

Sistema Socio Sanitario



Regione
Lombardia



Fondazione IRCCS
Policlinico San Matteo

ASST Pavia

ATS Pavia



UNIVERSITÀ
DI PAVIA

GRAND ROUNDS CLINICI DEL MERCOLEDÌ con il Policlinico San Matteo

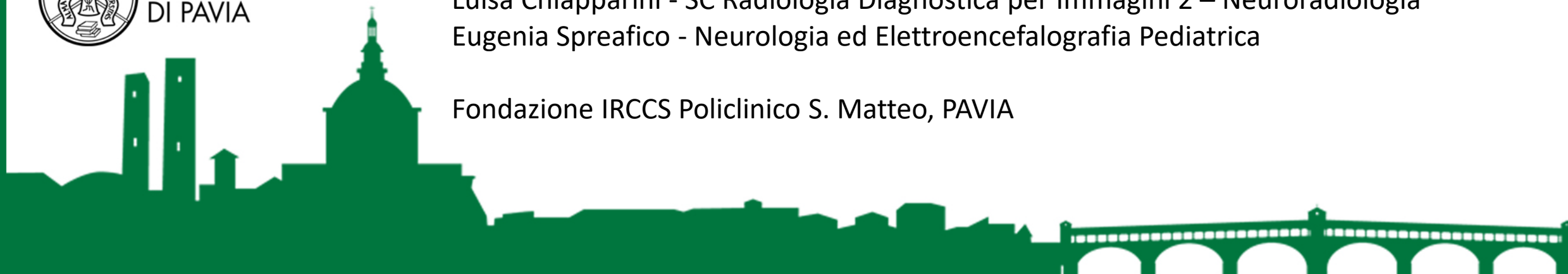
Aula Magna “C. Golgi” & WEBINAR

CASO CLINICO

Neurofibromatosi I: aspetti clinici e neuroradiologici

Luisa Chiapparini - SC Radiologia Diagnostica per Immagini 2 – Neuroradiologia
Eugenia Spreafico - Neurologia ed Elettroencefalografia Pediatrica

Fondazione IRCCS Policlinico S. Matteo, PAVIA



F.Z.

9 mesi



Macchie CAL all'età di 4 mesi

2020



Nato a 35+3 SG da P.E.

P.N: 2650 gr, L: 48 cm, CC: 32 cm.

Buon adattamento perinatale

FOP con shunt sx-dx non emodinamicamente significativo

SPM normale



Mut. gene **NF1**

mut c.6971 T>G de novo



Fratello con una macchia CAL

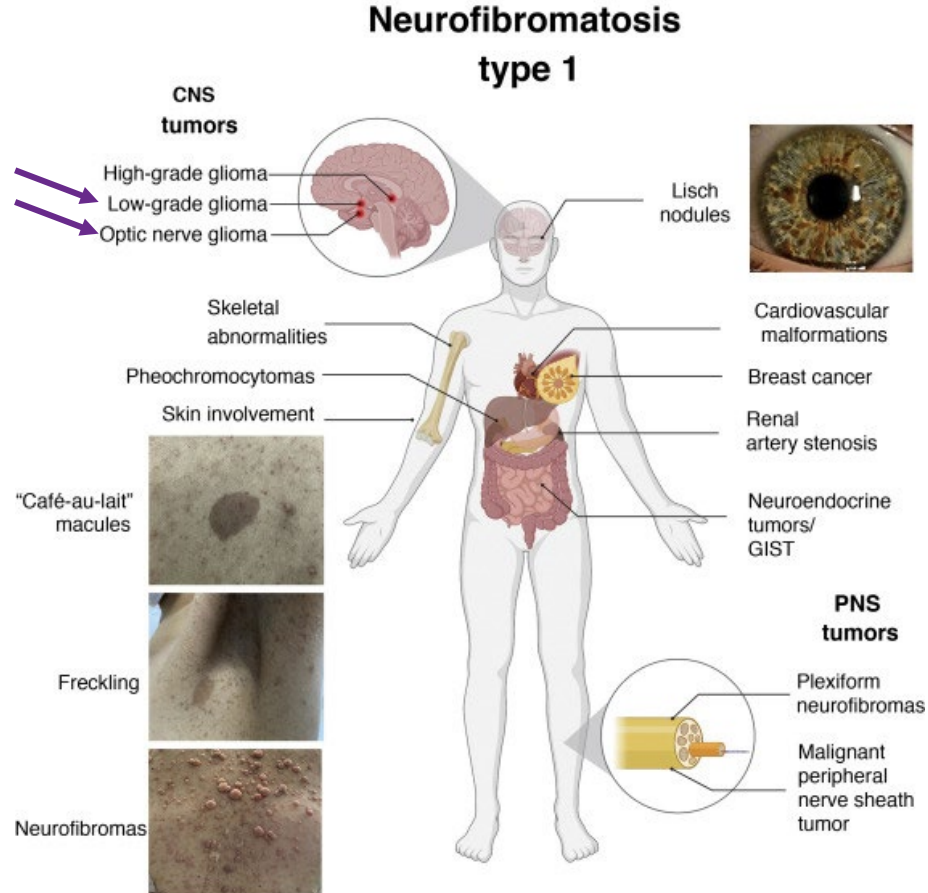
Non NF in famiglia

Non patologie neurologiche



GRAND ROUNDS CLINICI DEL MERCOLEDÌ

Caratteristiche cliniche



NBOs a livello di:

- nucleo dentato cerebellare sx,
- peduncolo cerebellare medio sx,
- globo pallido sx
- talamo sx

Corpo calloso:

- Spessore > norma per età

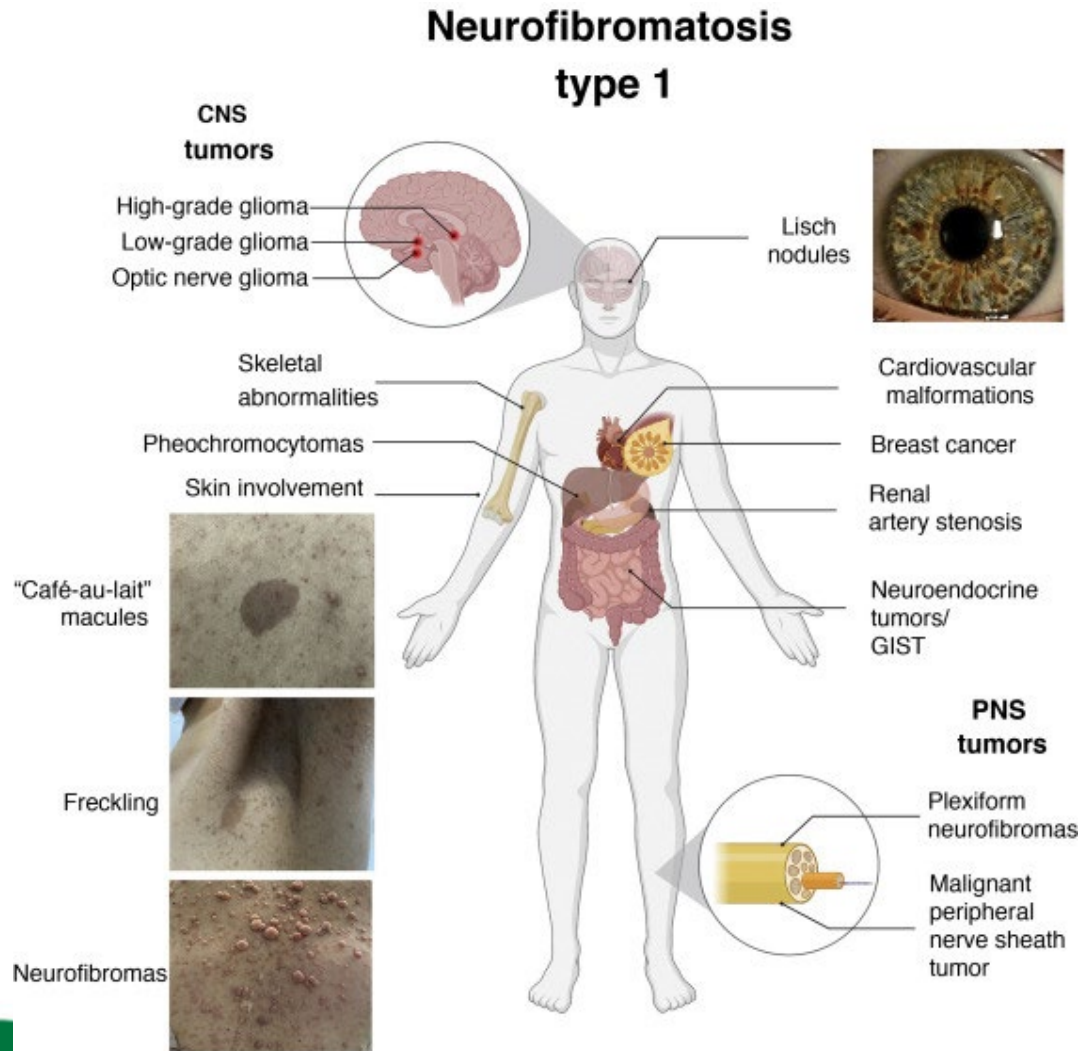
Glioma delle vie ottiche:

- **Sx>Dx**
- tratto retrobulbare distale-
intra canalicolare del nervo ottico
sinistro e del tratto retrobulbare
distale del nervo ottico destro

- **Epicanto**
- **Esotropia sinistra.**
- **Angioma** a livello della **glabella**
- **Macchie caffelatte diffuse** al tronco e agli arti inferiori, la maggiore a livello dorso-lombare destro di diametro max 5-6 cm.
- **Non neurofibromi alla palpazione.**



Caratteristiche cliniche



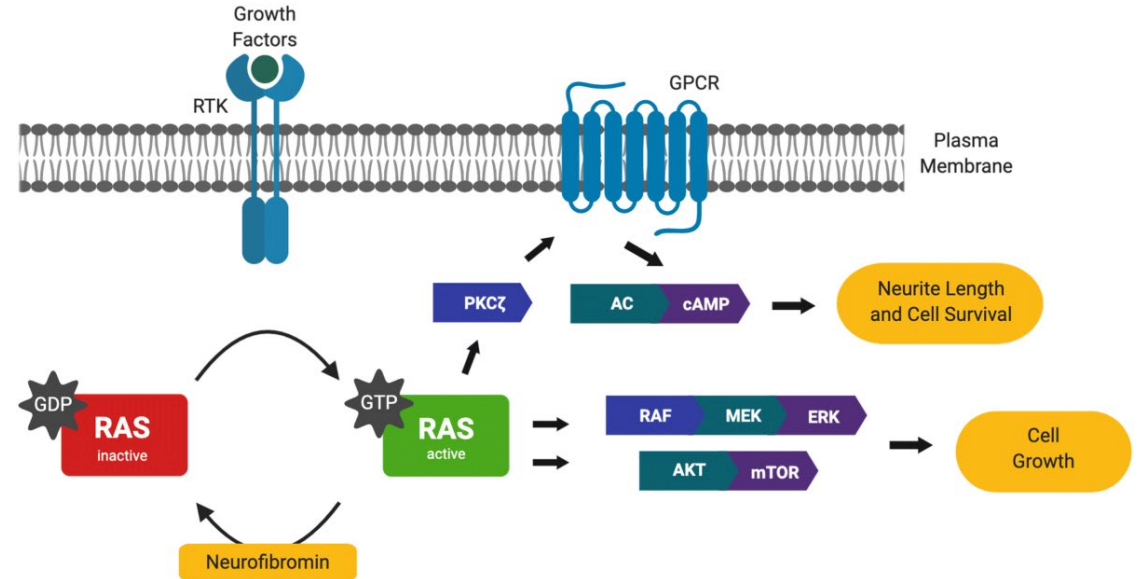
Diagnosi

due o più dei seguenti criteri:

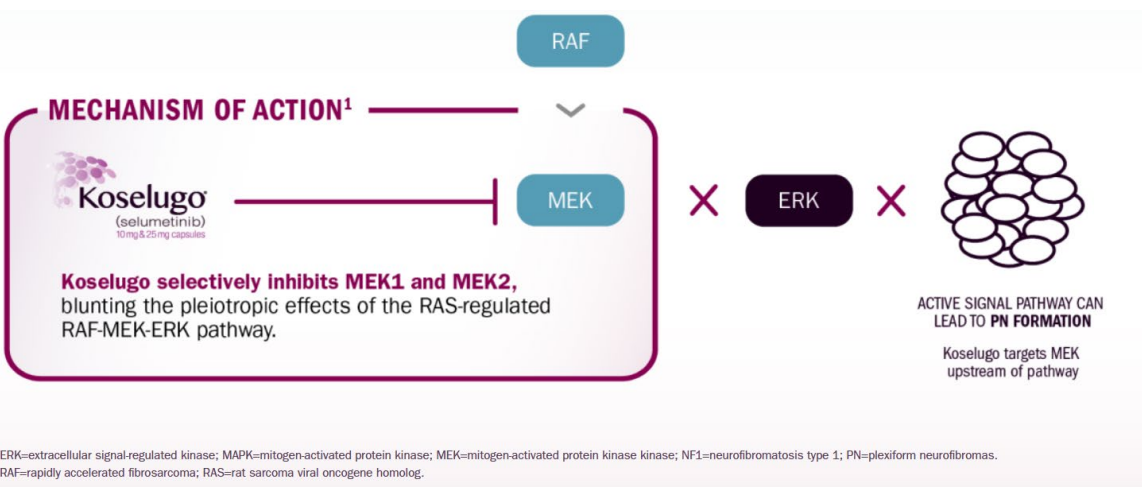
- ≥ 6 macchie café-au-lait di diametro superiore a 5 mm in età prepuberale e di diametro superiore a 15 mm in età postpuberale
- Lentiggini nella regione ascellare o inguinale
- Due o più neurofibromi di qualsiasi tipo o un neurofibroma plessiforme
- Glioma della via ottiche
- Due o più noduli di Lisch dell'iride identificati dall'esame con la lampada a fessura o due o più anomalie coroideali (CA), definite come noduli luminosi e a chiazze, visualizzati con la tomografia a coerenza ottica (OCT)/riflettanza nell'infrarosso vicino (NIR).
- Una lesione ossea distintiva, come la displasia dello sfenoide, l'inarcamento anterolaterale della tibia o la pseudartrosi di un osso lungo.
- **Una variante eterozigote patogena di NF1** con una frazione allelica di variante del 50% in tessuti apparentemente normali come i globuli bianchi.

ETIOPATOGENESI...

- **alterazioni in eterozigosi** a carico del gene **onco-soppressore NF1** (17q11.2), che codifica per la proteina **neurofibromina** coinvolta nella regolazione negativa del pathway RAS, implicato nella proliferazione e differenziazione cellulare
- maggior parte: mutazioni inattivanti (LoF) del gene NF1, con conseguente produzione di ridotti livelli di neurofibromina
- circa il 5% dei pazienti microdelezione a carico della regione 17q11.2 comprendente l'intero gene NF1



...E PROSPETTIVE TERAPEUTICHE



Selumetinib è indicato in monoterapia per il trattamento del neurofibroma plessiforme (PN) **inoperabile, sintomatico** in pazienti pediatrici con neurofibromatosi di tipo 1 (NF1) a partire dai 3 anni di età.

AIFA

Dosing 25 mg/m² taken orally twice daily on an empty stomach

Warnings Cardiomyopathy, rash, ocular toxicity, GI toxicity, elevated CPK





Selumetinib normalizes Ras/MAPK signaling in clinically relevant neurofibromatosis type 1 minipig tissues in vivo

[Sara H Osum](#)¹, [Alexander W Coutts](#)², [Dylan J Duerre](#)², [Barbara R Tschida](#)², [Mark N Kirstein](#)^{1,3}, [James Fisher](#)^{1,3}, [W Robert Bell](#)^{1,4}, [Oona Delpuech](#)⁵, [Paul D Smith](#)⁵, [Brigitte C Widemann](#)⁶, [Christopher L Moertel](#)¹, [David A Largaespada](#)¹, [Adrienne L Watson](#)^{2,5}

Follow-up neuro-radiologico

RMN encefalo e tronco encefalico

Nov 22

NBOs

- nucleo dentato cerebellare sx,
- peduncolo cerebellare medio sx,
- globo pallido sx
- talamo sx

Corpo calloso:

- Spessore superiore alla norma rispetto all'età

Glioma delle vie ottiche:

- **Sx>Dx**
- tratto retrobulbare distale-intracanalicolare del nervo ottico sinistro e del tratto retrobulbare distale del nervo ottico destro

Dic 23

Progressione del glioma delle vie ottiche:

- **Sx>Dx**

Lug 24

Sovraponibile a reperti precedenti

Follow-up visivo

PEV

2021

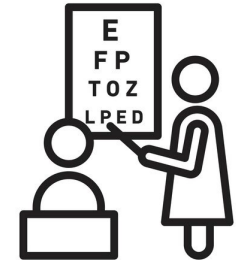
- risposte corticali nella norma

Feb 23

- OD: componenti a e b dell'ERG riproducibili. Risposta corticale riproducibile con asimmetria di latenza della componente IV rispetto al controlaterale e presenza di picco intermedio di latenza circa 94 ms di non sicuro significato patologico.
- OS: componenti a e b dell'ERG riproducibili. Risposta corticale riproducibile.

Lug 24

- Possibile lieve sofferenza delle vie visive centrali bilateralmente.



-Visite oculistiche ed ortottiche: nei limiti di norma

Cancer risk: 2.5 times higher than that of the general population (Ann Oncol 2020;31(7):873–883)

Tumours arising in individuals with NF1 and their frequency

Cutaneous neurofibroma: frequency 40–60%

Internal nerve sheath tumour (intranural and plexiform neurofibroma): frequency 60%

Malignant peripheral nerve sheath tumour: frequency 8–13% (the most common malignancy in patients with NF1)

Optic pathway glioma: frequency 15–20%

Malignant glioma: frequency 0.8%

Leukaemia: frequency <1%, although a 200 to 500-fold increased risk of JMML

Pheochromocytoma: frequency 0.1–13%

Rhabdomyosarcoma: frequency 1–6%

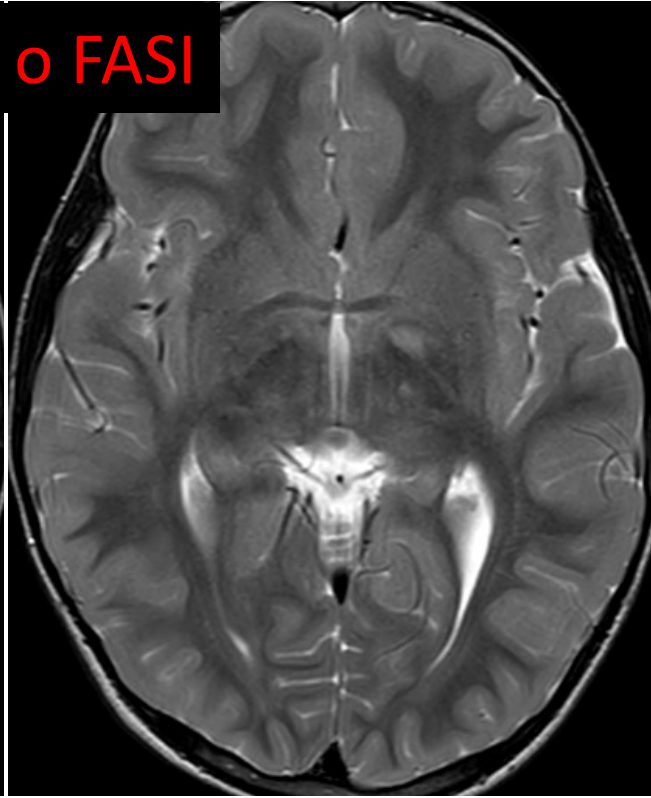
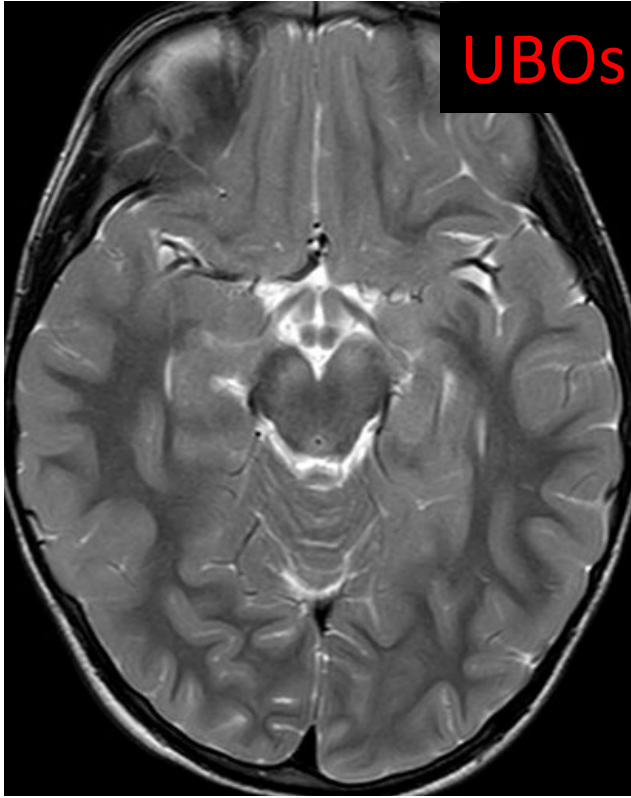
Gastrointestinal cancers, eg, GIST: frequency 5–30%

Breast cancer: frequency 8.4% by age 50

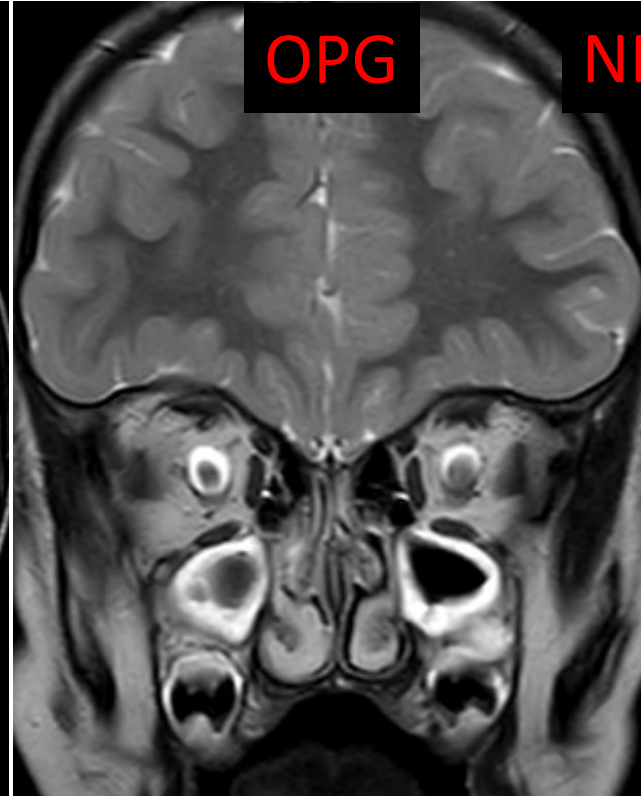
Lin, A. L. & Gutmann, D. H.
NATURE REVIEWS CLINICAL ONCOLOGY 2013

I pazienti con NF1 hanno una maggiore predisposizione allo sviluppo di tumori benigni e maligni.
Tra questi sviluppano tumori della cellule di Schwann (neurofibromi, neurofibromi maligni) tumori delle vie ottiche specialmente gliomi ed altri tumori gliali maligni

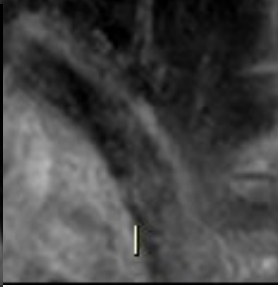
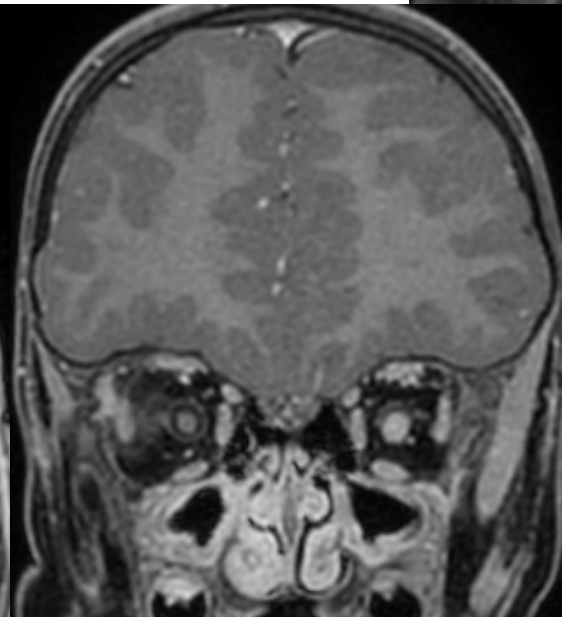
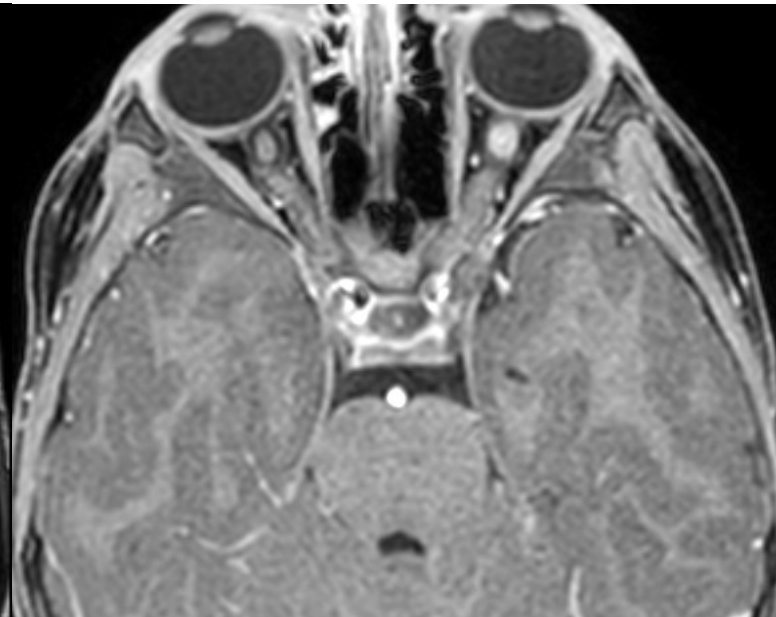
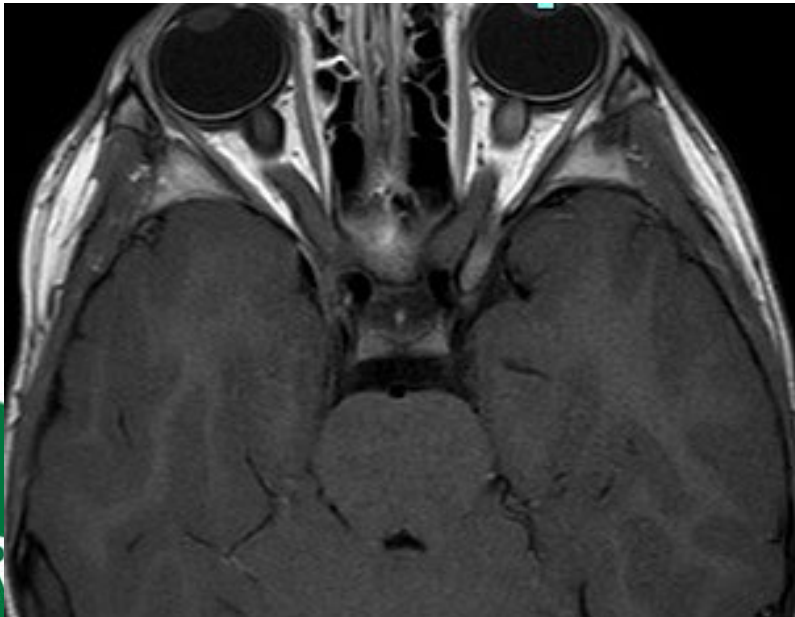
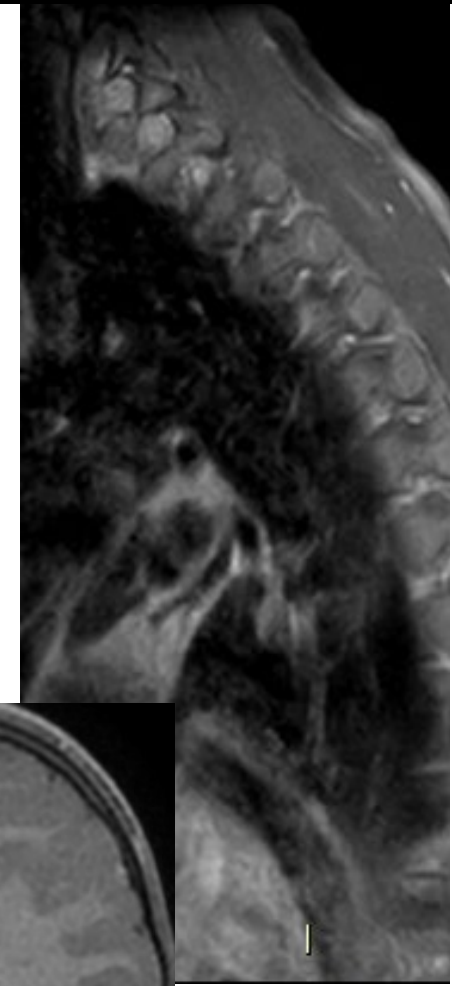
UBOs o FASI



OPG



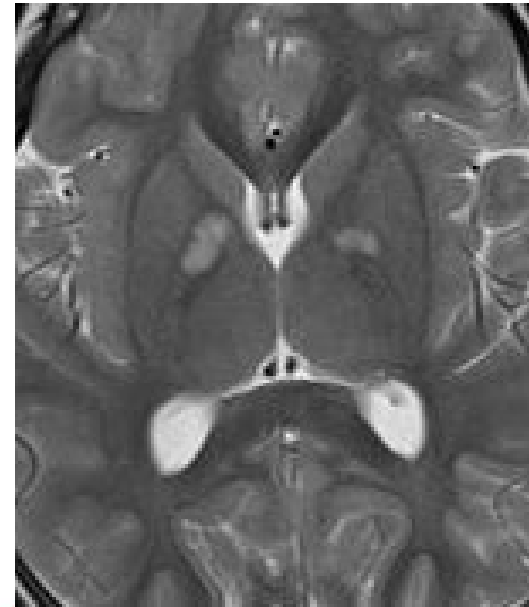
NEUROFIBROMAS



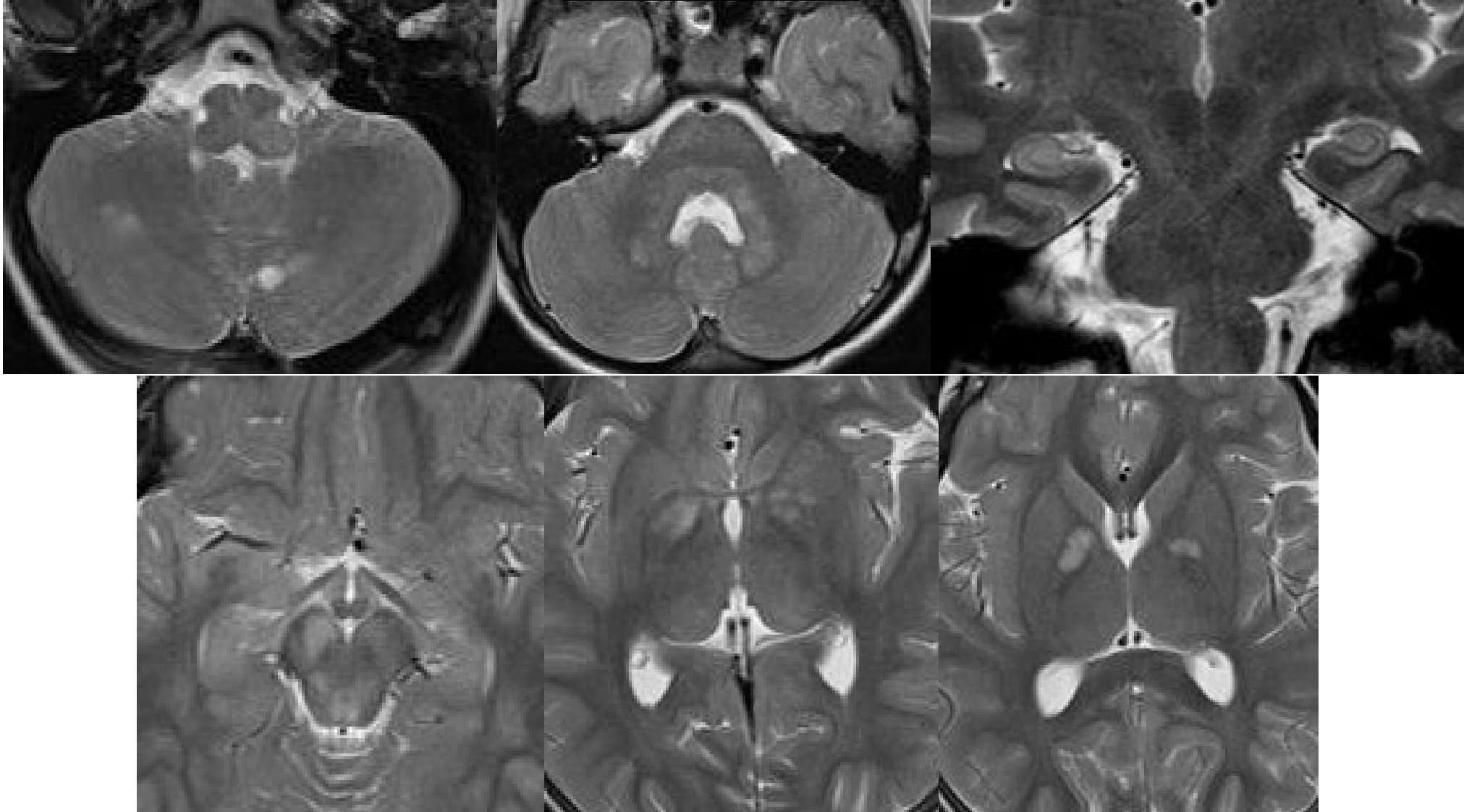
SNC

Unidentified Bright Objects or Focal Abnormal Signal Intensities

- regions of increased signal intensity visible on T2, 60-80% of pediatric patients
- no mass effect or enhancement
- basal ganglia, thalami, brainstem and cerebellum
- not associated with neurological deficits
- rarely occur in isolation
- largest mostly located in the cerebellum

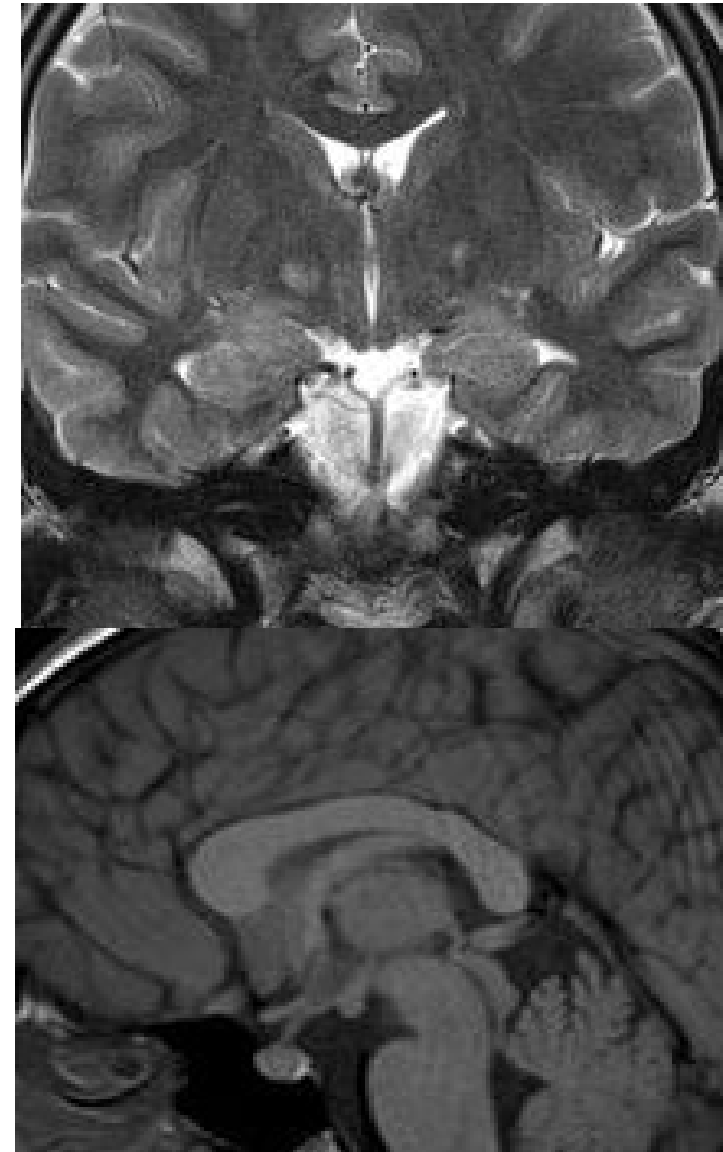
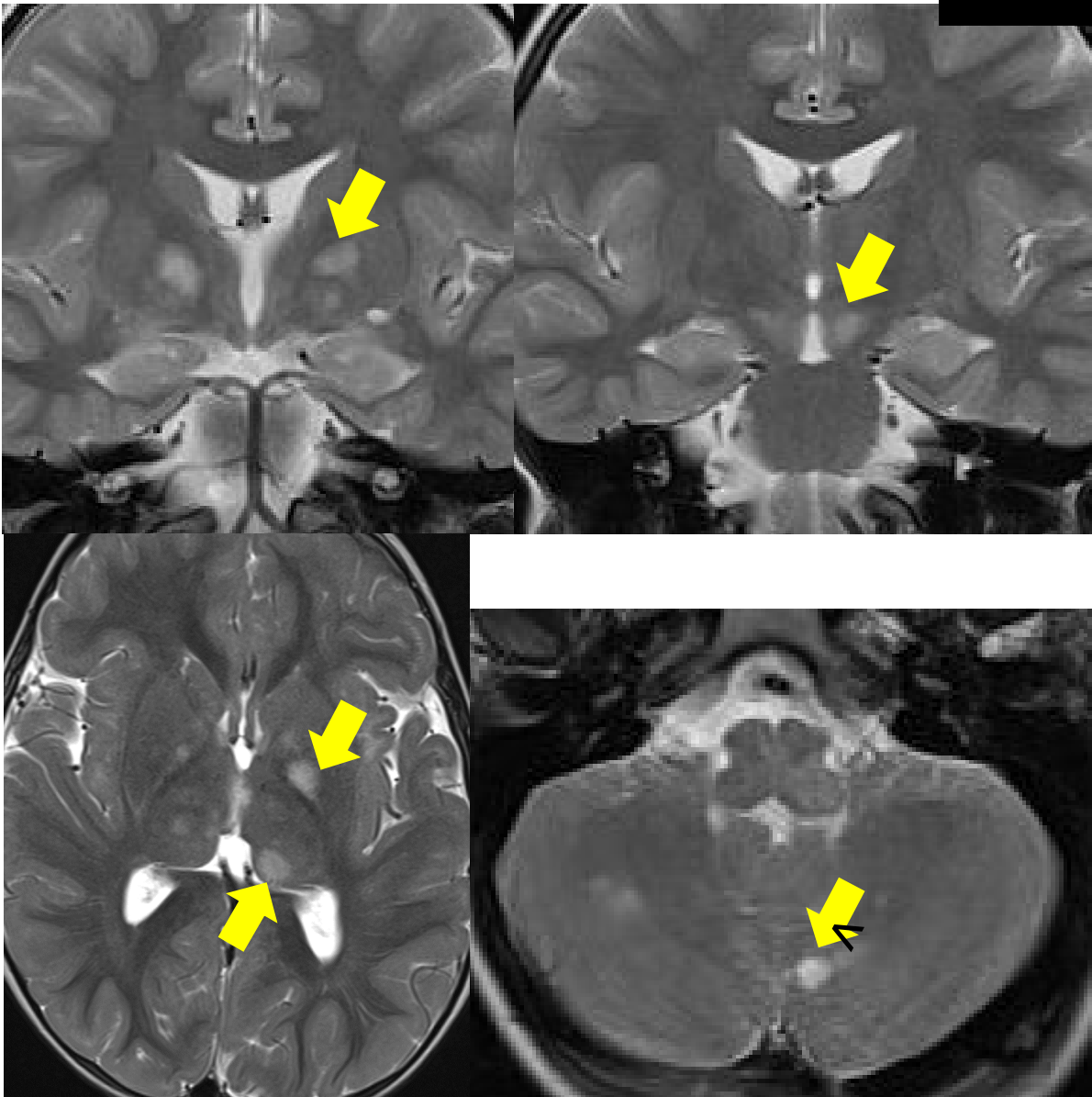


UBOs o FASI



Sono molto frequenti presenti nei bambini con NF1 tra i 4 e i 10 anni e sono alterazioni di segnale iperintense in T2 che di solito non si vedono in T1, non hanno effetto massa e generalmente non hanno enhancement dopo contrasto. AP: corrispondono ad aree di vacuoli o spongiosi o aree amartomatose o aree di mielinizzazione alterata.

UBOs o FASI

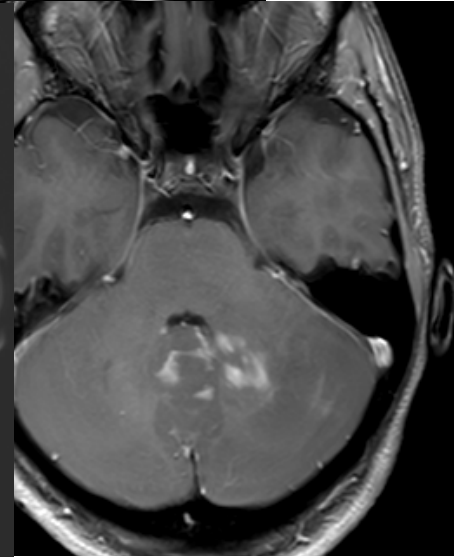
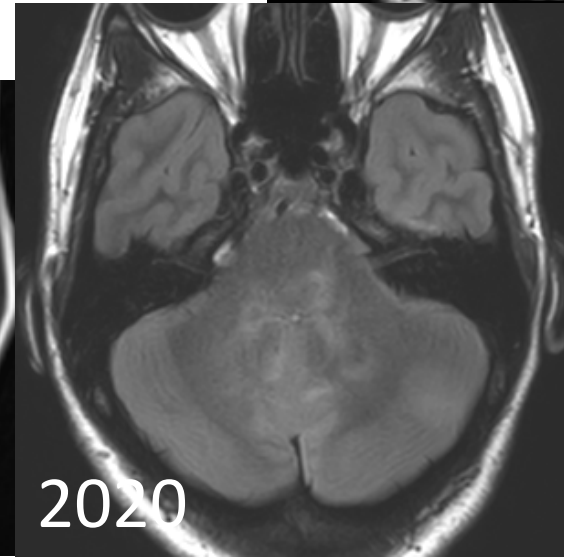
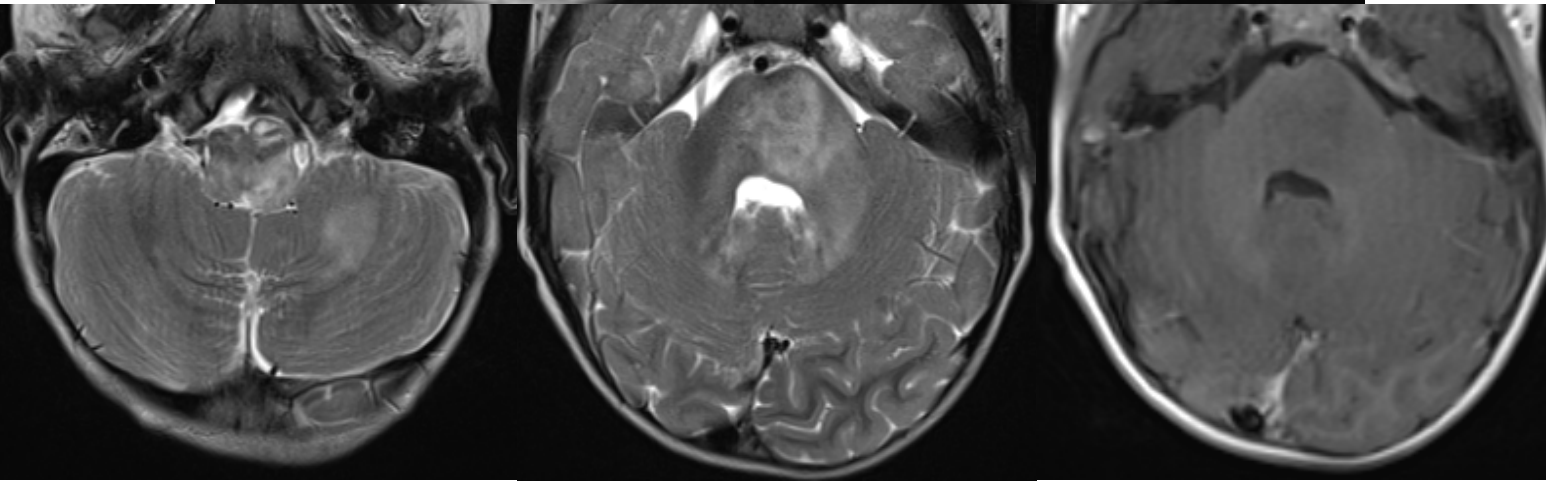
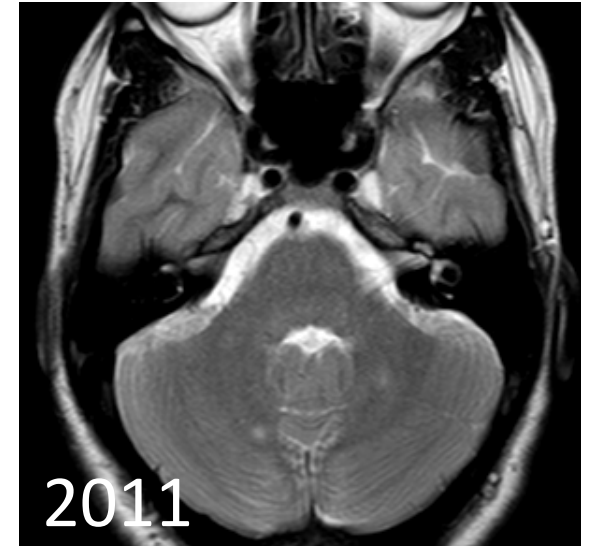
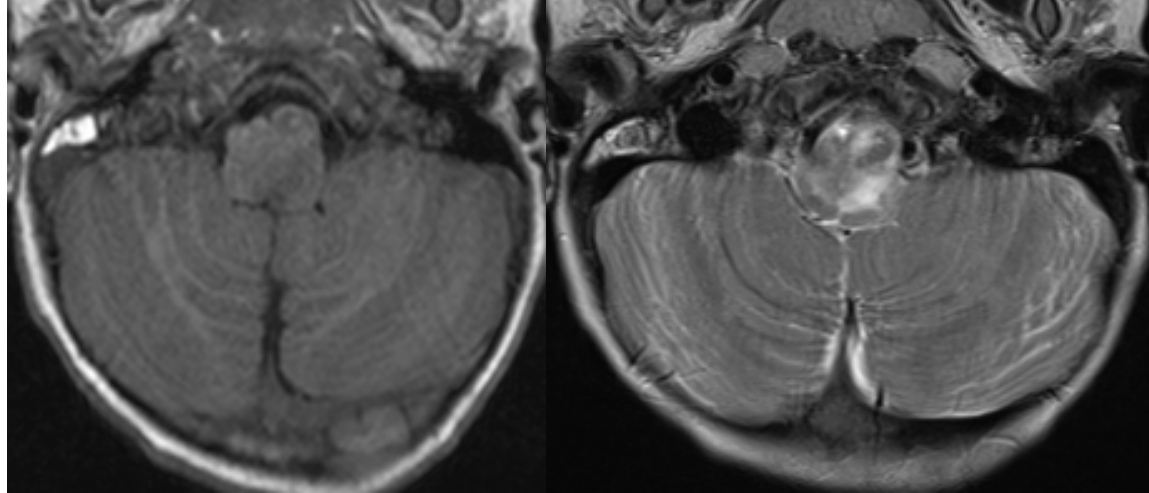


corpo calloso dismorfico

Le aree più colpite sono il GP, il talamo, il tronco e il cervelletto.
Aumentano di numero e di grandezza nella prima infanzia poi tendono a sparire.



UBOs o FASI



Courtesy of Dr. Marco Moscatelli

quando dobbiamo preoccuparci?



Table 8 Details of patients with NF1 showing mass effect and/or enhancement of focal abnormal signal intensities (FASI)

Patient study number	Age at finding in years (y)	Location	FASI diameter (cm)	Mass effect	Enhancement	FASI outcome
7	17.7	L cerebellum, R basal ganglia	1.2, 0.8	–	+	Remained stable in size with persisting enhancement on a repeat scan 1.3y later. Died at age 28.1y from a pelvic sarcoma
8	12.8	L cerebellum	3.7	+ initially only	+	Enlarged to 4 cm at age 13.1y then shrunk to 2.8 cm with resolution of mass effect and enhancement at age 13.5y. Disappeared at 21.3y
	12.8	R cerebellum	2	+	+	Enlarged to 2.7 cm. Partial excision at age 13y (benign ganglioma). Remnant enhanced then resolved at age 21.8y. Died at age 23.4y from a malignant nerve sheath tumor
13	2.8	L cerebellum	1.2	+	–	Decreased to 0.8 cm with resolution of mass effect at age 5.5y. Disappeared at age 7.6y
	2.8	R cerebellum	1	–	+	Decreased to 0.5 cm with resolution of enhancement at age 5.5y. Disappeared at age 7.6y
	7	R cerebellum	0.8	+	+	Resolved at age 11.2y
20	1.9	L thalamus	1.6	+	–	Resolved at age 2.3y
33	3	R periventricular region	5.6 (few confluent FASI)	+ initially only	+ at 4.6y	Diameter was 4 cm and enhancement persisted on last scan at age 16y
	3	Midbrain	1.6	–	+	Resolved at age 4y
41	11.7	Pons/ L superior cerebellar peduncle	1.6	+	+	Enlarged to 2.2 cm at age 17.2y then shrunk to 1.3 cm with resolution of mass effect at age 19.9y. Enhancement persisted on last scan at age 19.9y
	14.2	L cerebellum	0.8	–	+ at 18.8y	Enlarged to 2 cm and developed into a cystic lesion with a solid component. Fully resected and proven to be a low grade pilocytic astrocytoma
44	1.8	Bilateral basal ganglia	4.9 each	+	+	Shrunk to 2.5, 2.7 cm at age 2.3y then enlarged to 3.9, 5 cm on last scan at age 3.8y. Both mass effect

Atypical characteristics

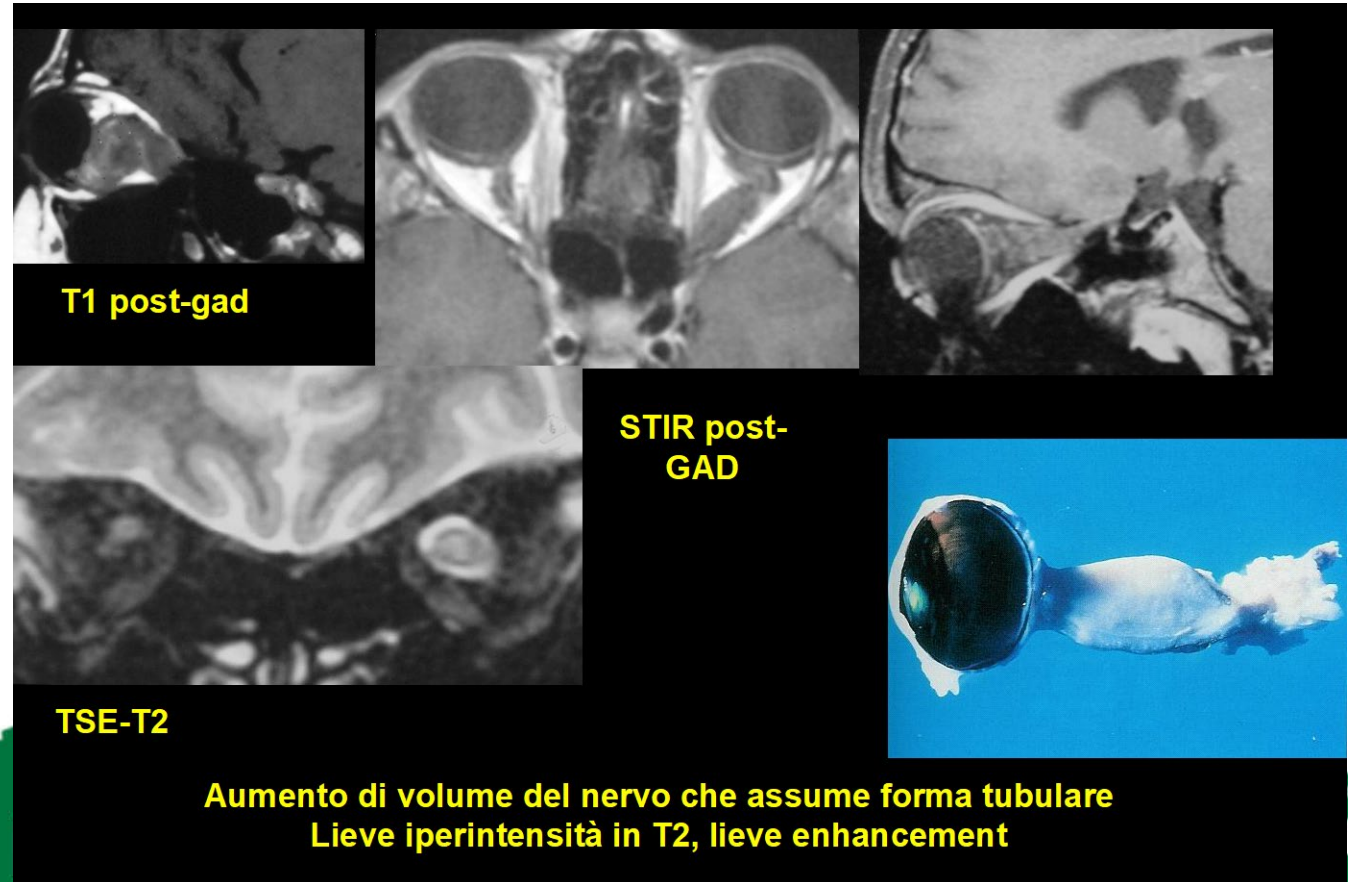
- Mass effect
- Enhancement
- Size variations

Salman, Michael S., et al. "Cerebellar radiological abnormalities in children with neurofibromatosis type 1: part 1-clinical and neuroimaging findings." *Cerebellum & ataxias* 5.1 (2018): 1-12.

SNC

OPG (Optic Patway Glioma)

- Thickening of the optic nerve, chiasm or optic tract
- 15–20% of patients with NF1, usually presenting in the first decade of life
- 40% of them visual symptoms
- Symptoms mass effect
- Histological Type: Low Grade Glioma
 - pilocytic astrocytoma
 - xanthoastrocytoma
 - ganglioglioma
- Can grow and regress
- May enhance





OPG

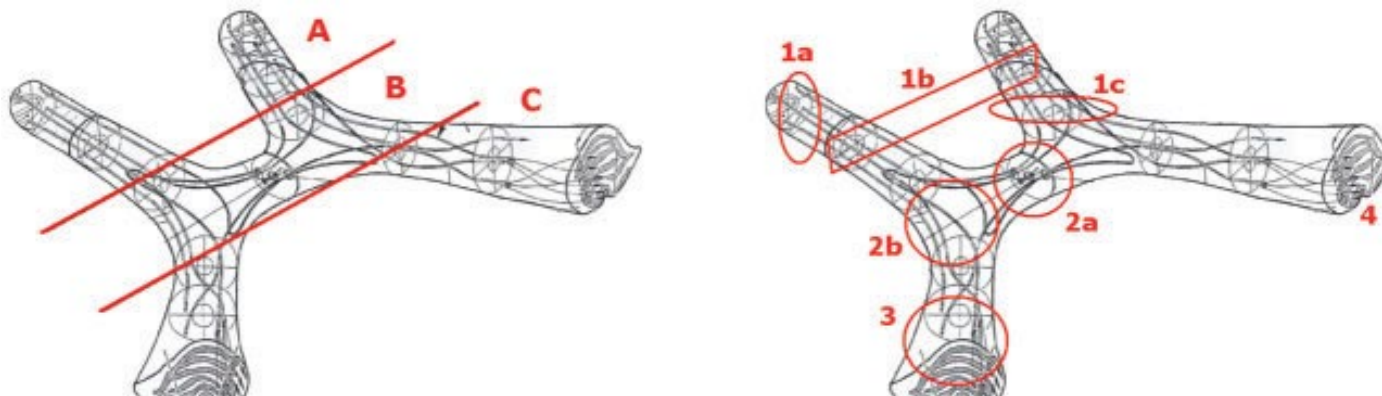
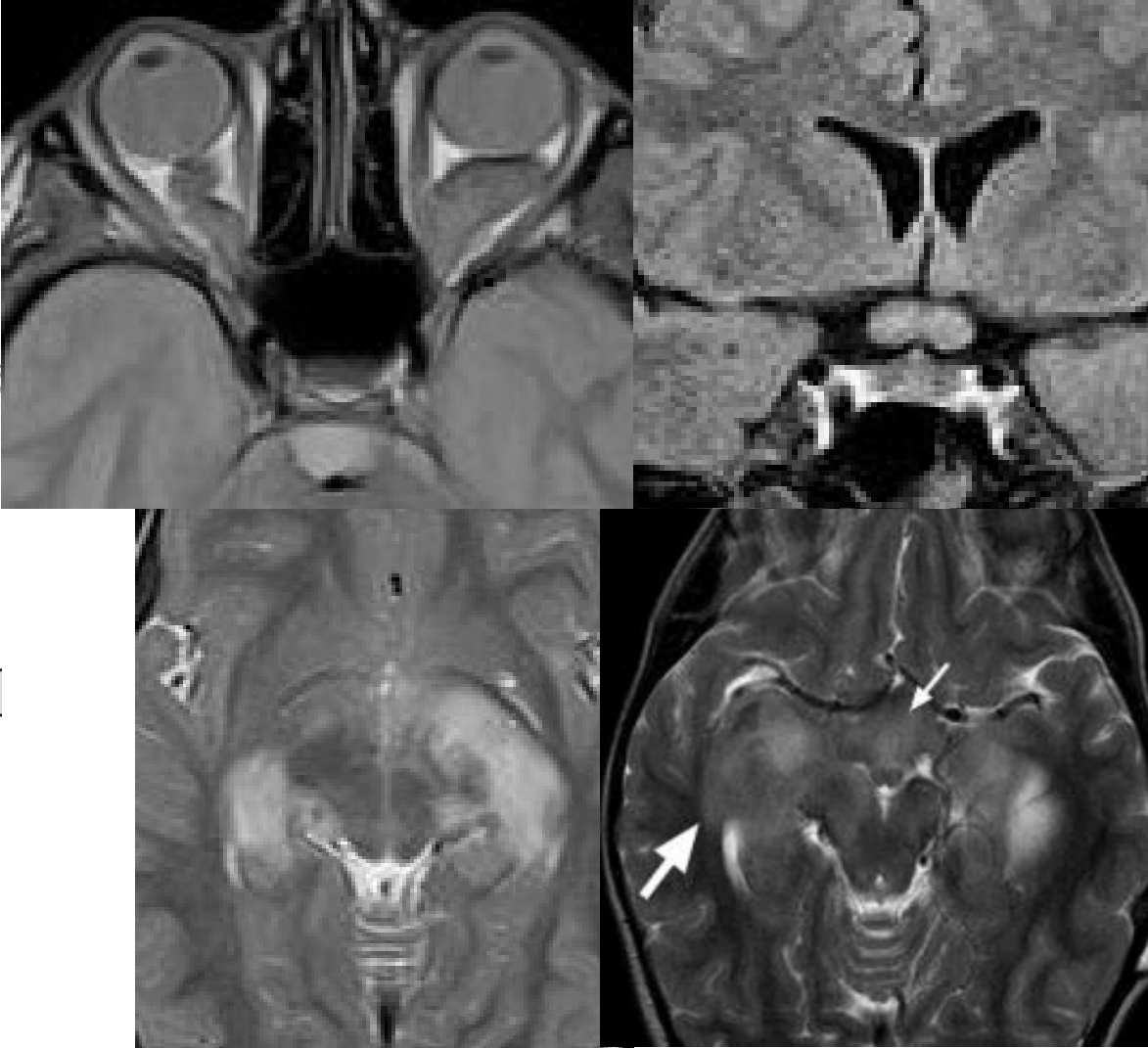


Table 1. The Dodge classification

Original DC	MDC	Description	Subcategories	Description
A	1a	Single optic nerve	1a L/R	left/right
	1b	Bilateral optic nerve	1b L/R	left>right/right>left
	1c	Cisternal segment optic nerve	1c L/R/B 1cb L/R	left/right/bilateral left>right/right>left
B	2a	Central chiasmatic	2a	
	2b	Asymmetric chiasmatic	2b L/R 2c L/R	left>right/right>left left only/ right only
	3	Optic tracts	3 L/R/B	
C	3b	Asymmetric tracts	3b L/R	left>right/right>left
	4	Diffuse posterior tracts	4 L/R/B	left/right/bilateral
	4b	Asymmetric posterior tracts	4b L/R	left>right/right>left
	H+/-	Hypothalamic involvement		
	LM+/-	Leptomeningeal dissemination		
	NF1+/-	Neurofibromatosis type 1		

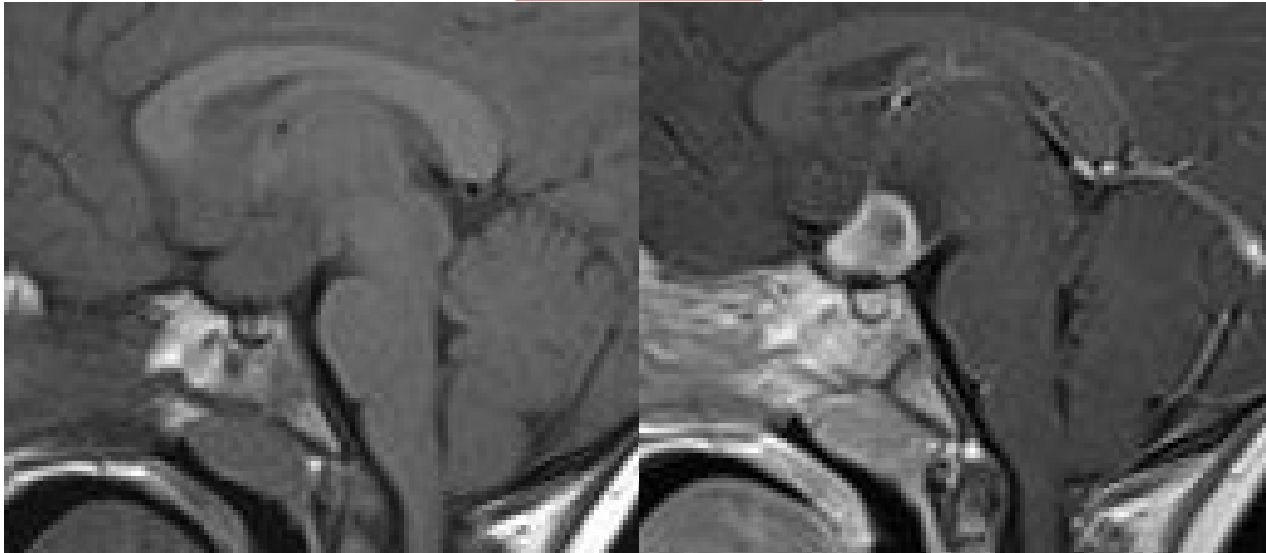
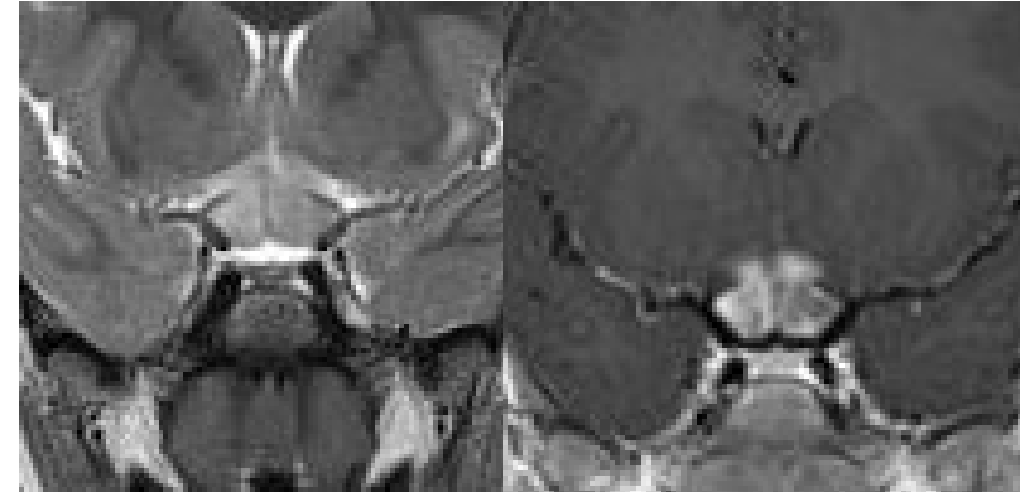
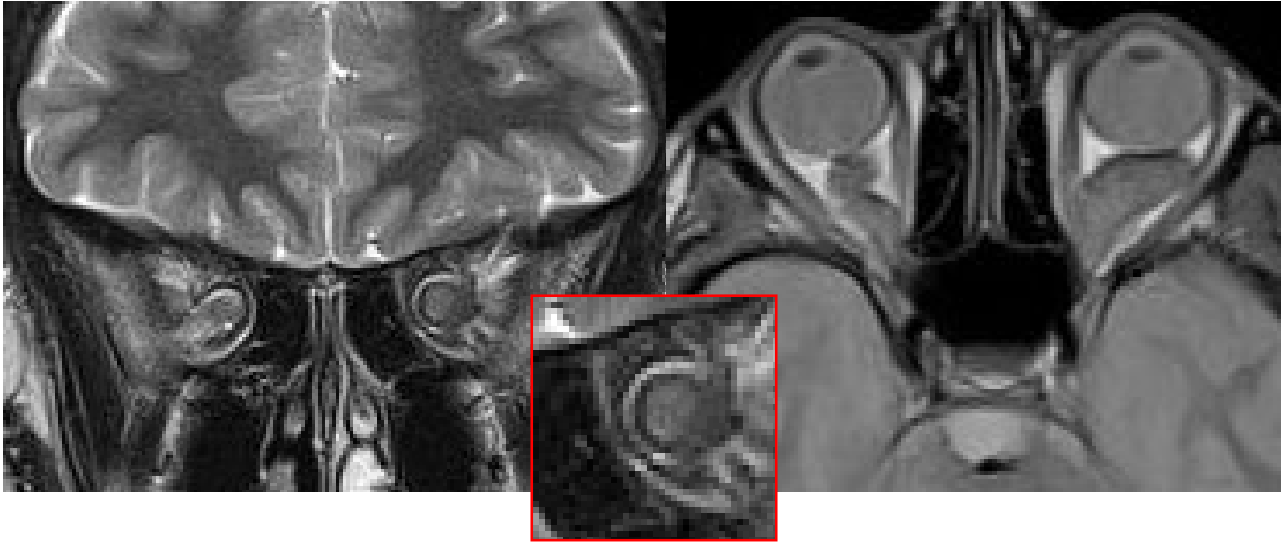


I gliomi delle vie ottiche sono classificati dal punto di vista anatomico radiologico secondo la classificazione di Dodge e Dodge modificata.

Possono interessare il nervo ottico, il chiasma, i tratti ottici e le radiazioni ottiche. Si riscontrano in bambini più piccoli di 7 anni e perlopiù si tratta di astrocitomi pilocitici.

OPG

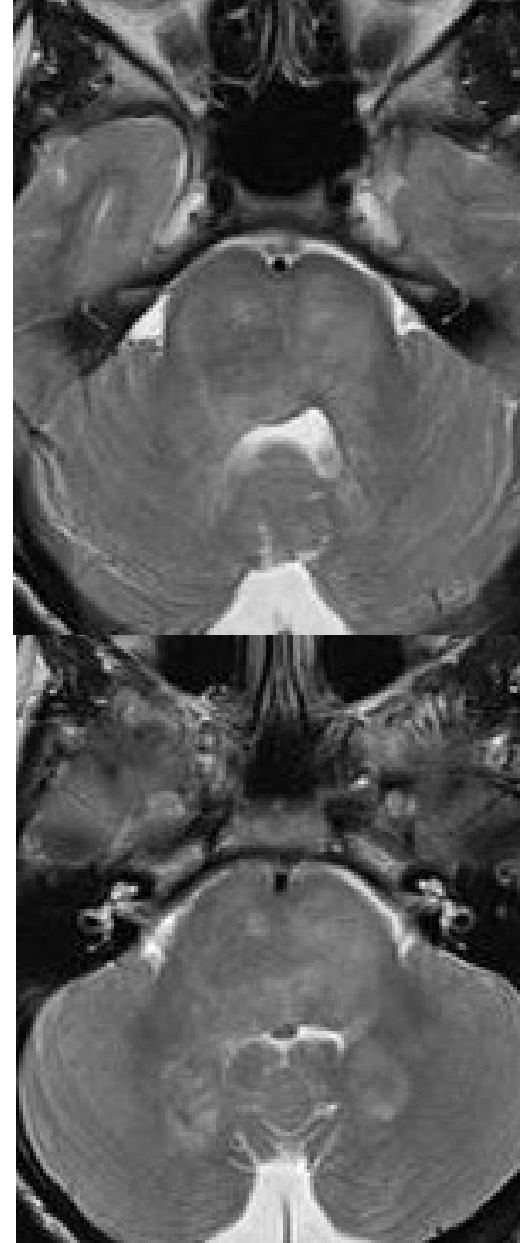
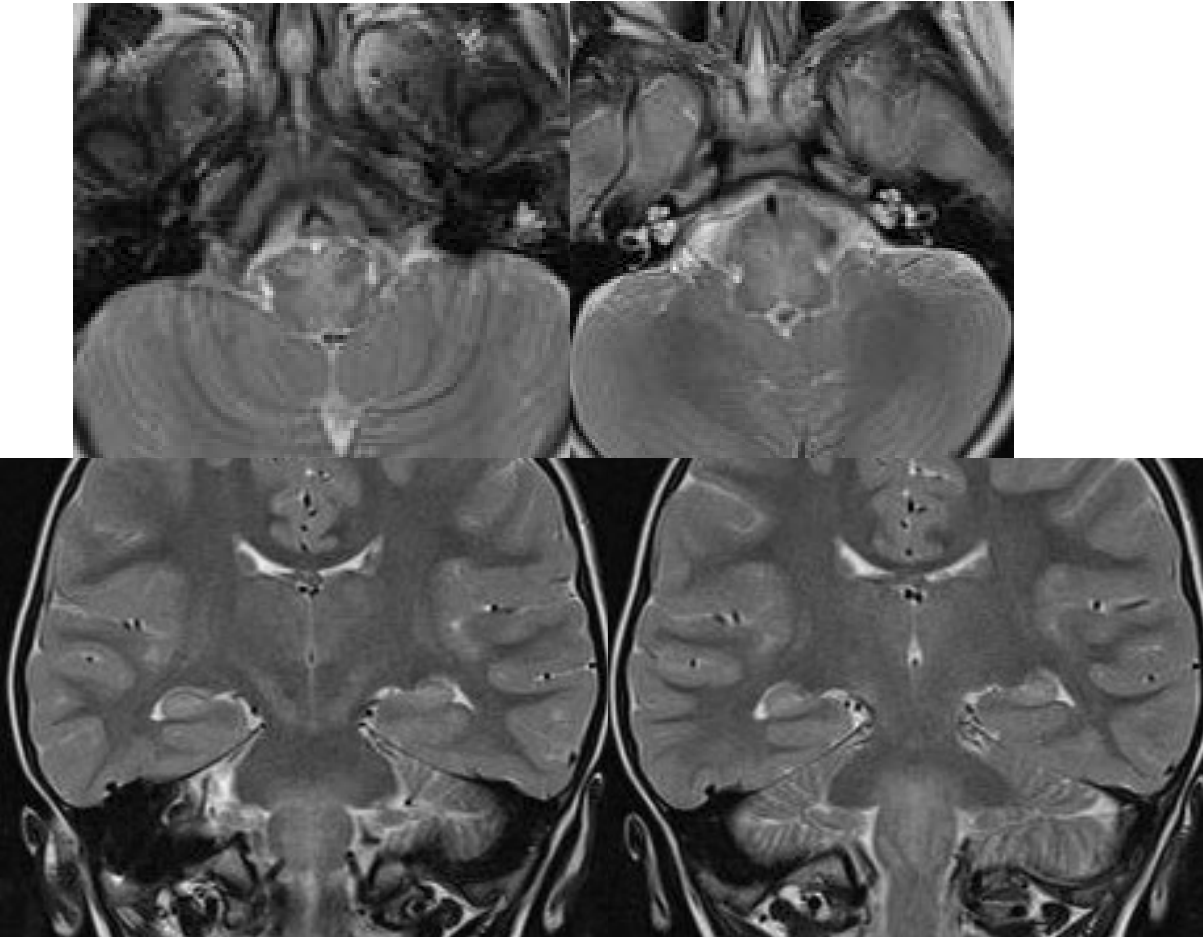
L'interessamento bilaterale dei nervi ottici è di comune osservazione ed è un reperto patognomonico di NF1. Di solito queste neoplasie hanno un decorso benigno. Meno della metà di questi tumori è sintomatica, quando ci sono i sintomi i bambini si presentano con calo del visus o pro-optosi o pubertà precoce. Il nervo ottico presenta volume aumentato, decorso tortuoso, tenue iperintensità in T2 ed enhancement + o - e assume forma tubulare



Courtesy of Dr. Marco Moscatelli

SNC

Brainstem Glioma



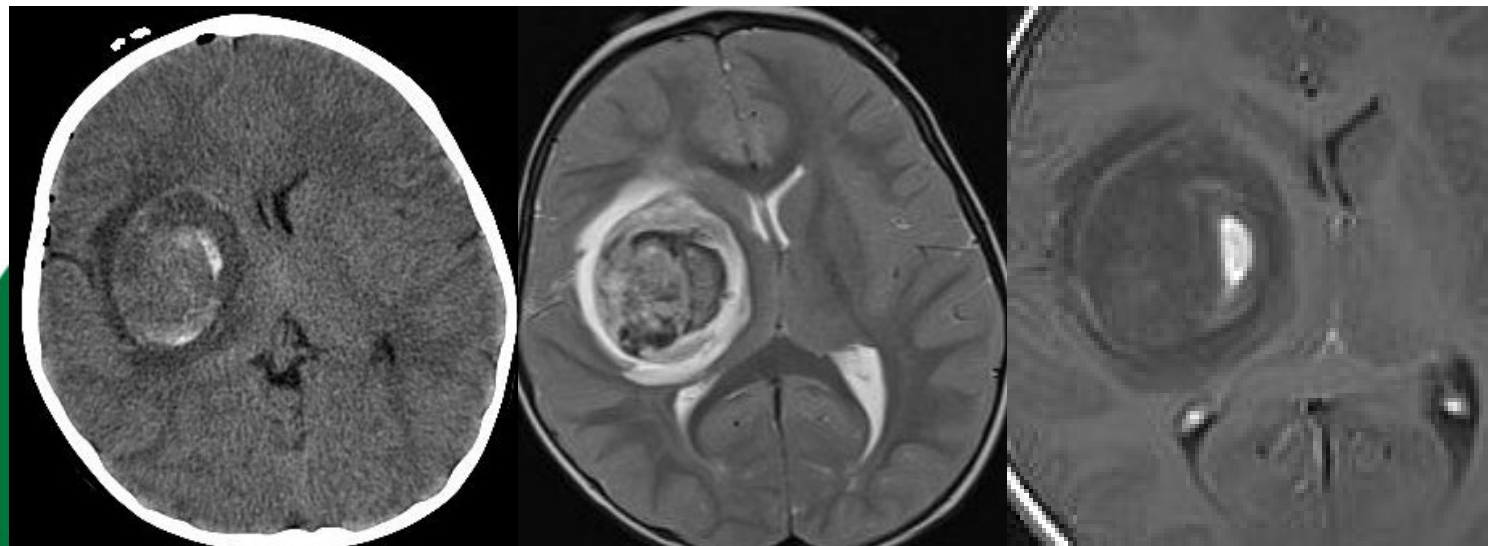
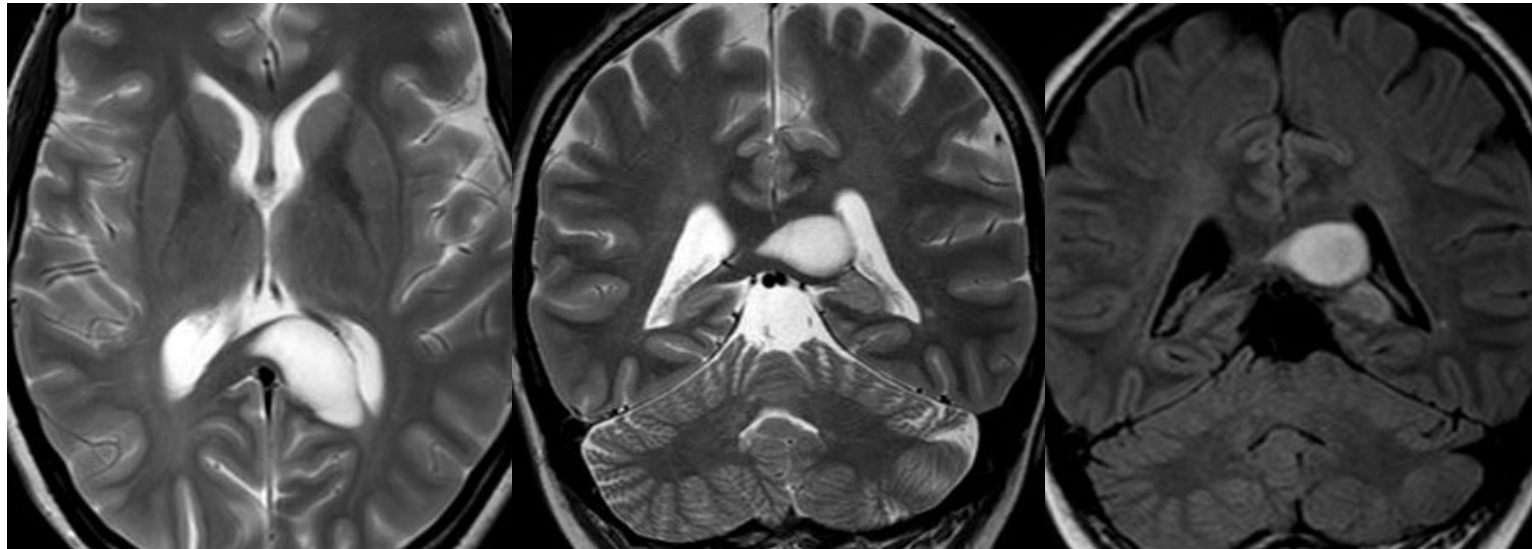
Courtesy of Dr. Marco Moscatelli

Oltre ai tumori delle vie ottiche possono osservarsi gliomi nel tronco, nel cervelletto e negli emisferi cerebrali.
I gliomi del tronco di solito iniziano a crescere nel bulbo e poi si estendono nel ponte e possono dare disfunzioni del tronco inclusa la disartria e l'incoordinazione



SNC

Hemispheric Glioma



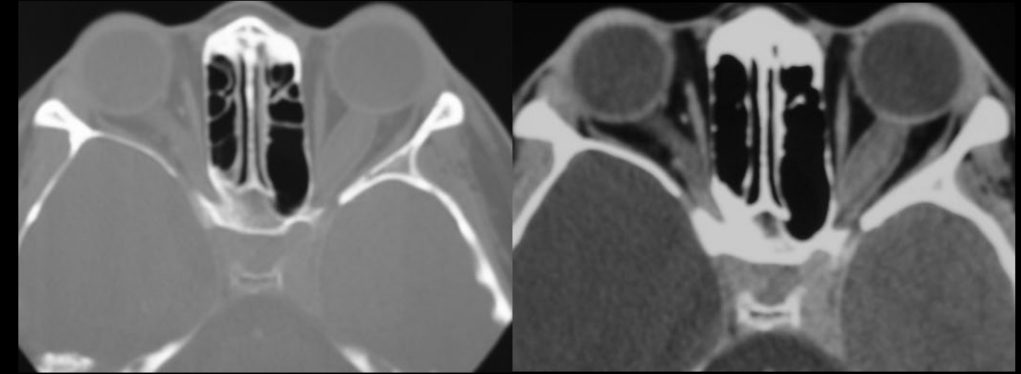
SNC

Other

OTHER

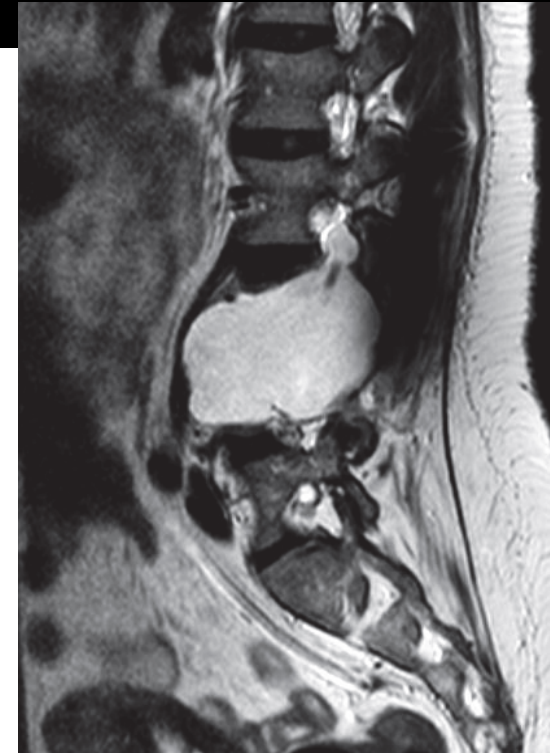
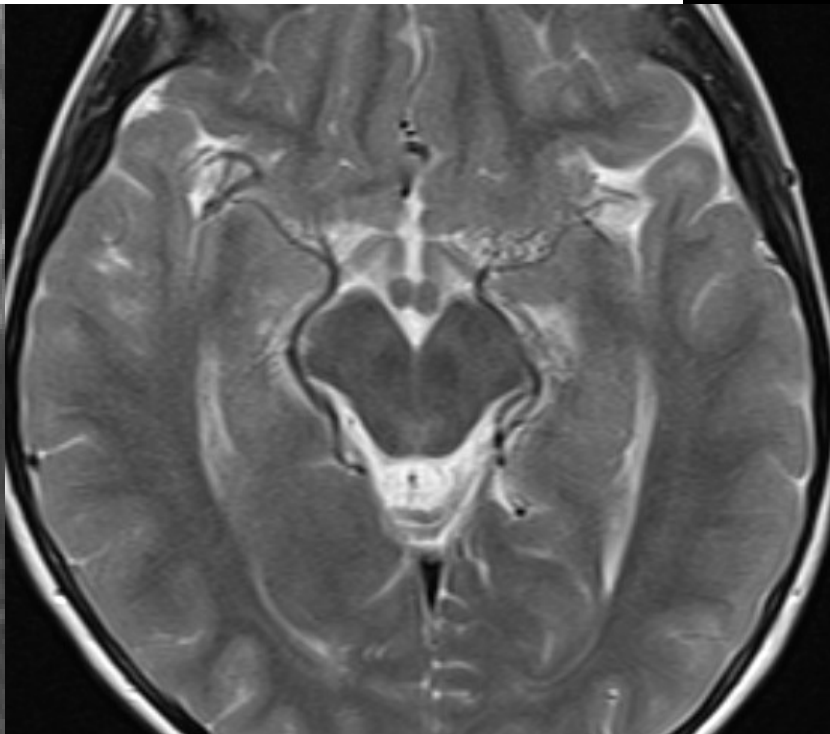
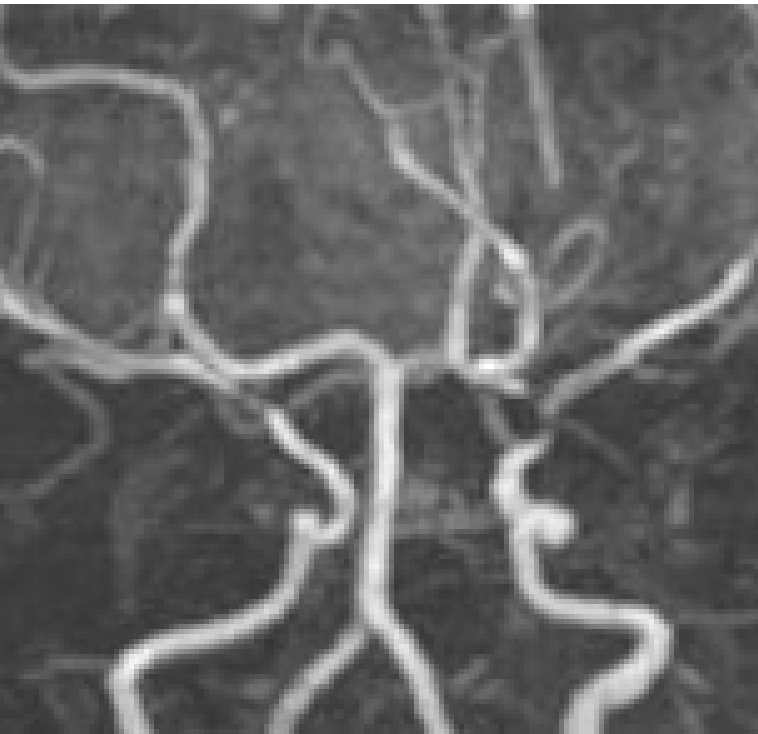
- moyamoya-type vasculopathy
- sphenoid dysplasia
- Dura mater dysplasia with pseudomeningocele and dural ectasia.

DISPLASIA DELLA GRANDE ALA DELLO SFENOIDE IN NF1



TC algoritmo per osso

TC con m.d.c



SNP

Neurofibromas

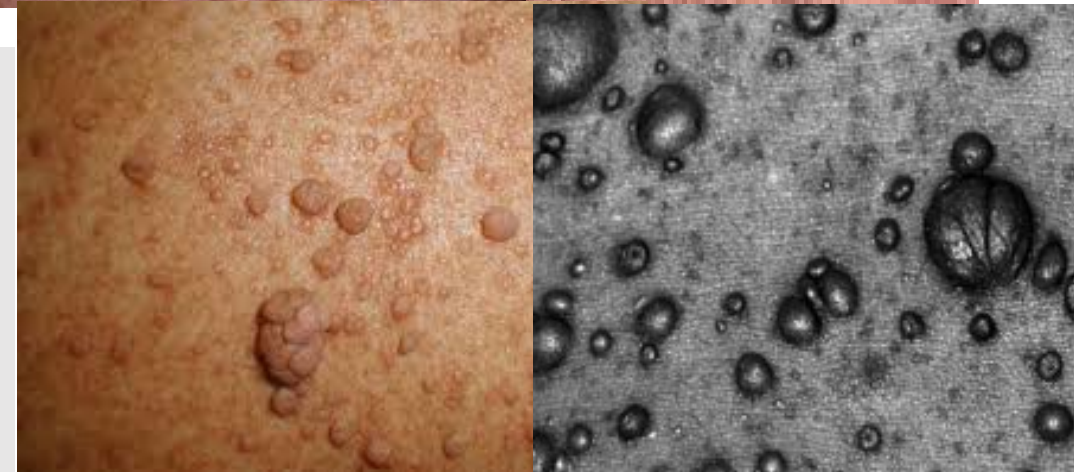
Most common tumors associated with NF1



Il neurofibroma cutaneo è la lesione di gran lunga più frequente, può apparire come una lesione nodulare, pedunculata o come una placca diffusa, e può variare da pochi mm ad alcuni centimetri.

Non è presente nella prima infanzia, cresce durante l'adolescenza e continua a crescere in numero durante l'età adulta.

E' importante ricordare che questi tumori non si trasformano in lesioni maligne, ma la loro presenza è un fattore di rischio per la coesistenza di un neurofibroma plessiforme sottostante.

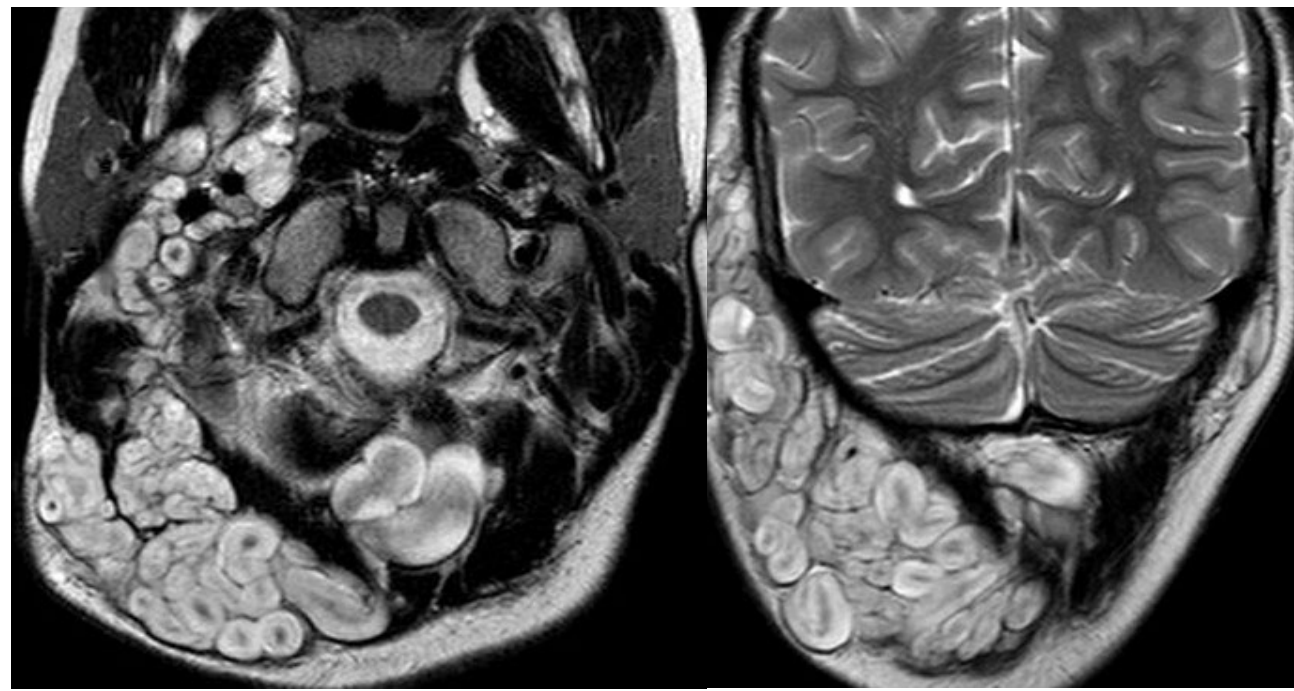


SNP

Plexiform Neurofibromas

MRI features:

- Virtually pathognomonic for NF1
- Well defined lesions
- T1 isointense
- T2 hyperintense
- Fascicular sign
- Target sign
- Enhancement
- Bag of worms

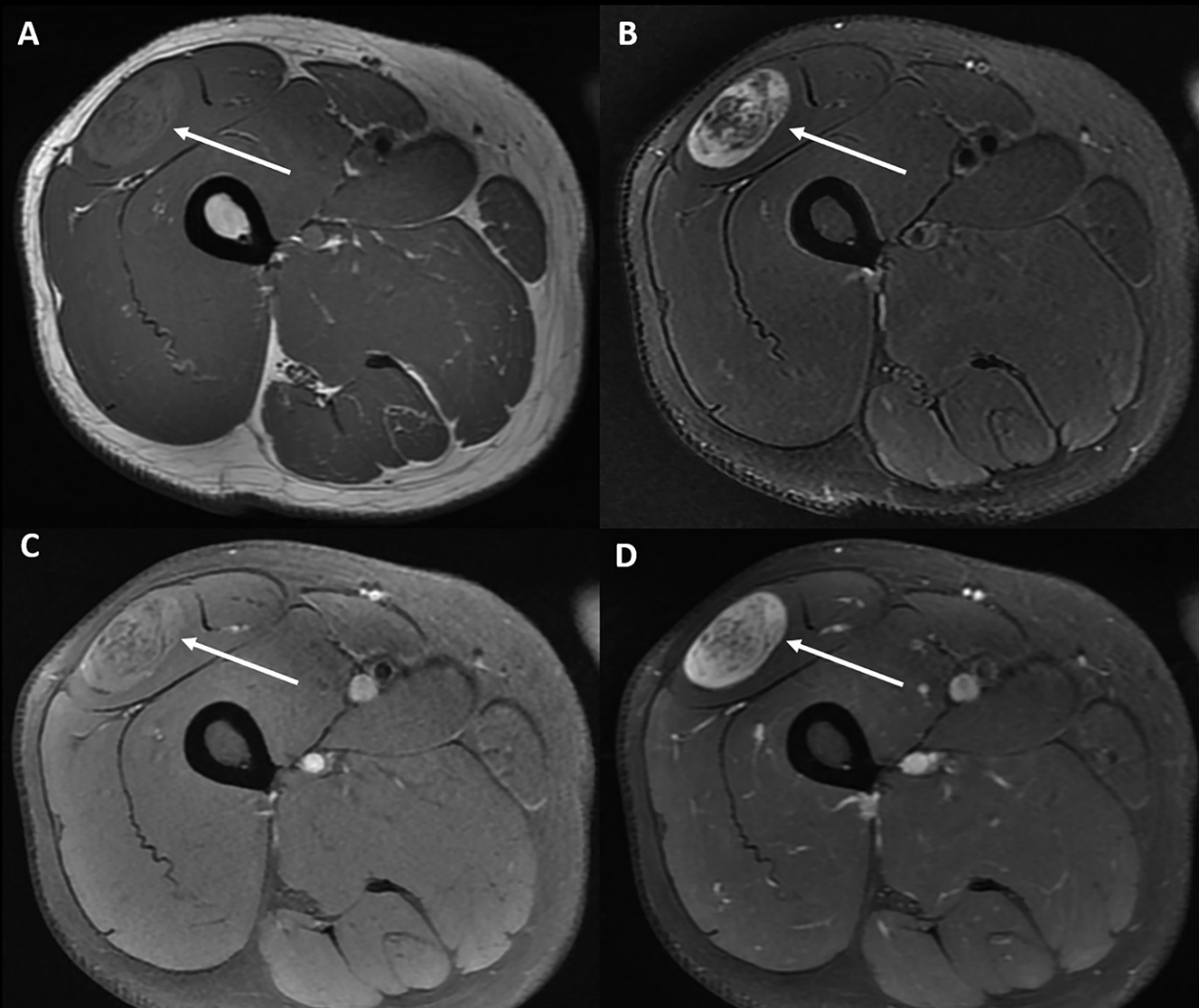


Possono nascere da qualsiasi nervo del SNP.

Interessano multipli fascicoli nervosi di un nervo o di un plesso, tendono a crescere secondo il decorso del nervo e dei suoi rami e si presentano sottoforma di singoli noduli agglomerati.

Si riscontrano già alla nascita e tendono a crescere rapidamente durante la prima decade.

Fascicular sign



“Fascicular sign”: Multiple ring-like structures with a hyperintense periphery on T2-weighted images representing the fascicular bundles within the nerves

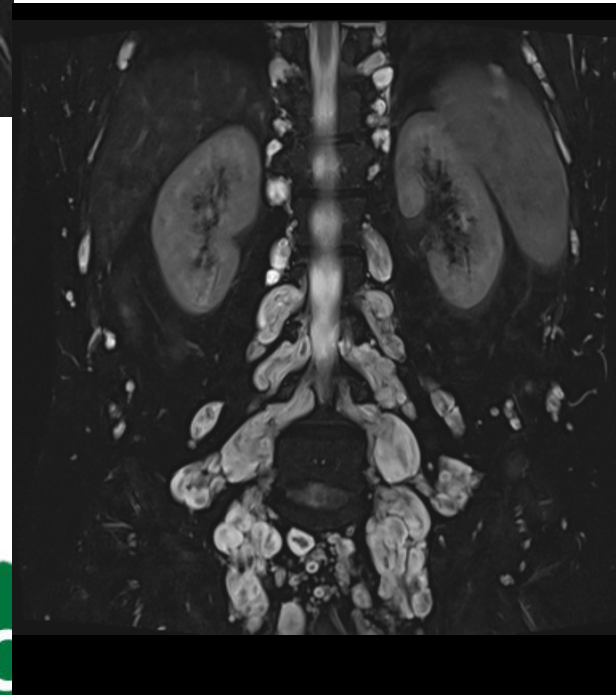
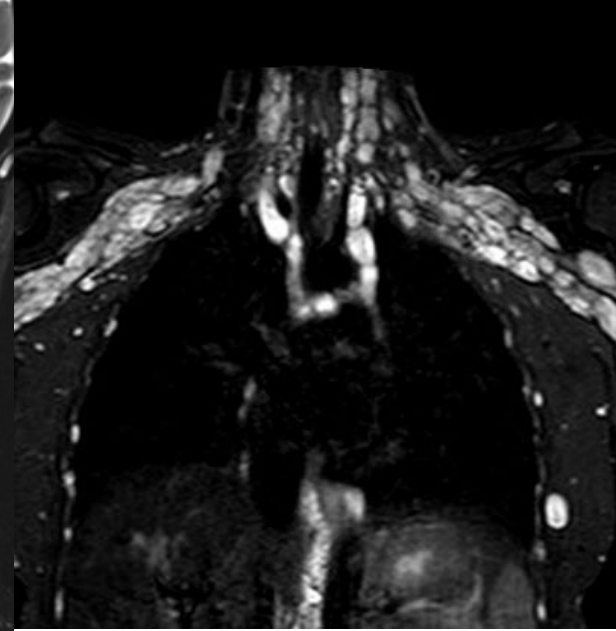
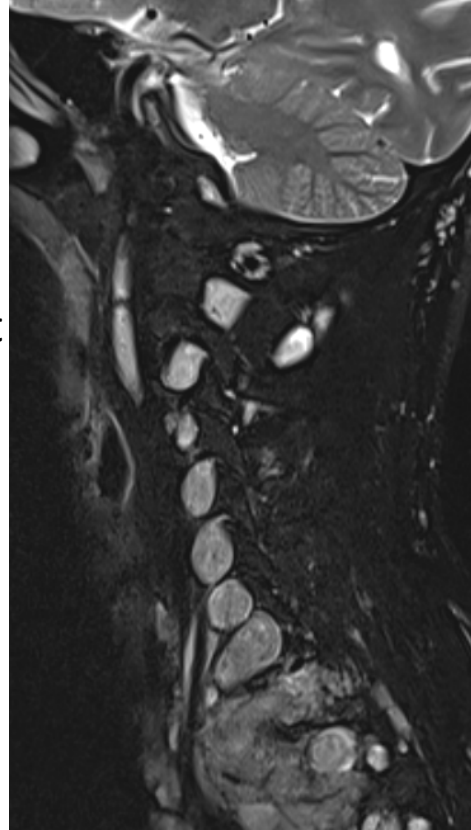
Target sign



SNP

Spine

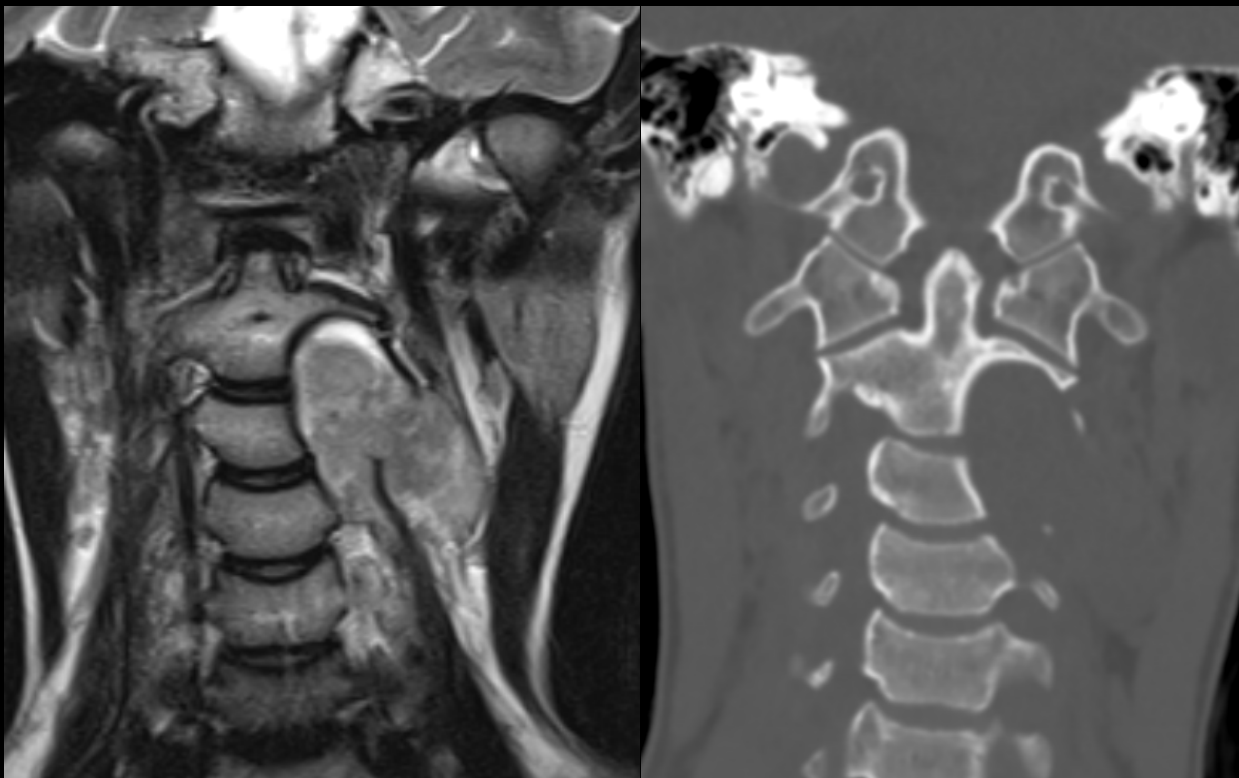
- Complex and multilevel spinal involvement
- Bony alterations
 - Scoliosis
 - Deformation of the foramina
- Anatomical classification
- Neurologic deficit
 - Bilateral tumours at the same level
 - Lumbar region involvement
 - Intradural lesions



Courtesy of Dr. Marco Moscatelli



GRAND ROUNDS CLINICI DEL MERCATO

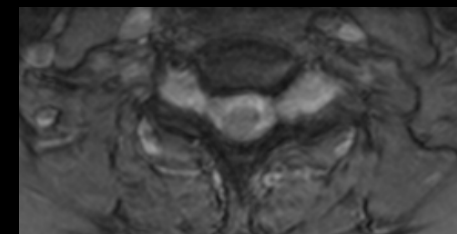
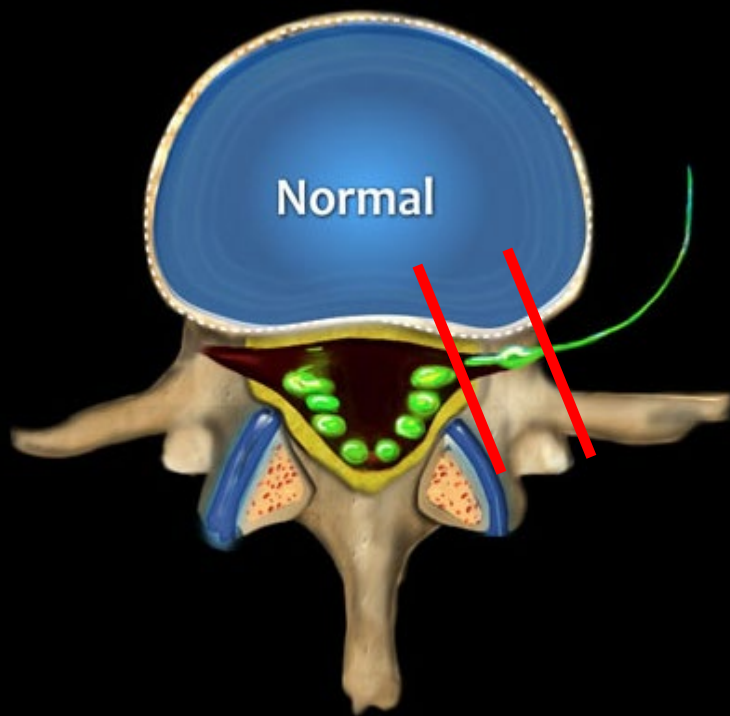


possono esercitare effetto massa e comprimere le strutture vicine tipo grossi vasi e trachea e determinare erosioni ossee e possono dare dolore.

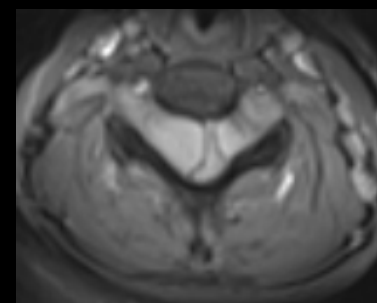
Possono comprimere il midollo spinale e diventare sintomatici.



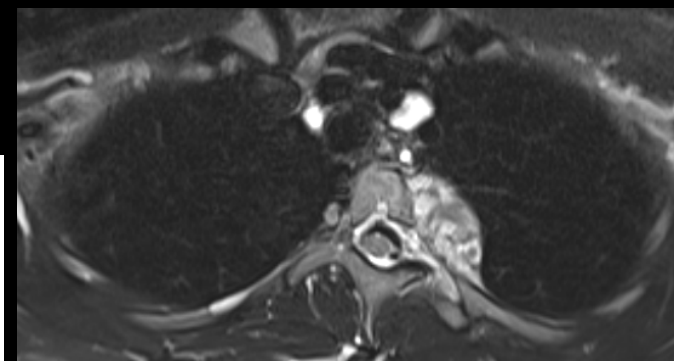
Courtesy of Dr. Marco Moscatelli



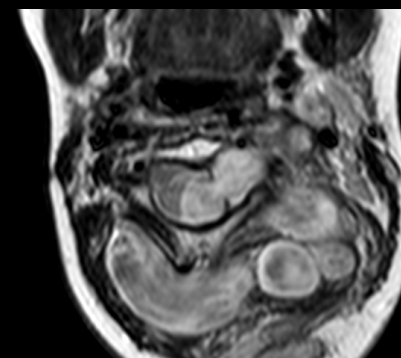
Foraminal



Kissing



Paraspinal



Intradural

Anatomical classification of spinal tumors in NF1 [29]

Foraminal tumor	A tumor involving the nerve roots and the neuro-foramen
'Kissing' tumors	Bilateral-foraminal tumors that approximated each other at the same level, with significant compression of the cord or thecal sac (Fig. 2)
Paraspinal tumor	A tumor epicentered lateral to the neuro-foramina, having a large soft tissue component outside of the spinal canal
Intra-dural tumor	A tumor that is epicentered inside the thecal sac

SNP

Malignant peripheral nerve sheath tumour

Conventional radiologic features

- Perilesional oedema
- Ill defined margins
- Size
- Cystic degeneration/necrosis
- Heterogeneous enhancement
- ADC
- GROWTH

PET FDG ++

Il neurofibroma plessiforme può andare incontro ad una trasformazione maligna che dal punto di vista clinico si presenta con dolore e spesso deficit neurologico.

Alla RM la trasformazione può essere suggerita dall'aumento di volume della lesione, margini mal definiti, mancanza del segno target nelle sequenze T2 pesate, disomogeneità della lesione e necrosi centrale.

La PET con Fluorodeossiglucosio può aiutare a distinguere lesione maligna da benigna con un aumento dell'uptake del glucosio.

Diagnostic Accuracy of MRI for the Detection of Malignant Peripheral Nerve Sheath Tumors: A Systematic Review and Meta-Analysis

Mitchell P. Wilson, MD¹, Prayash Katlariwala, BSc¹, Gavin Low, MBChB, MPhil¹, Mohammad H. Murad, MD², Matthew D. F. McInnes, MD, PhD³, Line Jacques, MD, MSc⁴, Andrew S. Jack, MD, MSc^{4,5}

Evidence Synthesis and Decision Analysis · Original Research

Keywords

accuracy, malignant, MRI, nerve sheath tumor, peripheral nerve

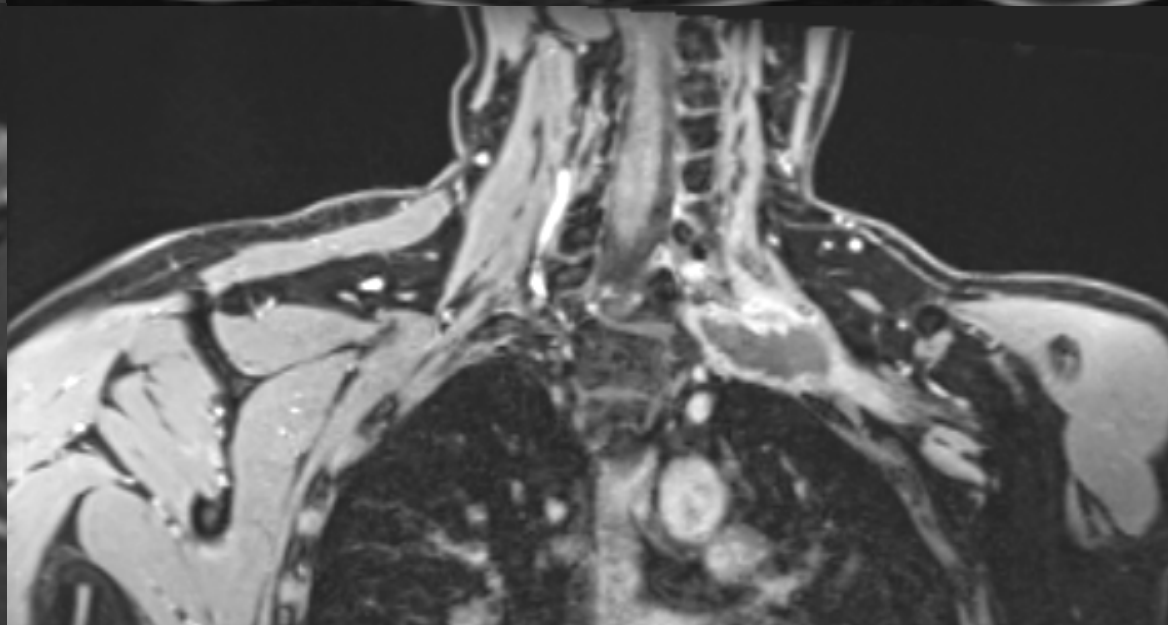
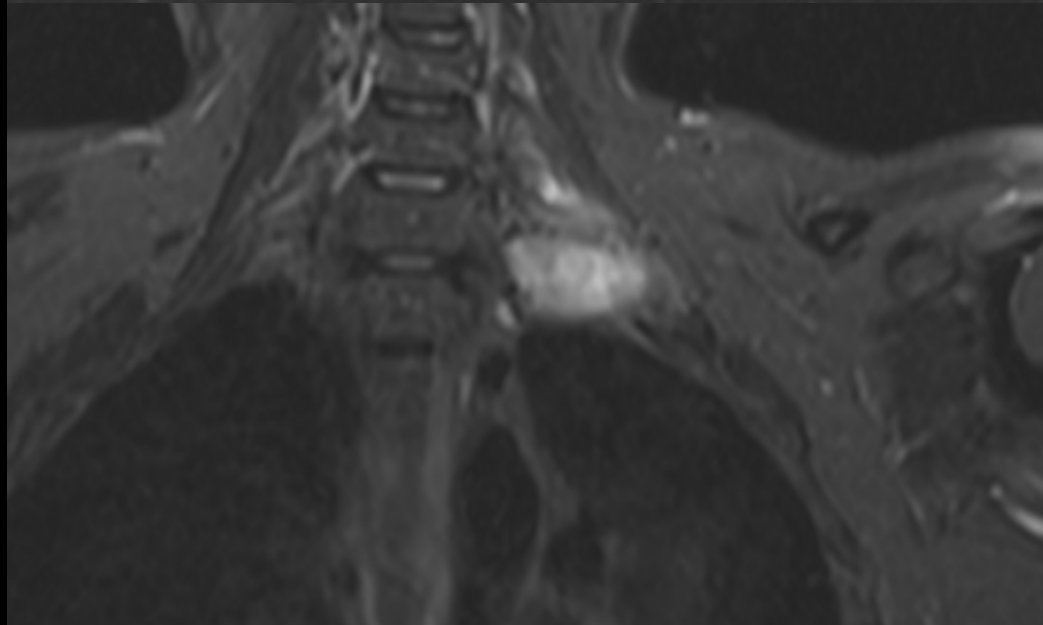
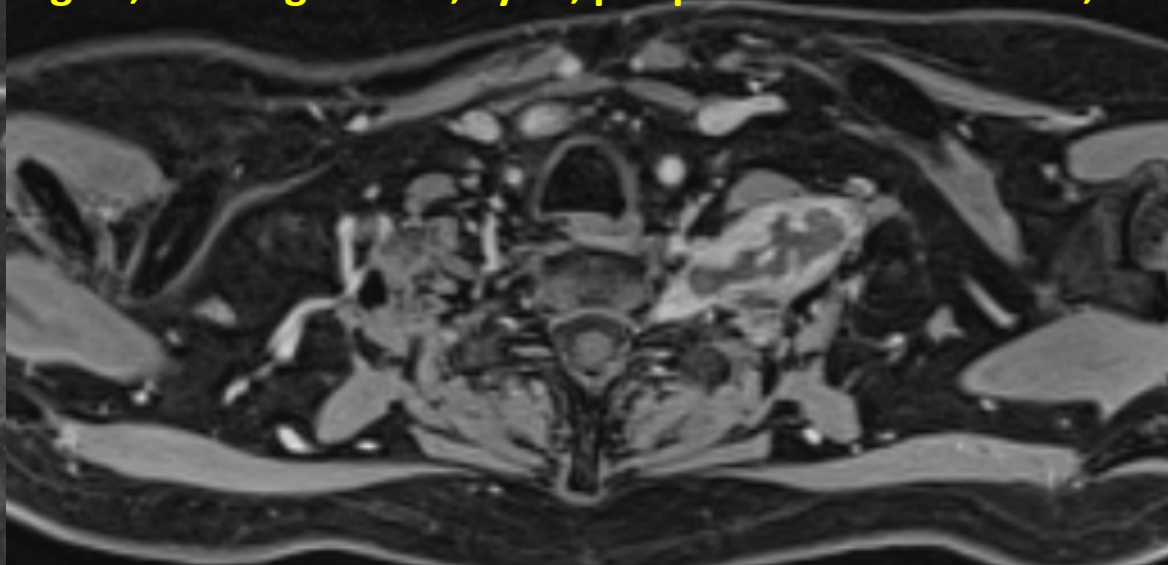
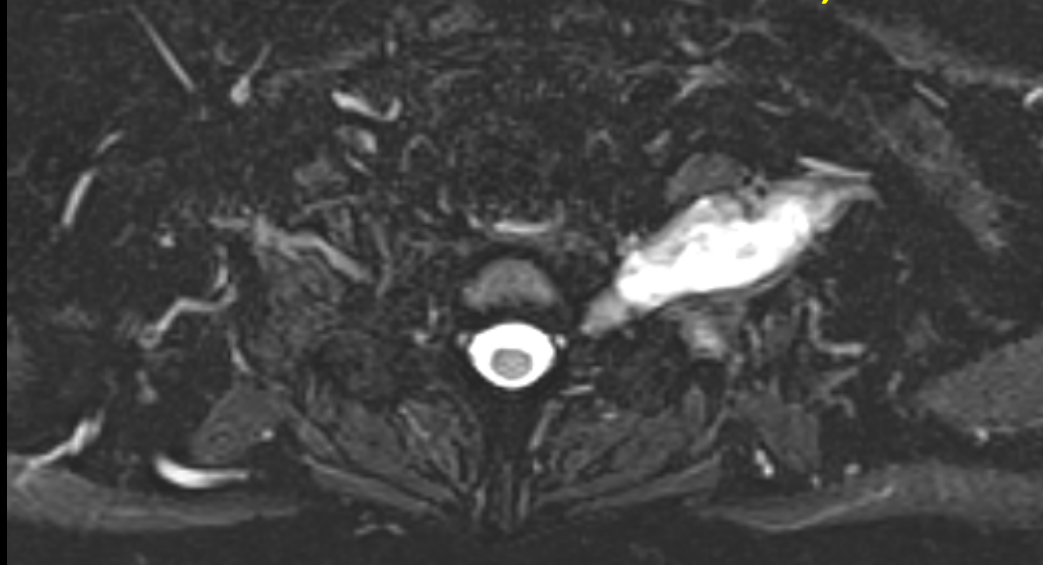
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OBJECTIVE. This systematic review and meta-analysis evaluates the diagnostic accuracy of MRI for differentiating malignant (MPNSTs) from benign peripheral nerve sheath tumors (BPNSTs).

MATERIALS AND METHODS. A systematic review of MEDLINE, Embase, the Cochrane Library, and the gray literature from inception to December 2019 was performed. Original articles that involved at least 10 patients and that evaluated the accuracy of MRI for detecting MPNSTs were included. Two reviewers independently extracted clinical and radiologic data from included articles to calculate sensitivity, specificity, NPV, and accuracy. A meta-analysis was performed using a binomial model.



malignant transformation (MPNST) in NF1 in about 5% typically from a preexisting plexiform or large intraneural neurofibroma
RAPID GROWTH and EXACERBATION OF PAIN, blurred margins, heterogeneous, cysts, peripheral enhancement, oedema.



Tali tumori maligni sono molto difficili da trattare perché spesso resistenti alla terapia e danno metastasi. Dovrebbero essere diagnosticati il più precocemente possibile.

Grazie dell'attenzione

SNP

Diffuse Neurofibroma

- Poorly defined lesion that spreads along connective tissue
- Skin and subcutaneous tissues
- Intense enhancement
- plaquelike (thick slab without interposed tissue)
- infiltrative (poorly defined margins with interposed uninvolved tissue)

Imaging Appearance of Diffuse Neurofibroma

Douglass S. Hassell¹
Laura W. Bancroft¹
Mark J. Kransdorf^{1,2}
Jeffrey J. Peterson¹
Thomas H. Berquist¹
Mark D. Murphey^{2,3}
Julie C. Fanburg-Smith⁴

OBJECTIVE. The purposes of this study were to describe the imaging appearance of diffuse neurofibroma in 10 patients and to summarize demographic data on a large group of patients.

MATERIALS AND METHODS. Retrospective review of the pathology and radiology teaching databases at two institutions yielded the cases of 339 patients with a pathologic diagnosis of diffuse neurofibroma. Diagnostic-quality images were available for 10 patients. Images from MRI ($n = 8$), CT ($n = 5$), and sonographic ($n = 1$) examinations were evaluated for lesion location, size, depth of involvement, growth pattern, and intrinsic signal intensity, attenuation, or echogenicity. Demographic information, associated lesions, and tumor location were recorded for all patients.

RESULTS. Among 10 patients with images, eight of whom had neurofibromatosis, diffuse neurofibroma involved the skin and subcutaneous tissues ($n = 8$) and frequently extended

