Vogelflug:
Phakomatosen und Neuroonkologie

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Neurofibromatose: neue Diagnosekriterien

ARTICLE

Revised diagnostic criteria for neurofibromatosis type 1 and Legius syndrome: an international consensus recommendation

Eric Legius[1,85]✉, Ludwine Messiaen[2,85], Pierre Wolkenstein[3,85], Patrice Pancza[4,85], Robert A. Avery[5], Yemima Berman[6], Jaishri Blakeley[7], Dusica Babovic-Vuksanovic[8], Karin Soares Cunha[9], Rosalie Ferner[10], Michael J. Fisher[11], Jan M. Friedman[12], David H. Gutmann[13], Hildegard Kehrer-Sawatzki[14], Bruce R. Korf[2], Victor-Felix Mautner[15], Sirkku Peltonen[16,17], Katherine A. Rauen[18], Vincent Riccardi[19], Elizabeth Schorry[20], Anat Stemmer-Rachamimov[21], David A. Stevenson[22], Gianluca Tadini[23], Nicole J. Ullrich[24], David Viskochil[25], Katharina Wimmer[26], Kaleb Yohay[27], International Consensus Group on Neurofibromatosis Diagnostic Criteria (I-NF-DC)*, Susan M. Huson[28,85], D. Gareth Evans[29,85] and Scott R. Plotkin[30,85]

Genetics in Medicine (2021) 23, 1506-1513

Diagnosekriterien NF1

- Mindestens 6 Café-au-lait-Flecken
  > 0,5 cm präpubertär, > 1,5 cm postpubertär
- Axilläre/inguinale Sommersprossen
- 2 Neurofibrome jeden Typs / 1 plexiformes Neurofibrom
- Optikusgliom
- >2 Lisch-Knötchen oder >2 Choroidea-Knötchen
- Typische Knochendysplasien
- Pathogene Variante des NF1-Gens

Die Diagnose kann gestellt werden,

wenn 2 dieser Kriterien erfüllt sind

ODER

wenn 1 Kriterium erfüllt ist und ein Elternteil die Diagnosekriterien erfüllt

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Genetics in Medicine (2021) 23, 1506-1513

Diagnosekriterien Legius-Syndrom

- Mindestens 6 Café-au-lait Flecken (bilateral)
- Axilläre/inguinale Sommersprossen
- Keine sonstigen NF1-typischen Befunde
- Pathogene Variante des SPRED-1 Gens

Diagnosekriterien NF1

- Mindestens 6 Café-au-lait-Flecken
  > 0,5 cm präpubertär, > 1,5 cm postpubertär
- Axilläre/inguinale Sommersprossen
- 2 Neurofibrome jeden Typs / 1 plexiformes Neurofibrom
- Optikusgliom
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- Typische Knochendysplasien
- Pathogene Variante des NF1-Gens

Genetik alleine reicht nicht

Die Diagnose kann gestellt werden,
wenn 2 dieser Kriterien erfüllt sind
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wenn 1 Kriterium erfüllt ist und ein Elternteil die Diagnosekriterien erfüllt

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Genetics in Medicine (2021) 23, 1506-1513

Gibt es überhaupt noch eine NF2?

Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: An international consensus recommendation

Scott R. Plotkin[1,*], Ludwine Messiaen[2], Eric Legius[3], Patrice Pancza[4], Robert A. Avery[5], Jaishri O. Blakeley[6], Dusica Babovic-Vuksanovic[7], Rosalie Ferner[8], Michael J. Fisher[9], Jan M. Friedman[10], Marco Giovannini[11], David H. Gutmann[12], Clemens Oliver Hanemann[13], Michel Kalamarides[14], Hildegard Kehrer-Sawatzki[15], Bruce R. Korf[2], Victor-Felix Mautner[16], Mia MacCollin[17], Laura Papi[18], Katherine A. Rauen[19], Vincent Riccardi[20], Elizabeth Schorry[21], Miriam J. Smith[22], Anat Stemmer-Rachamimov[23], David A. Stevenson[24], Nicole J. Ullrich[25], David Viskochil[26], Katharina Wimmer[27], Kaleb Yohay[28], International Consensus Group on Neurofibromatosis Diagnostic Criteria (I-NF-DC), Susan M. Huson[29], Pierre Wolkenstein[30], D. Gareth Evans[22]

Genetics in Medicine (2022) 24, 1967-1977

Gibt es überhaupt noch eine NF2?

Neurofibromatose Typ 1 (NF1)	Schwannomatosen	
	NF2-assoziierte Schwannomatose (frühere Bezeichnung: NF2)	Schwannomatose • SMARCB1-assoziiert • LZTR1-assoziiert • 22q-assoziiert • NOS (not otherwise classified)
Diagnosekriterien Mindestens 6 Café-au-lait-Flecken > 0,5 cm präpubertär, > 1,5 cm postpubertär Axilläre/inguinale Sommersprossen 2 Neurofibrome jeden Typs oder 1 plexiformes Neurofibrom Optikusgliom >2 Lisch-Knötchen oder >2 Choroidea-Knötchen Typische Knochendysplasien Pathogene Variante des NF1-Gens	**Diagnosekriterien** 1.) Bilaterale Vestibularisschwannome (VS) *oder* 2.) Identische pathogene NF2-Genvariante in 2 verschiedenen NF2-assoziierten Tumoren *oder* 3) 2 Hauptkriterien *oder* 4.) 1 Haupt- und 2 Nebenkriterien **Hauptkriterien** • Unilaterales Vestibularisschwannom • Verwandter 1. Grades mit NF2 • Pathogene NF2-Genvariante z.B. in Blut **Nebenkriterien** • Meningiom, Schwannom, Katarakt	Diagnosekriterien vorhanden *Plotkin et al.Genetics in Medicine (2022) 24, 1967–1977*

Neurofibromatose Typ 1: Genervt von ungenauen radiologischen Befunden?

Neurofibromatosis from Head to Toe: What the Radiologist Needs to Know

Wang MX et al.
Radiographics 2022;42:1123-1144

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Jeffrey Guccione, MD
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Serageldin Kamel, MD
Prasad M. Panse, MD
Corey T. Jensen, MD
Khaled M. Elsayes, MD

Abbreviations: CNS = central nervous system, FASI = focal area of signal intensity, NF1 = neurofibromatosis type 1, NF2 = neurofibromatosis type 2, PNST = peripheral nerve sheath tumor

RadioGraphics 2022; 42:1123–1144

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Content Codes: CT GI GU MR NR PD

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Neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2) are autosomal dominant inherited neurocutaneous disorders or phakomatoses secondary to mutations in the *NF1* and *NF2* tumor suppressor genes, respectively. Although they share a common name, NF1 and NF2 are distinct disorders with a wide range of multisystem manifestations that include benign and malignant tumors. Imaging plays an essential role in diagnosis, surveillance, and management of individuals with NF1 and NF2. Therefore, it is crucial for radiologists to be familiar with the imaging features of NF1 and NF2 to allow prompt diagnosis and appropriate management. Key manifestations of NF1 include café-au-lait macules, axillary or inguinal freckling, neurofibromas or plexiform neurofibromas, optic pathway gliomas, Lisch nodules, and osseous lesions such as sphenoid dysplasia, all of which are considered diagnostic features of NF1. Other manifestations include focal areas of signal intensity in the brain, low-grade gliomas, interstitial lung disease, various abdominopelvic neoplasms, scoliosis, and vascular dysplasia. The various NF1-associated abdominopelvic neoplasms can be categorized by their cellular origin: neurogenic neoplasms, interstitial cells of Cajal neoplasms, neuroendocrine neoplasms, and embryonal neoplasms. Malignant peripheral nerve sheath tumors and intracranial tumors are the leading contributors to mortality in NF1. Classic manifestations of NF2 include schwannomas, meningiomas, and ependymomas. However, NF2 may have shared cutaneous manifestations with NF1. Lifelong multidisciplinary management is critical for patients with either disease. The authors highlight the genetics and molecular pathogenesis, clinical and pathologic features, imaging manifestations, and multidisciplinary management and surveillance of NF1 and NF2.

Online supplemental material is available for this article.

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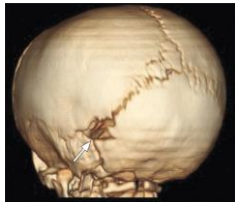
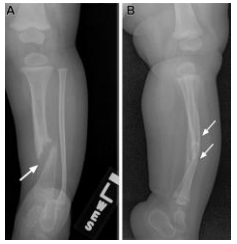




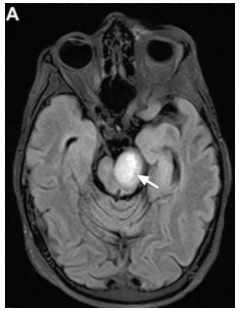
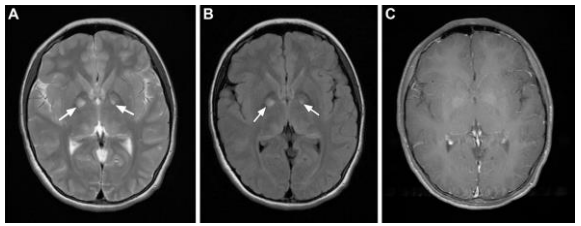
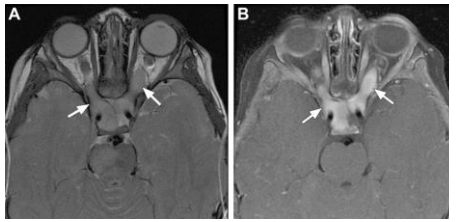


Table 3: Imaging Features of Common NF1-related Manifestations

Common Manifestations	Commonly Used Imaging Modality or Modalities	Imaging Features
Neurofibromas	US, CT, MRI	US: well-defined oval hypoechoic masses contiguous with peripheral nerves CT: soft-tissue masses with low attenuation MRI: target sign (T2 hyperintense peripheral rim and hypointense central component), enhancement of central component
Plexiform neurofibromas	MRI	Multinodular confluent masses with multiple target signs and mass effect on surrounding structures
Malignant PNSTs	MRI	Similar to plexiform neurofibromas with suggestive features: large size, peripheral enhancement pattern, perilesion edemalike zone, intratumor cystic changes
Sphenoid wing dysplasia	CT, MRI	Hypoplastic sphenoid wing, widened middle cranial fossa, flattened posterior orbit, possible meningocele and meningoencephalocele
Focal areas of signal intensity (FASIs)	MRI	Focal or diffuse T2 hyperintensity in the basal ganglia, cerebellum, or brainstem without enhancement or mass effect
Optic pathway glioma	MRI	T1-hypointense, T2-hyperintense, and homogeneously enhancing enlargement of the optic nerve sheath complex
Non–optic pathway glioma	MRI	T1-hypointense or -isointense, T2-hyperintense, and variably enhancing intraparenchymal lesion, usually in the brainstem or cerebellum; may cause obstructive hydrocephalus
Dural ectasia, meningocele	CT, MRI	Well-circumscribed paravertebral mass following CSF signal intensity, often in the anterior or anterolateral aspect of the vertebral column
Interstitial lung disease	CT	Bilateral, symmetric, basal-predominant linear and ground-glass opacities; apical-predominant cysts and centrilobular nodules
GIST	CT, MRI	Submucosal bowel wall tumor with an endophytic, exophytic, or combined growth pattern
Pheochromocytoma or paraganglioma	CT, MRI	CT: well-circumscribed homogeneously enhancing adrenal gland mass (pheochromocytoma) or extra-adrenal mass (paraganglioma) MRI: often T2 hyperintense; possible T2 intermediate signal intensity due to hemorrhage, cystic changes, or myxoid degeneration
Rhabdomyosarcoma	CT, MRI	Heterogeneous enhancement with local invasion of organs and destruction of bone
Scoliosis	XR, CT	Lateral spinal curvature with sharply angulated segments of four to six vertebrae
Bone dysplasia	XR, CT	Posterior vertebral body scalloping; thinning of the pedicles, transverse processes, laminae; neural foramen enlargement; rib deformities; anterolateral tibial bowing, fracture, and pseudoarthrosis
Nonossifying fibromas	XR, CT, MRI	Slightly expansile cortically based lesions in the metaphysis of long bones with thin sclerotic borders and narrow zone of transition
Vascular dysplasia	US, CT, MRI	Narrowing and aneurysmal dilatation of various arteries (eg, renal artery, abdominal aorta, and terminal internal carotid artery)

Note.—CSF = cerebrospinal fluid, GIST = gastrointestinal stromal tumor, XR = radiography.





Neurofibromatose Typ 1: MRT-Diagnostik

Neuro-Oncology Advances

6(1), vdae021, 2024 | https://doi.org/10.1093/noajnl/vdae021 | Advance Access date 9 February 2024

Discrimination of benign, atypical, and malignant peripheral nerve sheath tumors in neurofibromatosis type 1 using diffusion-weighted MRI

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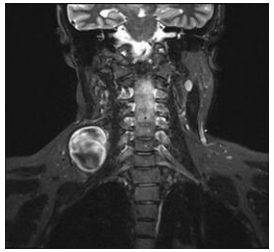
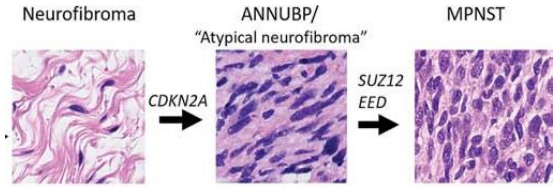
Hintergrund



- Plexiformes Neurofibrom (BNST)?
- Atypische Neurofibromatose-Neoplasie mit unsicherem biologischen Verhalten (ANNUBP)?
- Maligner peripherer Nervenscheidentumor (MPNST)?



Belakhoua SM et al
Neurosurgery 2021

ADC-Wert = Apparent Diffusion Coefficient

Bestimmt mit DWI-Messung (diffusion weighted imaging)
Maß für die Diffusion im Gewebe
invers proportional zur Zelldichte
Niedriger ADC-Wert = hohe Zellularität
Hoher ADC Wert = niedrige Zellularität

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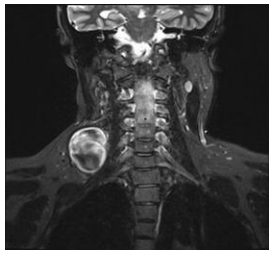

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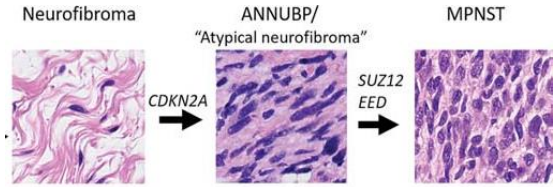

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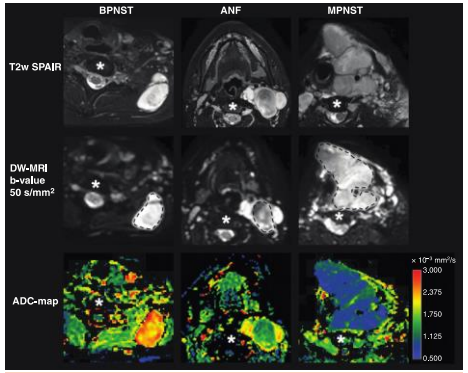

(A) Estimated marginal means	ADC parameter		BPNST (*n* = 60)	ANF (*n* = 13)	MPNST (*n* = 21)
	ADC_{mean} [× 10^{-3} mm^2/s] (95%-CI)		2.14 (2.05–2.24)	1.63 (1.49–1.78)	1.41 (1.29–1.53)
	ADC_{min} [× 10^{-3} mm^2/s] (95%-CI)		1.63 (1.52–1.74)	1.09 (0.91–1.26)	0.82 (0.68–0.97)
	ADC_{dark} [× 10^{-3} mm^2/s] (95%-CI)		2.07 (1.98–2.16)	1.57 (1.42–1.71)	1.30 (1.18–1.42)
(B) Pairwise comparisons	**ADC parameter**		**BPNST vs. ANF**	**BPNST vs. MPNST**	**ANF vs. MPNST**
	ADC_{mean}	Difference [× 10^{-3} mm^2/s] (95%-CI)	0.51 (0.35–0.67)	0.73 (0.62–0.85)	0.22 (0.06–0.39)
		P-value	<.0001	<.0001	.0096
	ADC_{min}	Difference [× 10^{-3} mm^2/s] (95%-CI)	0.54 (0.35–0.73)	0.81 (0.66–0.95)	0.26 (0.06–0.47)
		P-value	<.0001	<.0001	.0137
	ADC_{dark}	Difference [× 10^{-3} mm^2/s] (95%-CI)	0.51 (0.34–0.67)	0.77 (0.64–0.90)	0.26 (0.09–0.44)
		P-value	<.0001	<.0001	.0041

ADC-Wert = Apparent Diffusion Coefficient

Bestimmt mit DWI-Messung (diffusion weighted imaging)
Maß für die Diffusion im Gewebe
invers proportional zur Zelldichte
Niedriger ADC-Wert = hohe Zellularität
Hoher ADC Wert = niedrige Zellularität

ADC-Grenzwerte

BNST vs. ANNUBP +MPNST 1,6
BNST+ANNUBP vs. MPNST 1,4

Neurofibromatose Typ 1: Leitlinien und Handlungsempfehlungen

ERN GENTURIS tumour surveillance guidelines for individuals with neurofibromatosis type 1

Charlotte Carton,[a,o] D. Gareth Evans,[b,q] Ignacio Blanco,[c,o] Reinhard E. Friedrich,[d,o] Rosalie E. Ferner,[e,q] Said Farschtschi,[d,o] Hector Salvador,[f,o] Amedeo A. Azizi,[g,p] Victor Mautner,[d,o] Claas Röhl,[h,r] Sirkku Peltonen,[i,j,o] Stavros Stivaros,[k,l] Eric Legius,[m,o] and Rianne Oostenbrink,[n,o,] On behalf of the ERN GENTURIS NF1 Tumour Management Guideline Group*

Carton C et al.EClinicalMedicine.2023;56:101818.doi: 10.1016/j.eclinm.2022.101818.

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Beispiel:
Empfehlungen für Optikusgliome

Optic pathway glioma

No	Recommendations	Strength
1	Clinical assessment for OPG should begin immediately after diagnosis or suspicion of NF1 in childhood. Baseline ophthalmology assessment should be done at presentation whatever the age.	strong
2	Clinical assessment for OPG should take the form of examination by trained paediatric ophthalmologists or neuro-ophthalmologists or equivalent with experience in the assessment of NF1 related visual changes.	strong
3	Clinical assessment for OPG should include age-appropriate assessment of visual acuity, visual fields, pupillary testing, eye movements, and optic disc appearance.	strong
4	Assessment of retinal nerve fibre layer and retinal ganglion cell layer by optic coherence tomography is helpful and should be conducted whenever feasible.	moderate
5	For children until the age of 8 years without known OPG, ophthalmological assessment (see recommendation 1–3) should be repeated at least every year (every six months if feasible).	moderate
6	In children >8 years without known OPG formal annual visual screening is advised until adulthood. Diagnostic evaluation by an ophthalmologist is also indicated in those with new visual symptoms.	moderate
7	Imaging for OPG with MRI should be performed in people where ophthalmological examination is suggestive for OPG and in children older than 2 years with repeated inconclusive or unreliable ophthalmological exam, e.g. due to age or attention deficit. Abnormal, inconclusive or unreliable ophthalmological exam should be repeated within a short timeframe.	strong
8	Any patient with NF1 diagnosed with an asymptomatic OPG should receive a referral to a unit with expertise (e.g. paediatric, ophthalmology, and/or neuro-oncology) in the monitoring and management of NF1-OPG.	moderate
9	Any patient with NF1 diagnosed with a symptomatic OPG should receive an urgent referral to a unit with expertise (e.g. paediatric, ophthalmology, and/or neuro-oncology) in the management of NF1-OPG.	strong

Note. OPG = optic pathway glioma; NF1 = Neurofibromatosis type 1; MRI = magnetic resonance imaging.

Table 3: **Guideline recommendations for optic pathway glioma.**

Neurofibromatose Typ 1: Leitlinien und Handlungsempfehlungen „pocket guide“

Surveillance protocol for tumour screening/identification in individuals with NF1

	Surveillance	Interval	Age (years) / indication	Strength*	Refer^
Optic pathway glioma	Clinical assessment: 1. Visual assessment 2. Fundoscopy 3. Visual fields 4. Optic coherence tomography	1-3: At least yearly 4: When feasible	0 - 8	1. Strong 2. Strong 3. Moderate 4. Moderate	7.2 & 9.2 (rec. 1-4)
	Visual screening	Yearly	8 – transition adolescence to adult	Moderate	7.2 & 9.2 (rec. 5-6)
Brain or spine glioma	Patient history / Examination signs of brain tumours	Every visit	All ages	Moderate	7.3 & 9.3 (children) 7.4 & 9.4 (adults)
Plexiform neurofibroma	Clinical examination	Every visit	All ages	Moderate	7.5 & 9.5 (rec. 1-2)
	Whole body MRI	Once	Transition adolescence -adult	Weak	7.5 & 9.5 (rec. 3-4)
MPNST + ANNUBP	Clinical examination + history taking	Every visit	All ages	Strong	7.6 & 9.6 (rec. 1-2)
	Regional MRI combined with ^{18}FDG PET MRI or ^{18}FDG PET CT	On indication	Suspicion for malignancy	Moderate	7.6 & 9.6 (rec. 3)
Orbital & Periorbital Plexiform neurofibroma	Clinical assessment, refraction error, vision fields, ocular motility	Every visit	All ages	Strong	7.7 & 9.7 (rec. 1)
Cutaneous neurofibroma	Clinical examination	Every visit	All ages	Strong	7.8 & 9.8 (rec. 1)
Gastrointestinal stromal tumour	Clinical examination + history taking Abdominal MRI or CT	Every visit On indication	Adolescence and adults Clinical suspicion of presence based on symptoms	Moderate Moderate	7.9 & 9.9 (rec. 1-2) 7.9 & 9.9 (rec. 4)
Phaeochromocytoma and paraganglioma	Biochemical screening	On indication	Raised blood pressure	Moderate	7.10 & 9.10 (rec. 2)
	Biochemical screening	On indication	Pregnant women Consider if elective surgery requiring general anaesthesia	Weak	7.10 & 9.10 (rec. 1 and 3)
Breast cancer	MRI	Yearly	30 - 50	Moderate	7.11 & 9.11 (rec. 2-3)
	Breast screening per national guideline for the general population		> 50	Moderate	7.11 & 9.11 (rec. 2-3)
Glomus tumours of the digits	Screening for symptoms and visual inspection	Every visit	All ages, clinical suspicion	Moderate (Age, weak)	7.12 & 9.12 (rec. 1-3)
Juvenile myelomonocytic leukaemia	As part of normal clinical routine: patient history and physical examination	Every visit	<12	Moderate	7.13 & 9.13 (rec. 1-2)
Psychosocial needs	Psychosocial wellbeing and neuropsychological functioning	Every visit	All ages	Weak	7.14 & 9.14 (rec.1-3)

Carton C et al. eClinicalMedicine.2023;56:101818.doi: 10.1016/j.eclinm.2022.101818.

Neurofibromatose Typ 1: Leitlinien und Handlungsempfehlungen

Monatsschr Kinderheilkd
https://doi.org/10.1007/s00112-024-01955-3
Eingegangen: 21. Dezember 2023
Angenommen: 17. Februar 2024

Neurofibromatose Typ 1: Vorsorgebogen für Kinder und Jugendliche in Österreich

Konsensuspapier des österreichischen NF-Netzwerks

Azizi A. et al.,
Monatsschr Kinderheilkd 2024
doi.org/10.1007/s00112-024-01955-3

auch verfügbar unter
www.nfkinder.at

Checkliste für die Untersuchung von NF1-Patientinnen und –Patienten in Deutschland

Farschtschi S, Vaassen P, Kluwe L, Hartung T, Rosenbaum T
Eingereicht beim Dt. Ärzteblatt

NEUROFIBROMATOSE Typ 1 (NF1) Pädiatrischer Vorsorgebogen		Intervall:		Zeitpunkte:			
		Alter < 8a	Alter > 8a	Erstvorst.	Kontrolle:	Transition	Kommentar
Klinik	**Klinische Kontrolle / Anamnese (HW auf ZNS-Tu? oder MPNST[1]?)**	mind. einmal/Jahr bzw. bei Verschlechterung		X	X	X	
	Neurostatus	mind. einmal/Jahr bzw. bei Verschlechterung		X	X	X	
	Pubertätsstatus	einmal/Jahr + bei Pubertas praecox (♀ <8. / ♂ 9. LJ)		X	X	X	
	Auxiologie (Körperlänge, Gewicht, Kopfumfang)	mind. einmal/Jahr		X	X	X	
	Blutdruck	bei jeder KFA Kontrolle (mind. einmal/Jahr)		X	X	X	
	Hautstatus (CALM, Freckling, NF, PNF, Naevus anaemicus, juv. Xanthogranulome)	mind. einmal/Jahr		X	X	X	
	Kinderfachärztliche Kontrollen + Impfungen laut Eltern-Kind-Pass / Impfplan	Lt. Eltern-Kind-Pass					
Labor	**Genetik / genet. Beratung** (inkl. DD Legius-Syndrom, evtl.CMMRD)	mind. ein Diagn.-Krit. erfüllt oder durchNF-Spez. indiziert		X	X		
	BB, Serumchemie, Vit. D_3 erwägen	falls Blutabnahme erfolgt, nicht routinemäßig					
	Hormonstatus	bei klin. Notwendigkeit					
	Metanephrine im Blut	bei klin. Notwendigkeit (RR!)					
Radiologie	**Sonographie** (Abdomen, Retroperitoneum, evtl. Nervensonographie)	Ausgangsbefund, dann bei klin. Notwendigkeit		X		erwägen	
	MRT-Screening (Schädel: OPG?, Moyamoya? evtl.: Angio, TOF ohne KM)	Bei Sympt./ ab 2 Jahre erwägen.[2]	Bei Sympt. / klin.Notwendigk.[2]	[2]	[2]	X	
	MRT bei Optic Pathway Glioma (OPG) (ohne Therapie)	3 Mo, falls 1 Jahr stabil: 6 Mo mind 2 Jahre, dann einmal/Jahr					min. bis 8. LJ
	MRT (Ganzkörper)	bei Hochrisiko-Patienten für MPNST [3] und bei Transition			[3]	X	
	MRT (lokal)	z.B. bei wachsendem plexiformen NF, V.a. MPNST[1]			[1]		
	FDG-PET/MR oder PET/CT	bei V.a. MPNST[1], evtl. Screening bei High-risk-Pat.[3]			[1, 3]		
	MR-Angio (bei Vd.a. Moyamoya [Gehirn] oder Bluthochdruck [Nierenart.])	bei klin. Notwendigkeit					
Konsil	**Ophthalmologie** (Visus quant. c.c., Fundi, OCT, GF sobald möglich) (OPG: Jahr 1: alle 3 Mon. Ab 2. Jahr: 2-mal/Jahr bis 8. LJ (min. 2 Jahre). Ko.mind. bis 18 Jahre)	alle 6 Mo	einmal/Jahr bis 18 Jahre	X	X		Bei ↓ Compl.: Wiederhol. / MRT
	Orthopädie (Skoliose, Tibia-Dysplasie)	bei klinischer Notwendigkeit (evtl. einmal/Jahr Screening)		X	X		
	Hämatologie-Onkologie (bei V. a. Neoplasien, z.B. Gliom, Plex. NF, **Cave** JMML)	bei klin. Notwendigkeit (frühzeitig! auch bei asympt. OPG)					
	Neuropsychologische Diagnostik (Screening)	bei klin. Notwendigkeit + Empfehlung: Vorschulalter + 4. Kl. VS		(X)	X		
	Psycholog. Betreuung	Angebot bei Diagnosestellung und weiters bei Bedarf		X	X	X	
	Kontaktinfo Patientenorganisation / Aufklärungsbroschüre	bei Diagnosestellung / bei NF1 in Abklärung / bei Bedarf		X	(X)	X	
	Soziale Arbeit	bei Bedarf		(X)	(X)	(X)	
	Dermatologie	bei klin. Notwendigkeit					
	Endokrinologie (z.B. bei Pubertas praecox [♀ <8. / ♂ 9. LJ])	bei klin. Notwendigkeit					
	Gynäkologie	einmal/Jahr ab Pubertät (Info: Brustkrebsscreening ab ca. 35 Jahren)					
	EKG/Herzecho	bei klin. Notwendigkeit					
	EEG	bei klin. Notwendigkeit					
	Plastische Chirurgie (z.B. Nerventumoren)	bei klin. Notwendigkeit					
	Kinderchirurgie (z.B. bei Trichterbrust, Tumoren)	bei klin. Notwendigkeit					
	Vorstellung interdisziplinäres NF-Board / neuroonkologisches Tumorboard	bei klin. Notwendigkeit (z.B. V.a. MPNST, Hirntumor, …)				(X)	
	Rehabilitation (NF-spezifische Zyklen, Skoliose, Onko-Rehab …)	wiederholt, je nach Bedarf			X		

Neurofibromatose Typ 1: Langzeiterfahrungen mit Selumetinib-Therapie

Selumetinib-Indikation
Symptomatische, inoperable plexiforme Neurofibrome bei NF1-Patienten von 3 – 18 Jahren (Europa), zugelassen in Deutschland seit 2021
(USA: NF1-Patienten von 2 – 18 Jahren)

Long-term safety and efficacy of selumetinib in children with neurofibromatosis type 1 on a phase 1/2 trial for inoperable plexiform neurofibromas

Gross et al., Neurooncology 2024; doi.org/10.1093/neuonc/noad086

Safety and efficacy of selumetinib in pediatric and adult patients with neurofibromatosis type 1 and plexiform neurofibroma

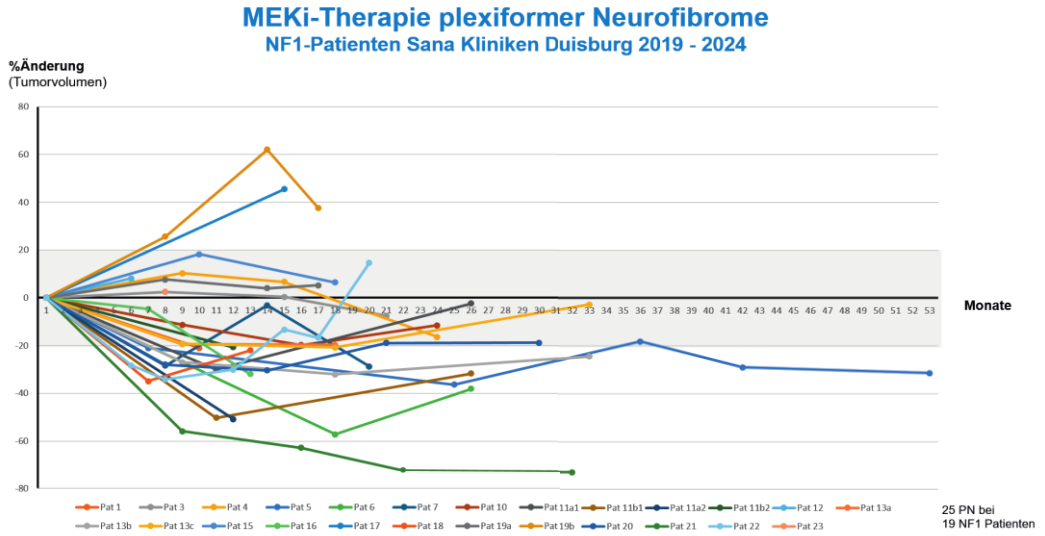
Kim et al., Neurooncology 2024;doi.org/10.1093/neuronc/noae121

Safety and Efficacy of Mek Inhibitors in the Treatment of Plexiform Neurofibromas: A Retrospective Study

Cacchione et al. Cancer Control. 2023;30:1-13

MEK-Inhibitor-Therapie NF1-assoziierter plexiformer Neurofibrome

Vaassen et al., Neuropaediatrie 2024; 23:122-130



Neurofibromatose Typ 1: Langzeiterfahrungen mit Selumetinib-Therapie

Selumetinib-Indikation
Symptomatische, inoperable plexiforme Neurofibrome bei NF1-Patienten von 3 – 18 Jahren (Europa), zugelassen in Deutschland seit 2021
(USA: NF1-Patienten von 2 – 18 Jahren)

Zusammenfassung der Langzeiterfahrungen

- Zuverlässige Volumenreduktion plexiformer Neurofibrome
- Verbesserung klinischer Symptome (oft schon vor einer messbaren Tumorvolumenreduktion)
- Hauptnebenwirkungen: Hautausschläge, Nagelbettentzündungen, asymptomatische CK-Erhöhung, gastrointestinale Beschwerden

- Keine bislang unbekannten Nebenwirkungen im Langzeitverlauf
- Bessere Verträglichkeit bei jungen Kindern

Cacchione et al. Cancer Control. 2023;30:1-13
Gross et al., Neurooncology 2024; doi.org/10.1093/neuonc/noad086
Kim et al., Neurooncology 2024; doi.org/10.1093/neuonc/noae121
Vaassen et al., Neuropaediatrie 2024; 23:122-130

Neurofibromatose Typ 1: Nebenwirkungsmanagement bei Selumetinib-Therapie

The Oncologist®

Symptom Management and Supportive Care

The Use of MEK Inhibitors in Neurofibromatosis Type 1–Associated Tumors and Management of Toxicities

Laura J. Klesse,[a] Justin T. Jordan,[b] Heather B. Radtke,[c,h] Tena Rosser,[d] Elizabeth Schorry,[e] Nicole Ullrich,[f] David Viskochil,[g] Pamela Knight,[h] Scott R. Plotkin,[b] Kaleb Yohay[i]

Klesse L et al., The Oncologist 2020; 25:e1109-e1116.
www.TheOncologist.com

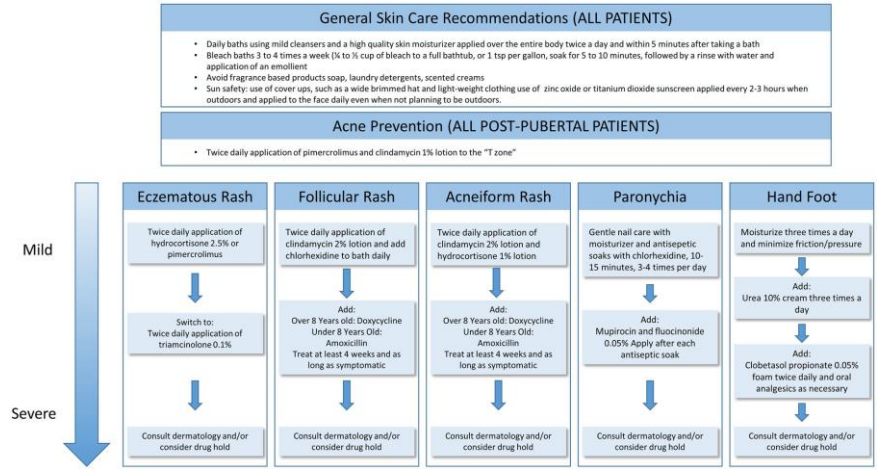


Figure 2. Schema for management of skin toxicity associated with MEK inhibitors.

Neuro-Oncology Practice

XX(XX), 1–17, 2024 | https://doi.org/10.1093/nop/npae038 | Advance Access date 27 April 2024

Consensus recommendations on management of selumetinib-associated adverse events in pediatric patients with neurofibromatosis type 1 and plexiform neurofibromas

Amedeo A. Azizi, Darren Hargrave, João Passos, Pierre Wolkenstein, Thorsten Rosenbaum, Claudia Santoro, Verena Rosenmayr, Thomas Pletschko, Paolo A. Ascierto, and Héctor Salvador Hernández

Azizi A. et al., Neuro-Oncology Practice 2024
doi.org/10.1093/nop/npae038

Table 1. Expert Recommendations for the Prevention and Management of AEs Potentially Associated with Selumetinib in Pediatric Patients with NF1-PN

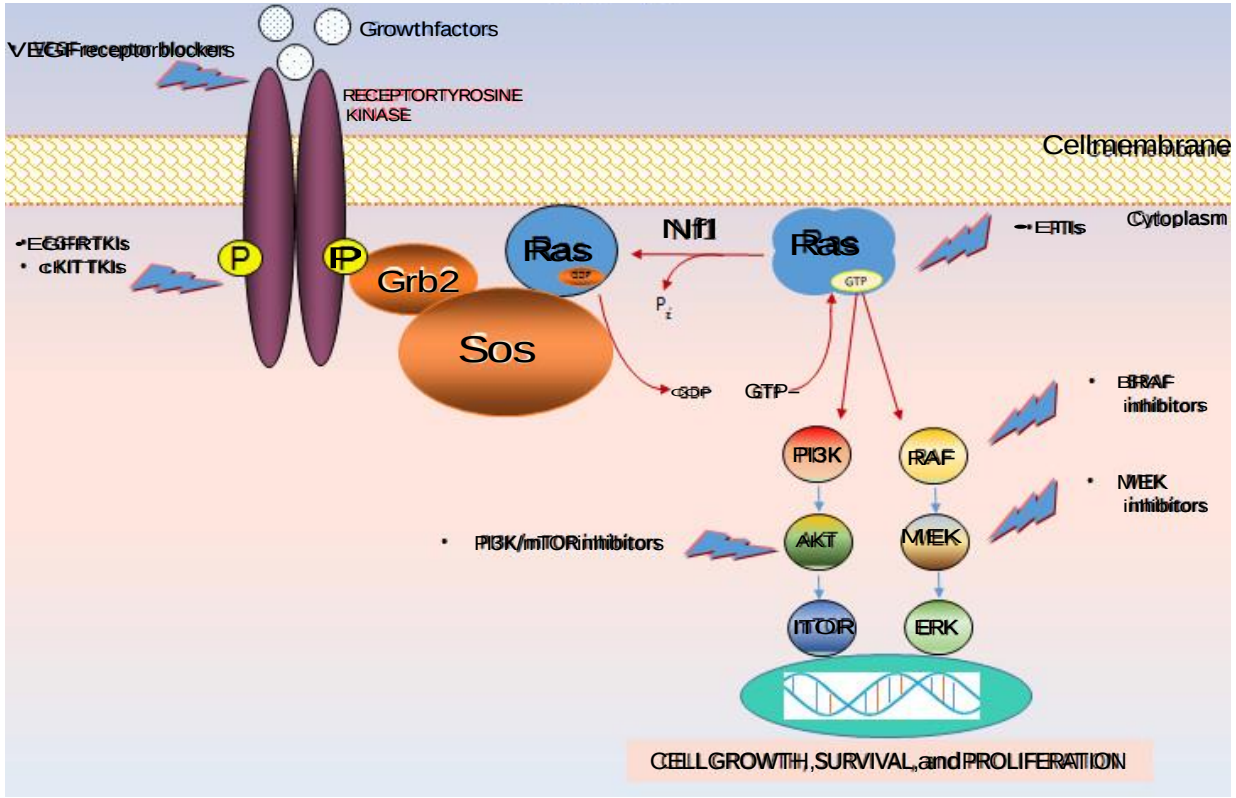
AE		Consensus statement	Level of consensus
Dermatologic			
Paronychia	1	**To prevent paronychia, patients should try to prevent potential traumas to the hands and feet (eg, avoiding tight shoes) and be advised on nail management (eg, not cutting the nails too short, avoiding cutting close to the nail fold)** • Soap substitutes: eg, Dermol® 500 lotion, Balneum Plus® bath oil, aqueous cream, Doublebase® emollient shower gel, Doublebase® bath additive, E45® bath additive, and Oilatum® shower gel	100%
	2	**For all grades of paronychia, the affected nail should be softened with an antiseptic bath twice daily using recently opened antiseptic agents** • Antiseptic agents: Diluted chlorhexidine, very diluted bleach soaks for nails, povidone–iodine solutions	100%
	3	**Infection should be managed with an antiseptic with or without a topical antibiotic, according to local practice** • Topical antibiotics: Mupirocin 2% w/w ointment, baneocin, topical clindamycin lotion (eg, DalacinT® lotion) applied twice daily, clindamycin, and silver sulfadiazine 1% cream • Combined corticosteroid and topical antibiotic: Betamethasone valerate 0.1% and neomycin sulfate 0.5% (eg, Betnovate®-N) or betamethasone valerate 0.1% and fusidic acid 2% (eg, Fucibet®) • Topical antifungal in combination with a topical antibiotic • If a systemic antifungal is required, **avoid** fluconazole or itraconazole[9]	100%

Neurofibromatose Typ 1: MEK-Inhibitoren auch für andere Indikationen?

Tuberöse Sklerose

Everolimus (Votubia®)
mTOR Inhibitor

- SEGAs



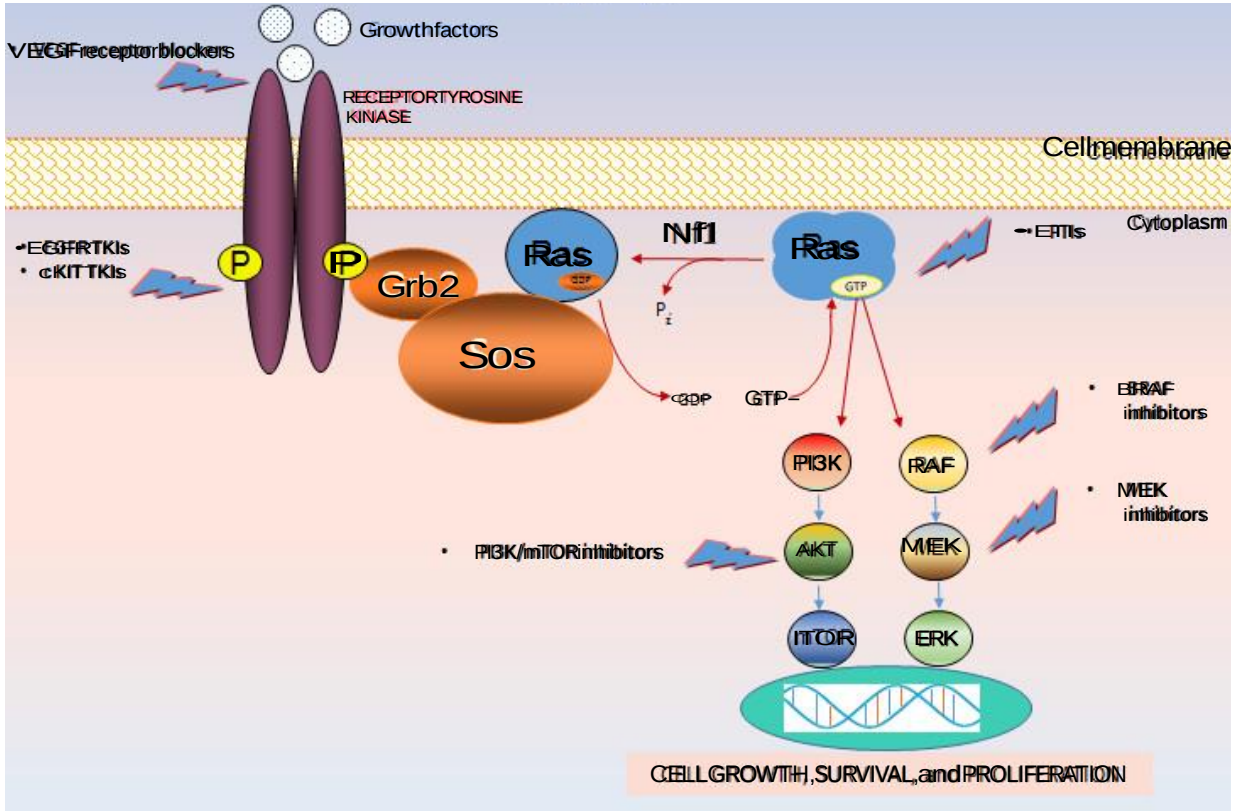
Neurofibromatose Typ 1: MEK-Inhibitoren auch für andere Indikationen?

Tuberöse Sklerose

Everolimus (Votubia®)
mTOR Inhibitor
zugelassen bei
- SEGAs
- Epilepsie (add-on)
- Angiomyolipomen

Hyftor®-Gel seit 2024
zugelassen bei
- fazialen Angiomyofibromen

Wirksamkeit bei
- LAM (Lymphangioleiomyomatose)
- Kardialen Rhabdomyomen
- TAND



Neurofibromatose Typ 1: MEK-Inhibitoren auch für andere Indikationen?

Tuberöse Sklerose

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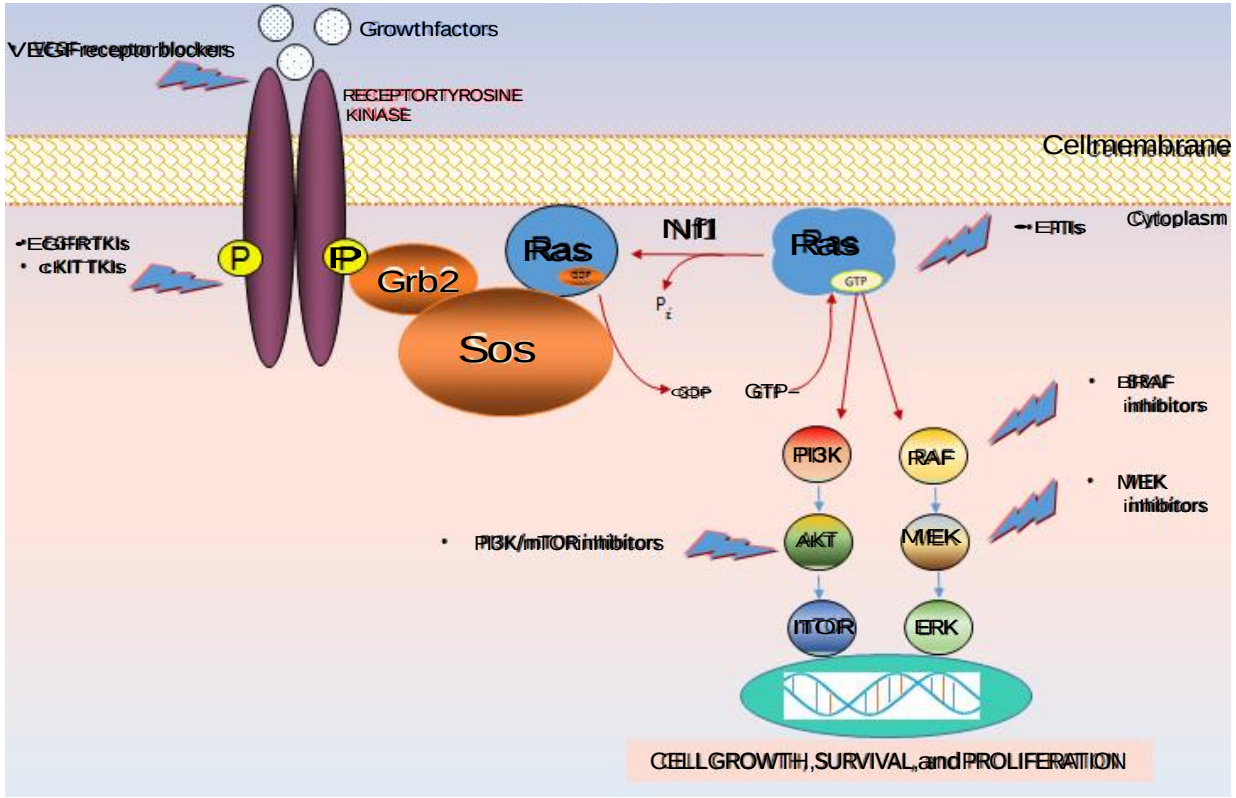


Neurofibromatose Typ 1

Selumetinib (Koselugo®)
MEK Inhibitor
zugelassen bei
- plexiformen Neurofibromen

Wirksamkeit bei
- Optikusgliomen

- Pseudarthrosen?
- Neuropsycholog. Störungen?

Neurofibromatose Typ 1: MEK-Inhibitoren auch für andere Indikationen?

Journal of Neuro-Oncology (2024) 167:447–454
https://doi.org/10.1007/s11060-024-04624-3

RESEARCH

Impact of trametinib on the neuropsychological profile of NF1 patients

Eve Lalancette[1] · Édith Cantin[3] · Marie-Ève Routhier[3] · Chantal Mailloux[4] · Marie-Claude Bertrand[4] · Dorsa Sadat Kiaei[1] · Valérie Larouche[5] · Uri Tabori[6] · Cynthia Hawkins[7] · Benjamin Ellezam[8] · Jean-Claude Décarie[9] · Yves Théoret[10] · Marie-Élaine Métras[10] · Tara McKeown[6] · Luis H. Ospina[11] · Stéphanie Vairy[12] · Vijay Ramaswamy[6] · Hallie Coltin[13] · Serge Sultan[1] · Geneviève Legault[14] · Éric Bouffet[6] · Lucie Lafay-Cousin[15] · Juliette Hukin[16] · Craig Erker[17] · Maxime Caru[2] · Mathieu Dehaes[1,20] · Nada Jabado[18] · Sébastien Perreault[19] · Sarah Lippé[1,21]

„...NF1 patients demonstrate cognitive improvement, in visuo-motor abilities, processing speed and verbal comprehension, when treated with MEKi...“

Impact of MEK Inhibitor Therapy on Neurocognitive Functioning in NF1

Karin S. Walsh, PsyD, Pamela L. Wolters, PhD, Brigitte C. Widemann, MD, Allison del Castillo, BA, Maegan D. Sady, PhD, Tess Inker, BA, Marie Claire Roderick, PsyD, Staci Martin, PhD, Mary Anne Toledo-Tamula, MA, Kari Struemph, PhD, Iris Paltin, PhD, Victoria Collier, RN, BSN, Kathy Mullin, BSN, Michael J. Fisher, MD, and Roger J. Packer, MD

Neurol Genet 2021;7:e616. doi:10.1212/NXG.0000000000000616

Borrie *et al. Molecular Autism* (2021) 12:53
https://doi.org/10.1186/s13229-021-00458-2

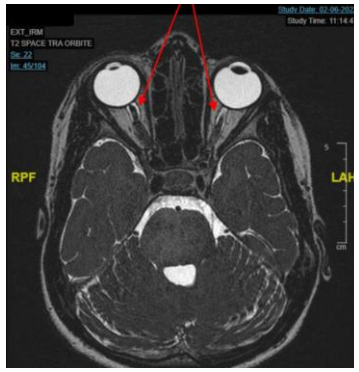
Molecular Autism

RESEARCH Open Access

MEK inhibition ameliorates social behavior phenotypes in a Spred1 knockout mouse model for RASopathy disorders

Sarah C. Borrie[1], Ellen Plasschaert[1], Zsuzsanna Callaerts-Vegh[2], Akihiko Yoshimura[3], Rudi D'Hooge[2], Ype Elgersma[4,5], Steven A. Kushner[4,6], Eric Legius[1] and Hilde Brems[1*]

Neurofibromatose Typ 1: MEK-Inhibitoren auch für andere Indikationen?



NF1
10 Jahre altes Mädchen
West-Syndrom
Übergang in epileptische Enzephalopathie
Versuche mit multiplen AEDs
Progredientes Optikusgliom
Trametinib-Therapie

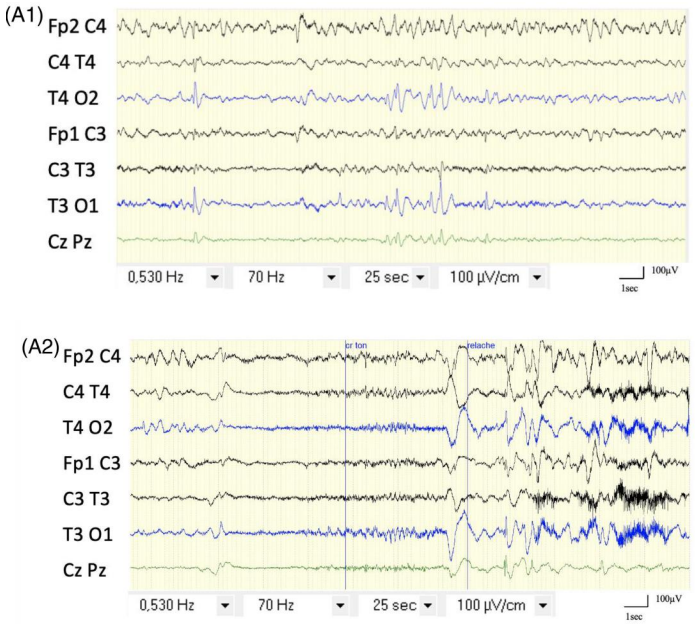
Received: 23 July 2023 | Accepted: 10 November 2023
DOI: 10.1002/epd2.20180

Epileptic Disorders

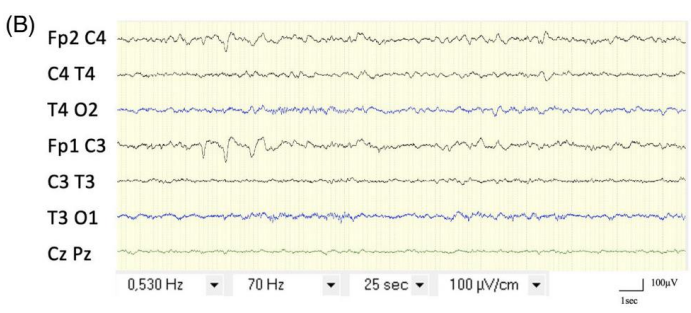
CLINICAL COMMENTARY

Antiseizure effect of MEK inhibitor in a child with neurofibromatosis type 1—Developmental and epileptic encephalopathy and optic pathway glioma

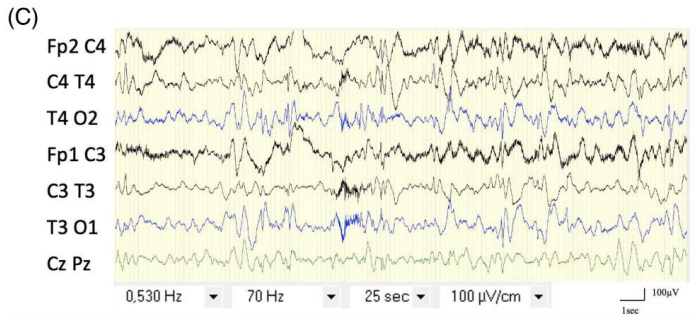
Sarah Barrière[1] | Cécile Faure-Conter[2] | Pierre Leblond[2] | Michael Philippe[2] | Vincent des Portes[3] | Laurence Lion François[4] | Julitta de Bellescize[5] | Isabelle Sabatier[1]



1 Jahr vor MEKi Therapie
Anfälle mindestens 3x/Woche



3 Monate nach Beginn MEKi Therapie
Keine Anfälle seit > 2 Monaten



4 Monate nach Ende MEKi Therapie
Anfälle 1x/Woche

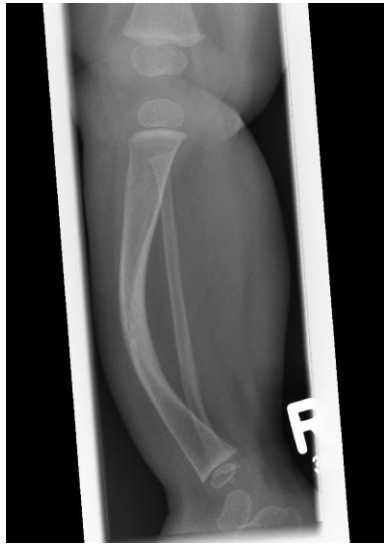
Neurofibromatose Typ 1: MEK-Inhibitoren auch für andere Indikationen?

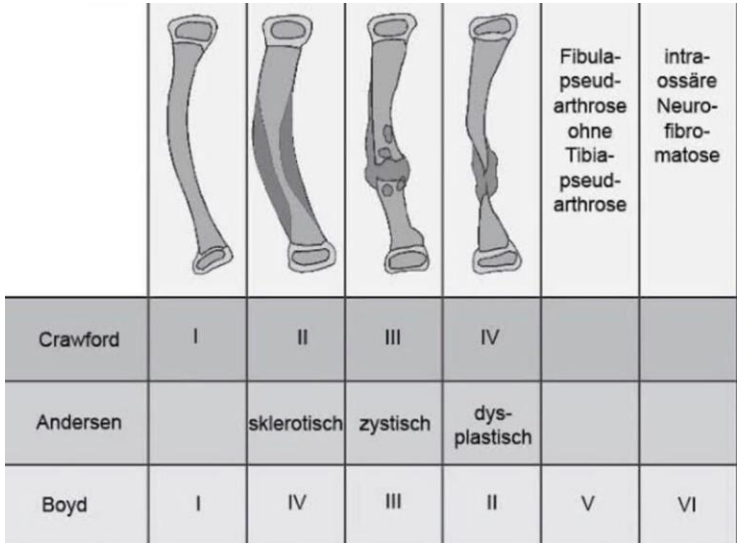
Tibia-Pseudarthrose

Bei 4-5 % der NF1-Patienten

Kongenital, bildet sich unter mechanischer Belastung aus

Therapie sehr herausfordernd





MEK-SHP2 inhibition prevents tibial pseudarthrosis caused by ***NF1*** loss in Schwann cells and skeletal stem/progenitor cells

Simon Perrin[1], Sanela Protic[1], Vincent Bretegnier[1], Ingrid Laurendeau[2], Oriane Duchamp de Lageneste[1], Nicolas Panara[2], Odile Ruckebusch[3], Marine Luka[4,5], Cécile Masson[6,7], Théodora Maillard[8], Fanny Coulpier[1], Stéphanie Pannier[9], Philippe Wicart[9], Smail Hadj-Rabia[10], Katarzyna J. Radomska[1], Mohammed Zarhrate[7,11], Mickael Ménager[4,5], Dominique Vidaud[2,8], Piotr Topilko[1], Béatrice Parfait[2,8], Céline Colnot[1]*

Perrin S. et al., Sci Transl Med 16,eadj1597 (2024)

NF1-Inaktivierung in skelettalen Stammzellen und Schwannzellen im Periost führt zu Fibrosierung und behindert Frakturheilung

MEK-/SHP2-Inhibition überwindet Fibrosierung und ermöglicht Frakturheilung

→ neue Therapieoption mit Selumetinib?

MEK-Inhibitoren auch für andere Indikationen bei NF1 / für andere Erkrankungen?

Contents lists available at ScienceDirect

Neoplasia

journal homepage: www.elsevier.com/locate/neo

Original Research

Pediatric low-grade glioma: Targeted therapeutics and clinical trials in the molecular era

Neevika Manoharan[a,b,1], Kevin X. Liu[c,1], Sabine Mueller[d,e], Daphne A. Haas-Kogan[c], Pratiti Bandopadhayay[f,*]

https://doi.org/10.1016/j.neo.2022.100857

Zahlreiche Studien zum Vergleich Standard-Chemotherapie vs. MEK-Inhibitoren

- bei NF1-Pat. mit Optikusgliomen / LGG
- bei non-NF1-Pat mit LGG mit bekannter Mutation im RAS-Pathway

Table 2
List of completed and ongoing consortium clinical trials for pLGG using targeted therapy.

Consortium	Phase; NCT #	Targeted therapy; type of pLGG	Status	Design/Primary Objective(s)	Results
COG ACNS1831	III; NCT03871257	Selumetinib vs. Carboplatin/ Vincristine for newly diagnosed NF1-associated pLGG	Ongoing	RCT; primary objectives are to characterize event-free survival and determine number of participants with visual acuity improvement	-
COG ACNS1833	III; NCT04166409	Selumetinib vs. Carboplatin/ Vincristine for newly diagnosed non-NF1 pLGG	Ongoing	RCT; primary objective is to characterize event-free survival	-
COG ACNS1931	III; NCT04576117	selumetinib vs. selumetinib/vinblastine for relapsed pLGG	Ongoing	RCT; primary objectives are to determine MTD/RP2D and event-free survival	
NFCTC RAD001 [49]	II; NCT01158651	Everolimus for relapsed NF1-associated pLGG	Completed	One-stage design; primary objective is to assess best response of progressive LGG in previously treated individuals with NF1.	23 pts (median age 9.4 y); 1 pt removed from study due to development of MPNST. 15/22 (68%) pts had response (1 CR, 2 PR, 12 SD); 10/15 had no progression after median follow-up of 33 months. All pts were alive.
NFCTC MEK162	I/II; NCT02285439	MEK162 for pLGG and other Ras/Raf/MAP pathway activated tumors	Ongoing	One-stage design; primary objective of phase I are to determine MTD, and of phase II: to determine the response rate	-
PBTC-029B [45]	I/II; NCT01089101	Selumetinib for relapsed pLGG	Completed	One-stage design; primary objectives of phase I are RP2D and MTD, and of phase II is objective response (complete response + partial response) rate sustained for 8 weeks	25 pts; 6 pts w/ PR, 14 pts w/ SD, 5 pts w/ PD; Median treatment courses = 26; 2-y PFS 78%
PBTC-055	I/II; NCT04201457	Dabrafenib, trametinib, hydroxychloroquine for relapsed BRAF-mutant pLGG after prior therapy with a RAF and/or MEK inhibitor	Ongoing	One-stage design; primary objectives of phase I are RP2D and MTD, and of phase II is sustained objective response rate defined as "better response" than the best response on prior RAF and/or MEK inhibitor	-
PNOC001 [56]	II; NCT01734512	Everolimus for relapsed pLGG	Completed	Two-stage design; primary objective is to characterize PFS at 6 Months	65 pts (median age 9 y); PFS at 6 months 63%; 1 CR, 1 PR, 33 SD, 17 PD
PNOC002 [46]	I/II; NCT01748149	Vemurafenib; relapsed BRAFV600E-mutant pLGG	Completed	One-stage design; primary objectives are to determine the RP2D and DLTs, and characterize objective response rates	I: 19 pts, RP2D 550 mg/m2 twice daily after DLT criteria adjustment for rash; 1 CR, 5 PR, 13 SD
PNOC014 [57]	I/II; NCT03429803	Tovorafenib/DAY101 (TAK-580/MLN2480) for relapsed RAS/RAF/MEK/ERK pathway activated pLGG	Ongoing	One stage design; primary objectives are to determine MTD and RP2D	9 pts treated at 280, 350, and 420 mg/m2. No DLTs. One patient with grade 3 CPK elevation. Best response: 2 CR, 2 PR, 3 SD, 2 PD with median time to response of 10.5 weeks
PNOC021	I; NCT04485559	Trametinib/ Everolimus for relapsed pLGG	Ongoing	One-stage design; primary objectives are to estimate RP2D, define DLTs, and characterize pharmacokinetic profile of trametinib and everolimus in combination.	-
PNOC026	II; NCT04775485	Tovorafenib/DAY101 (TAK-580/MLN2480) for BRAF-altered relapsed pLGG	Ongoing	One-stage design; primary objectives are to define overall response rate by RANO and RECIST v1.1 criteria and characterize safety and tolerability	-
POETIC [58]	II; NCT00782626	Everolimus for relapsed pLGG	Completed	One-stage design; primary objective is to determine if treatment demonstrated a response rate ≥25%	23 pts (median age 9.2 y); By week 48, response rate of 52% - 2 pts w/ PR, 10 w/ SD; median FU 1.8 years, 2-y PFS 39%, 2-y OS 93%

MEK-Inhibitoren auch für andere Erkrankungen?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabrafenib plus Trametinib in Pediatric Glioma with *BRAF* V600 Mutations

Eric Bouffet, M.D., Jordan R. Hansford, M.B., B.S., Maria Luisa Garrè, M.D., Junichi Hara, M.D., Ph.D., Ashley Plant-Fox, M.D., Isabelle Aerts, M.D., Franco Locatelli, M.D., Ph.D., Jasper van der Lugt, M.D., Ph.D., Ludmila Papusha, M.D., Ph.D., Felix Sahm, M.D., Ph.D., Uri Tabori, M.D., Kenneth J. Cohen, M.D., Roger J. Packer, M.D., Olaf Witt, M.D., Larissa Sandalic, M.S., Ana Bento Pereira da Silva, Ph.D., Mark Russo, M.D., Ph.D., and Darren R. Hargrave, M.B., Ch.B., M.D.

Bouffet E et al, N Engl J Med 2023; 389:12

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Dabrafenib plus Trametinib in Pediatric Glioma with *BRAF* V600 Mutations

Bouffet E et al. DOI: 10.1056/NEJMoa2303815

CLINICAL PROBLEM

Up to 20% of pediatric low-grade gliomas harbor the *BRAF* V600E mutation, which may make them less responsive to standard chemotherapy. Dabrafenib, a selective BRAF inhibitor targeting *BRAF* V600 mutations, has shown promising antitumor activity (both as monotherapy and in combination with trametinib) in patients with previously treated low-grade glioma with *BRAF* V600 mutations. Data on dabrafenib plus trametinib as first-line therapy are needed.

CLINICAL TRIAL

Design: A phase 2, open-label, randomized trial assessed the efficacy and safety of dabrafenib plus trametinib (a mitogen-activated protein kinase enzyme inhibitor), as compared with standard chemotherapy, in children who had low-grade glioma with *BRAF* V600 mutations and were scheduled to receive first systemic treatment.

Intervention: 110 children (<18 years of age) were assigned in a 2:1 ratio to receive oral dabrafenib plus trametinib or chemotherapy with carboplatin plus vincristine until loss of clinical benefit, development of unacceptable toxic effects, start of a new anticancer therapy, loss to follow-up, death, or (in the chemotherapy group) completion of the protocol-defined number of cycles had occurred. The primary outcome was the overall response (a best overall complete or partial response confirmed by independent assessment).

RESULTS

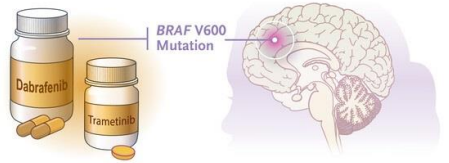
Efficacy: During a median follow-up of 18.9 months, the overall response was approximately four times as high with dabrafenib plus trametinib as with standard chemotherapy.

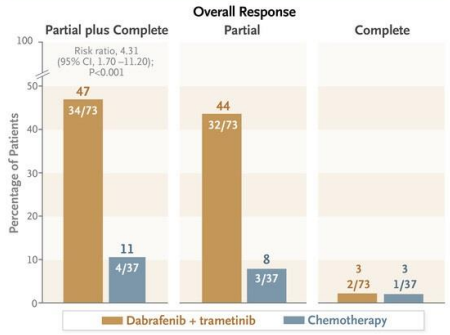
Safety: The proportion of patients with grade ≥3 adverse events was lower with dabrafenib plus trametinib than with standard chemotherapy.

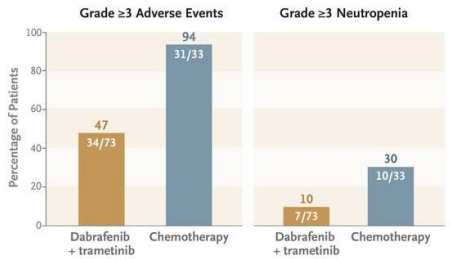
LIMITATIONS AND REMAINING QUESTIONS

- Indefinite treatment with dabrafenib plus trametinib may be required for children who have low-grade glioma with *BRAF* V600 mutations, and long-term safety in this population is unknown.
- Additional studies are needed to evaluate functional outcomes and determine the most effective duration of treatment.

Links: Full Article | NEJM Quick Take







CONCLUSIONS

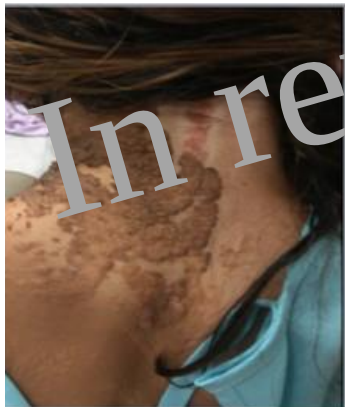
Among children with low-grade glioma with *BRAF* V600 mutations who were scheduled to receive initial treatment, dabrafenib plus trametinib resulted in significantly more overall responses than standard chemotherapy, at approximately 19 months of follow-up.

MEK-Inhibitoren für andere Erkrankungen?

Frontiers in Neurology 2024, in press

Case report: MEK inhibitor as treatment for multi-lineage mosaic KRAS G12D-associated epidermal nevus syndrome in a pediatric patient

Margarita Dionysiou[1], Stavriani C. Makri[1], Melike Guryildirim[2, 3], Kristin W. Barañano[2, 4], Mari L. Groves[2, 5], Pedram Argani[2, 6], Christine A. Pratilas[1*]



7 Jahre altes Mädchen mit epidermalem Nävus Syndrom

- verruköser Nävus epidermalis *(somatische KRAS-Mutation)*
- Vitium cordis
- polyzystische Nieren
- Epilepsie
- **hypertrophe Neuropathie**

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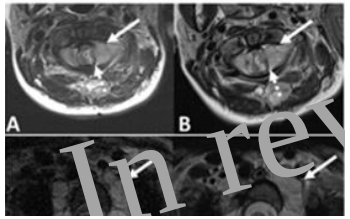

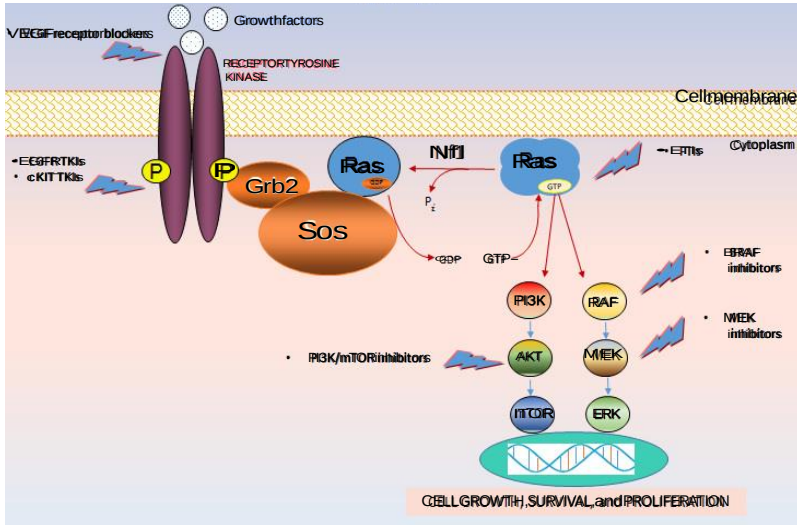

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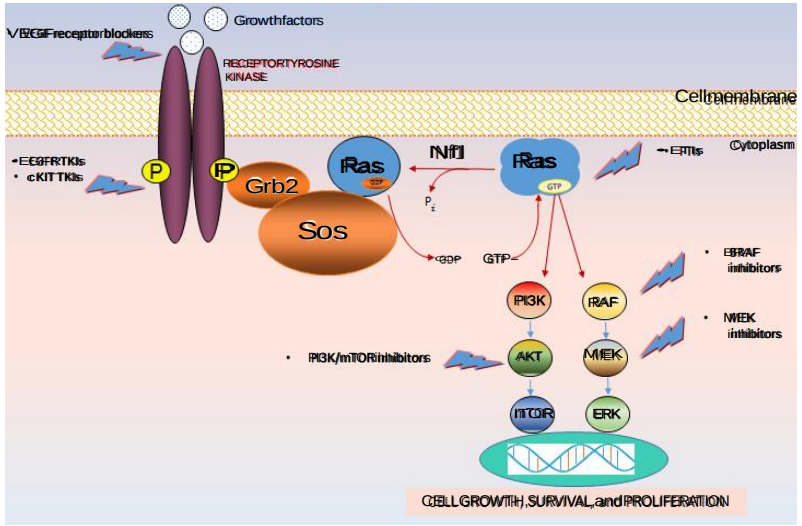

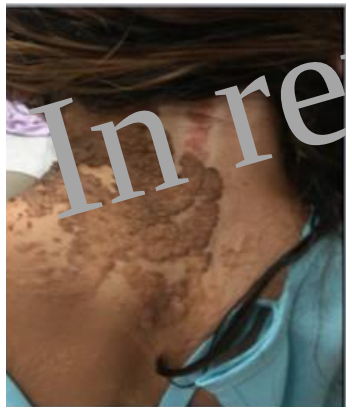

7 Jahre altes Mädchen mit epidermalem Nävus Syndrom

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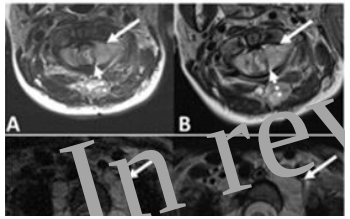
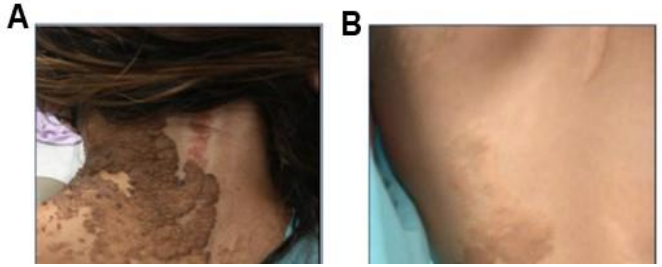
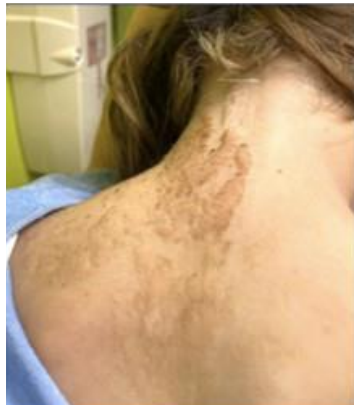
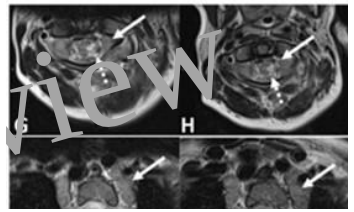






7 Jahre altes Mädchen mit epidermalem Nävus Syndrom nach 3 Monaten Selumetinib-therapie:

- Abblassung des verrukösen Nävus epidermalis
- Volumenreduktion der hypertrophen Neuropathie



VIELEN DANK!

Vogelflug: Phakomatosen und Neuroonkologie

Jahrestagung Gesellschaft für Neuropädiatrie
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