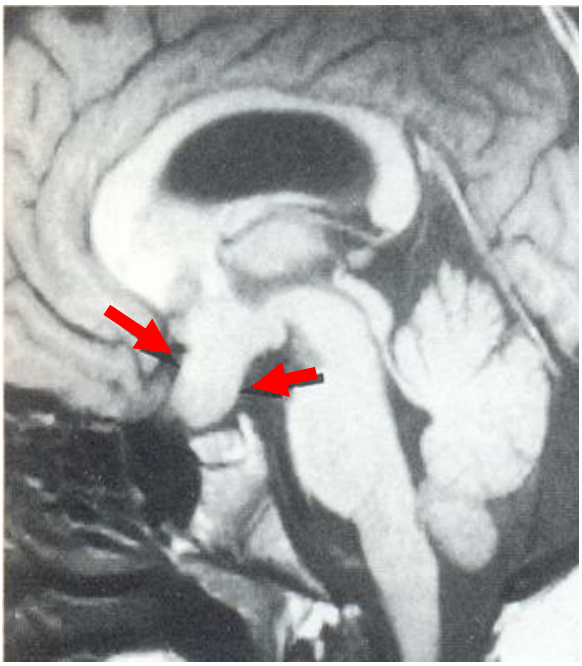


Fig. 9: MR in a 5yr old with NF1- Glioma of the optic nerves & chiasm (large arrows). Bright image in T2 weighted MRI.

Intracranial lesions include astrocytoma, glioblastoma and stenosis of acqueduct due to circumferential involvement by glioma. Nonoptic gliomas (most commonly low grade astrocytomas) occur with increased frequency in NF-1. Common locations are the tectal and periaqueductal regions, brain stem, etc. Occasionally anaplastic astrocytoma or glioblastoma multiforme may develop. Nonglial neoplasms are not a feature of NF1.

Vascular abnormalities include dysplastic stenosis of vessels at/near circle of Willis and intra / extracranial aneurysms

Cranial nerve tumors include schwannomas of cranial nerves III – XII are a feature of NF2, not NF1. Optic nerve (CNII) neoplasms are histologically brain neoplasms. CN1 (Olfactory) is also anatomically a brain tract, not a nerve and does not give rise to Schwannomas.

Axial skeletal lesions

Kyphoscoliosis presents in 1/3 – ½ of patients. It probably reflects primary mesodermal dysplasia. T3 – T7 levels are most common. A short segment angular deformity is usually mild but occasionally can be rapidly progressive, resulting in paraplegia. Radiological findings include kyphoscoliosis, vertebral scalloping of, posterior, anterior and lateral borders (fig. 10abcd).

Meningoceles may b e noted any where from cervical spine to sacrum with marked dural ectasia (fig. 11abcd)

Lateral meningoceles may be seen. Agenesis or hypoplastic pedicles dysplastic vertebrae are noted. The ribs may be widened and distorted, generally named as “twisted ribbon ribs”. Vertebral scalloping due to dural ectasia is a common finding. Meningoceles may be noted any where from cervical spine to sacrum.

Lateral meningoceles are due to weakened, dysplastic meninges that protrude through enlarged intervertebral foramina (Pulsion diverticulae). Thoracic region is most common, usually on right side. Lumbosacral and cervical region also occur but are less common. CT shows dumb bell shaped CSF – attenuation lesion protruding through enlarged neural foramen with adjacent thinned pedicle, scalloped vertebral body. MR shows CSF signal on all sequences (fig. 12ab).

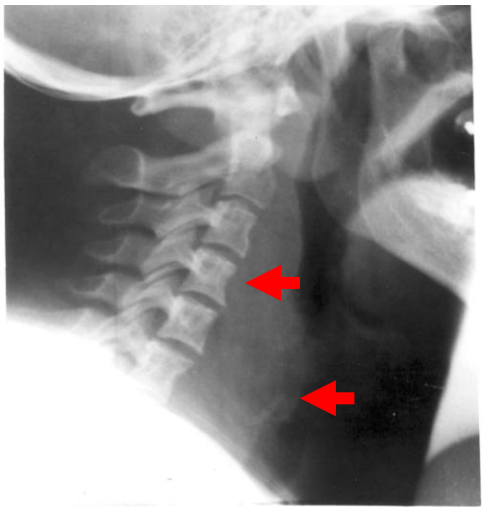


Fig 10a: Plexiform neurofibromatosis. Note anterior scalloping of vertebrae with a precervical mass.

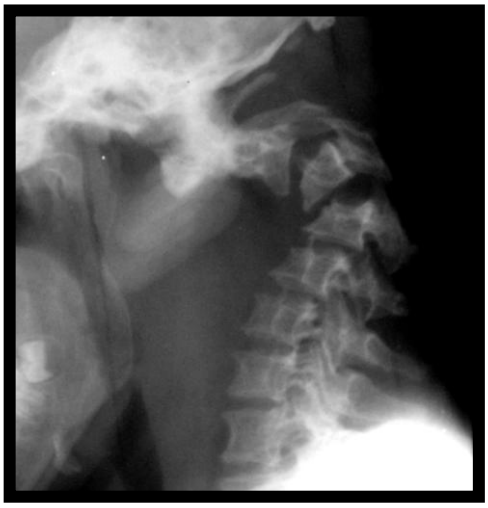
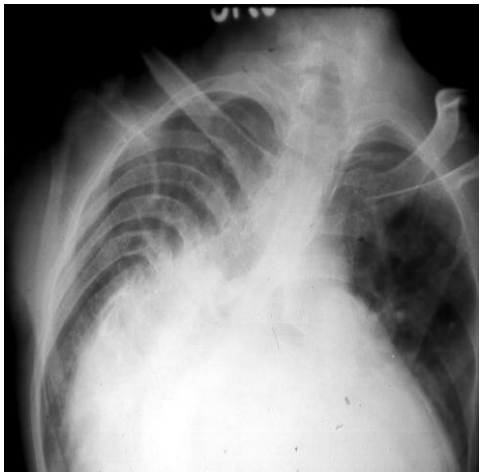
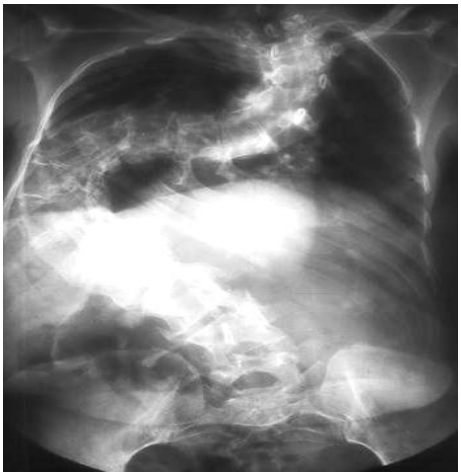


Fig 10b: 12 year old boy with increasing kyphotic deformity of the neck- note the precervical mass with dysplasia of the vertebrae.



c



d

Fig. 10 c & d: Scoliosis with thin & twisted ribs.

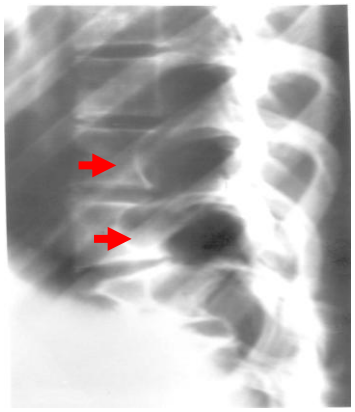


Fig. 11a: Marked posterior vertebral scalloping

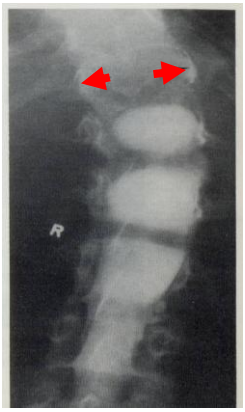


Fig. 11b: Myelogram - Dural ectasia. Note thinned pedicles, widened canal. No neurofibromas are identified.

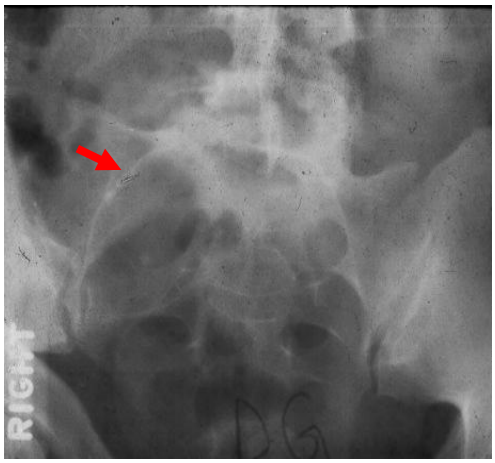


Fig. 11c: Sacral meningocele in NF1 with erosion of right pedicles.

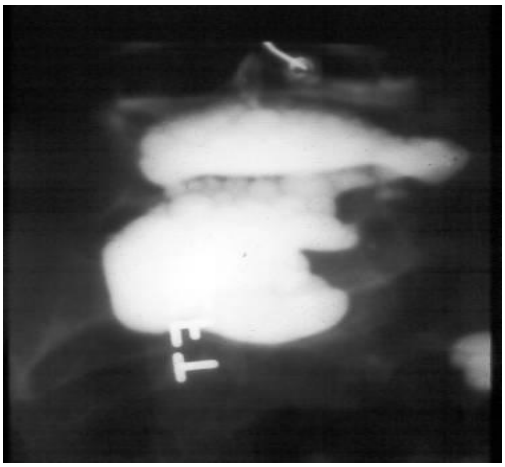


Fig. 11d: Myelogram – Note the contrast in the dilated dural sac.

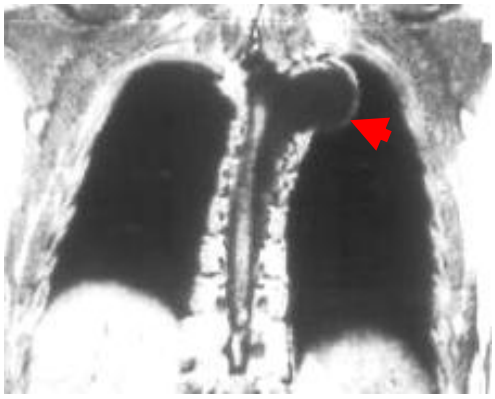


Fig. 12a: MRI - Lateral thoracic meningocele on left.

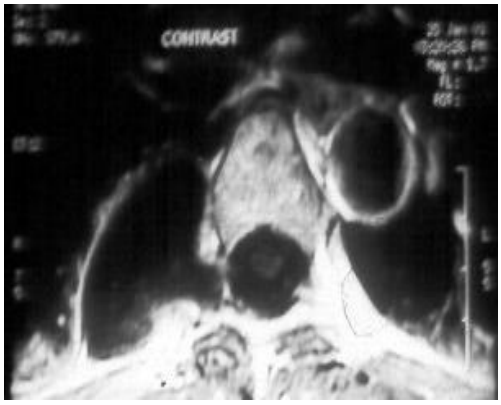


Fig. 12b: Coronal section – Lateral thoracic meningocele on left.

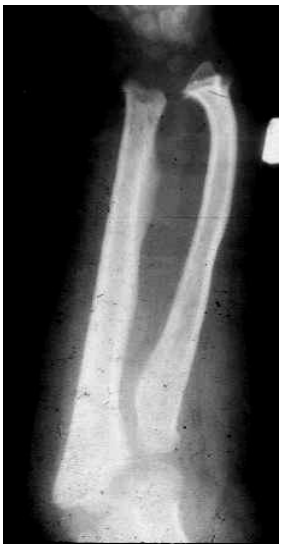


Fig 13a: Forearm Hypertrophy of soft tissues and deformed radius

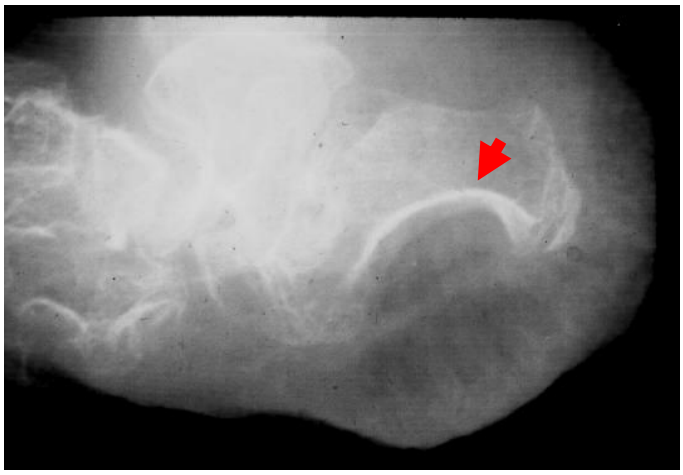


Fig. 13b: NF1 involving foot. Note hypertrophy of the soft tissues and erosion of calcaneum.

Peripheral skeletal manifestations include hypertrophy, atrophy of bones erosions, intraosseous cystic lesions and medullary streaking. Soft tissue swellings of various sizes are also noted (fig. 13abc).

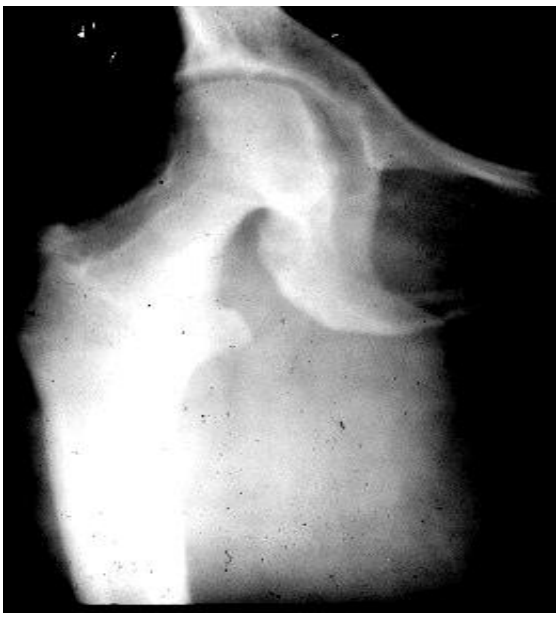
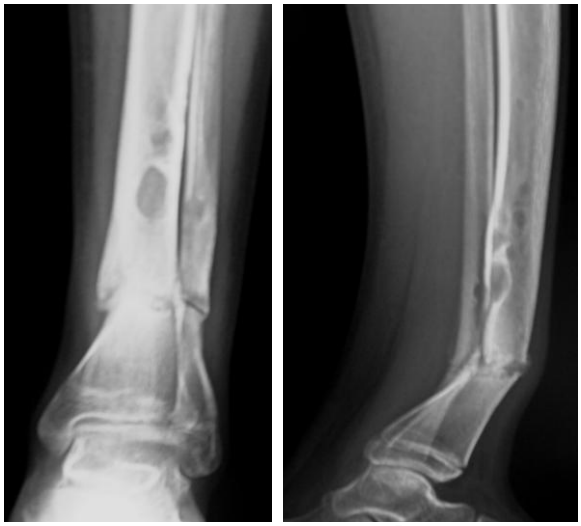


Fig. 13c: Soft tissue swelling, deformity of the head & neck of femur, hypoplastic obturator ring.



a **b**

Fig. 14ab: Pseudoarthrosis - 11 yr old girl with progressive deformity of right leg since 6 months. Note the lucencies which represent mesenchymal dysplasia and not necessarily neurofibromata.

Pseudoarthrosis is one of the common manifestations of NF1, mostly involving the tibia (fig. 14ab).

MRI shows the neurofibromata as well as pseudoarthrosis (fig. 15ab).

Other associated manifestations are shown in Table V.

Table V:

- **Pheochromocytomas**
- **Interstitial lung disease – fibrosing alveolitis**
- **Renal artery stenosis, compression by NF producing hypertension**
- **Fibrous dysplasia**
- **Medullary thyroid carcinoma**
- **Other tumors of endocrine glands e.g. MEA 2B & 3 Syndromes**
- **Rickets / Osteomalacia**
- **Atlanto axial dislocation**
- **Cardiovascular – Congenital heart, aortic stenosis & coarctation.**

Associated malignant tumor include carcinoids, pheochromocytoma, embryonal tumors of kidney e.g. wilm's, neuroblastoma, rhabdomyosarcoma and miscellaneous entities.

Neurofibromatosis 2 (NF2)

NF2 was first described in 1882 by Wishart. The disease was not separated from Von Recklinghausen disease until 1987. Mutations in (or rarely deletion of) the *NF2* gene located on the long arm of ***chromosome 22***. The disease is autosomal dominant with a high degree of penetrance. Many patients have a strong family history.

Inherited autosomal dominant syndrome characterized by multiple schwannomas, meningiomas, and ependymomas.The most common tumor associated with the syndrome is the vestibulocochlear (VIII) schwannoma, and as many as 10% of patients with this tumor have NF2. It is also termed as schwannomatosis or MISME syndrome, the acronym – Multiple Inherited Schwannomas, Meningiomas and Ependymomas. Incidence: Approximately 1 in 50,000 (much less common than NF – 1) (fig. 16).

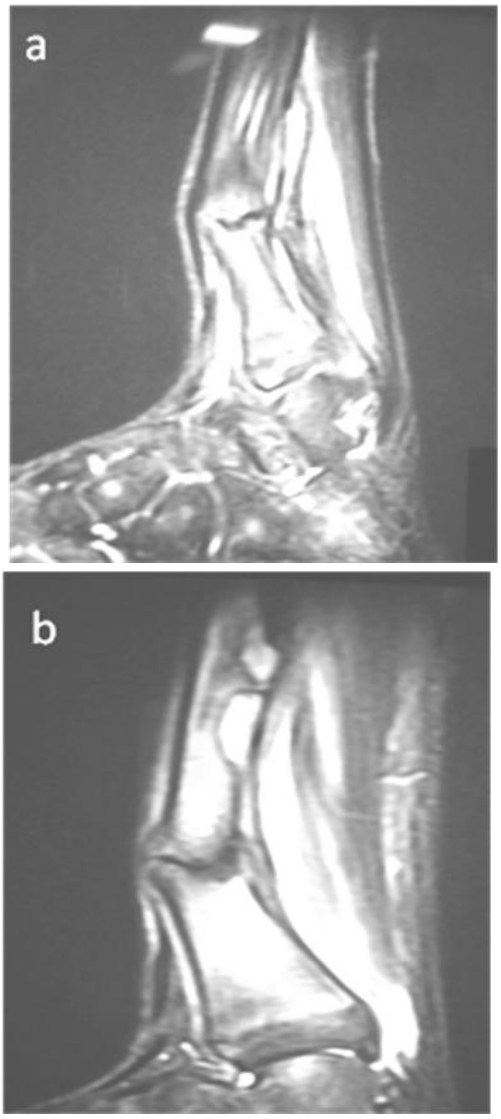


Fig 15ab: MRI – Pseudoarthrosis with neurofibromata.

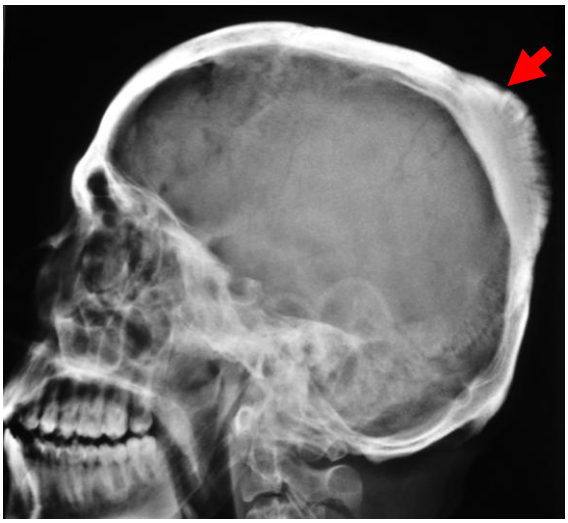


Fig. 15: NF2 - Hyperostosis of parietal bone due to underlying Meningioma.

Bilateral CN VIII masses seen with appropriate imaging techniques. A first-degree relative with NF2 and either a unilateral CN VIII mass or any of two of the following in Table VI (fig. 16)

Table VI:

- **Neurofibroma.**
- **Meningioma**
- **Glioma**
- **Schwannoma**
- **Juvenile posterior subcapsular lenticular opacity**

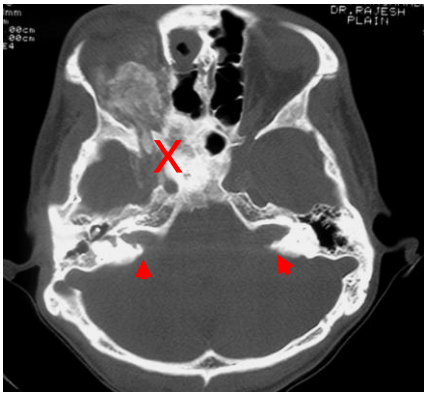


Fig. 16: NF2 - CT showing enlarged internal Auditory canals (↑). Recurrence of optic nerve Sheath meningioma (X).

Revised diagnostic criteria of NF2 was proposed that adds a section for presumptive or probable diagnosis of NF2.

Definite diagnosis of NF2 (*Gutmann et al, 1997*)

- Bilateral CN VIII schwannomas on MRI or CT scan (no biopsy necessary)
- First-degree relative with NF2 and either unilateral early-onset CN VIII schwannoma (age <30 y) or any 2 of the following:
  - Meningioma
  - Glioma
  - Schwannoma
  - Juvenile posterior subcapsular lenticular opacity (juvenile cortical cataract)

Presumptive diagnosis of NF2

- Early onset of unilateral CN VIII schwannomas on MRI or CT scan detected in patients younger than 30 years and 1 of the following:
  - Meningioma
  - Glioma
  - Schwannoma
  - Juvenile posterior subcapsular lenticular opacity

- Multiple meningiomas (>2) and unilateral CN VIII schwannoma or 1 of the following:
  - Glioma
  - Schwannoma
  - Juvenile posterior subcapsular lenticular opacity

CNS Manifestations - NF -2 include vestibulocochlear schwannomas, schwannomas of other cranial nerves (III – XII) and solitary / multiple meningiomas (both spinal, intracranial) (Fig. 17ab).

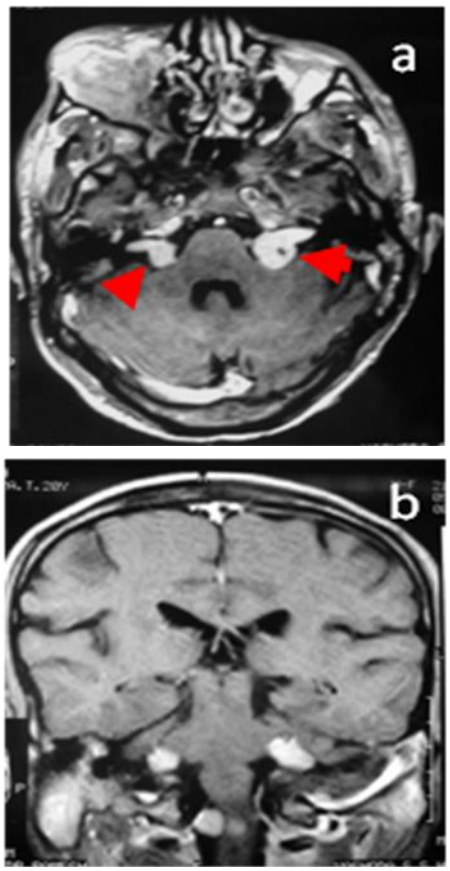


Fig 17ab: MRI - Bilateral acoustic schwannomas with bright signals (Same patient as in fig.16)

Other Tumors

Questionable whether patients with NF-2 develop intracranial gliomas, astrocytomas of cord, ependymomas of cord (most common intrinsic cord neoplasm in NF-2) and multiple paraspinal schwannomas (often large, bilateral multilevel). It is important to survey the entire spinal canal in NF2 as there is greater incidence of tumors in spinal canal in NF2 (predominantly extra medullary tumors).

Important Points to Remember:

- Cause of NF is due to mutation of NF1 gene
- Clinical diagnosis of NF1 is simple

- Every organ in the body may be involved in NF1
- Isolated neurofibromas can occur any where without NF1
- Different types of NF exist
- Genetic disorder, hence many associated congenital abnormalities exist
- NF2 expresses at a later age
- Imaging of spinal cord should be included in NF2.

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