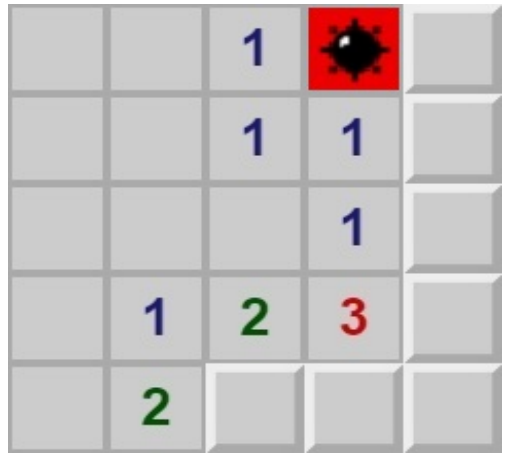
Państwowy Instytut Medyczny MSWiA



Menopauza i osteoporoza w NF1

Katarzyna Życińska

Klinika Reumatologii, Chorób Tkanki Łącznej i Chorób Rzadkich
Centrum Chorób Rzadkich i Niezdiagnozowanych

Państwowy Instytut Medyczny MSWiA w Warszawie

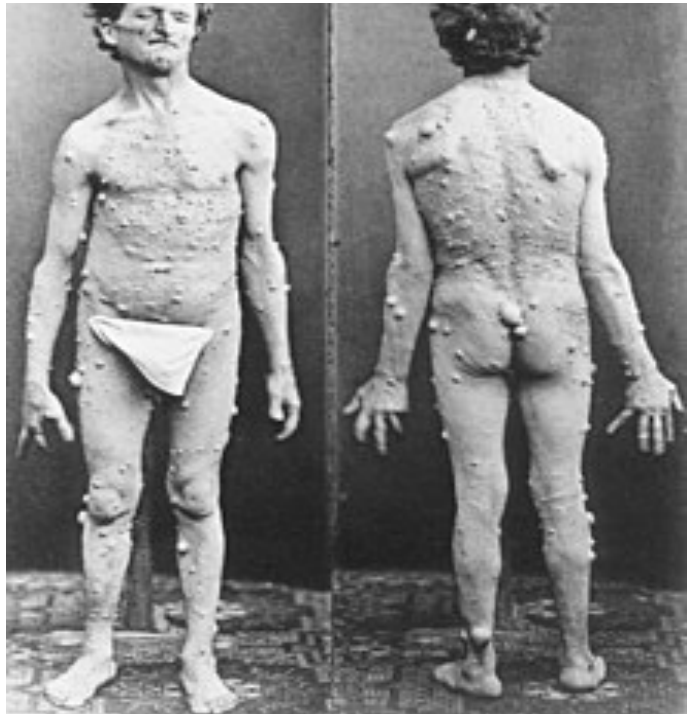
Kierownik: Prof. dr hab. n. med. Katarzyna Życińska

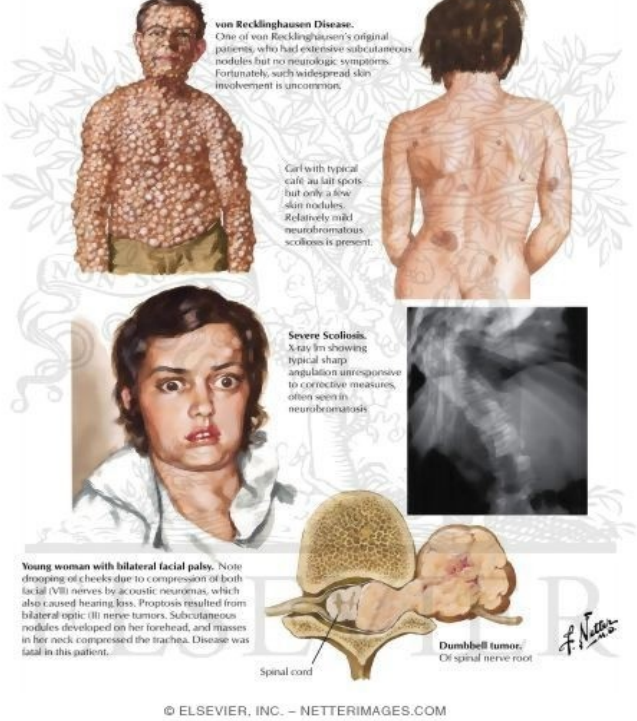
riedrich Daniel von Recklinghausen, hysician

2. December 1833 in
ütersloh (Westphalia)
16. August 1910 in
trasbourg

fter successfully studying
ıedicine in Bonn, Würzburg
nd Berlin, Friedrich Daniel
on Recklinghausen gained
is doctorate in 1855. Ten
ears later he returned to the
MU as professor and taught
t the Chair of Pathologic
natomy and Medical History.
rom 1865 to 1872 the
hysician successfully
onducted research in
/ürzburg and was able to
ain groundbreaking

Friedrich Daniel von Recklinghausen
Bild: Universität Würzburg





Neurofibromatozy-historia

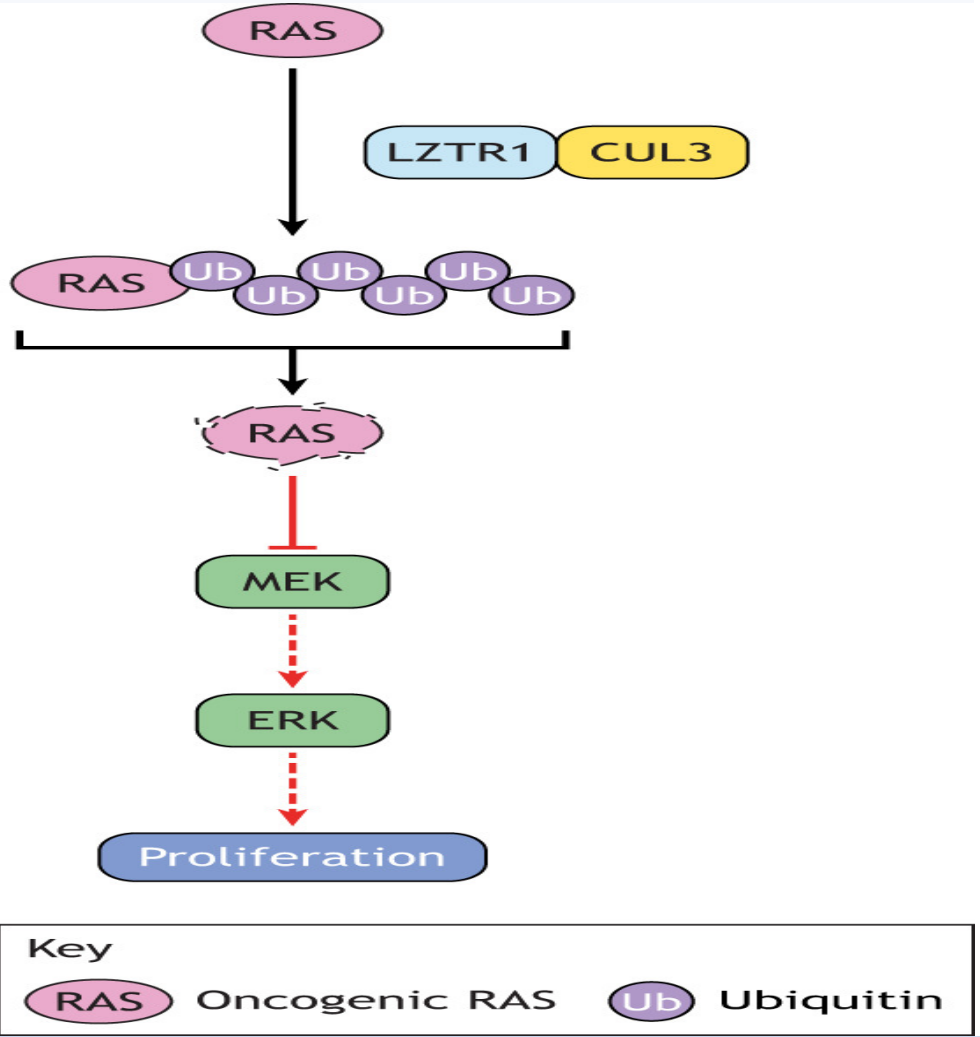
- 1882 r- pierwszy opis choroby patolog niemiecki F. von Recklinghausen , Prof. Uniwersytetu w Wurzburgu
- Fakomatozy (ch. skórno-nerwowe/ektoderma)
- RAS-opatie (rodzina kinaz protoonkogennych)
- NF1- choroba Recklinghausena i Legius syndrome- **mutacja ch. 17**
- NF2- (BAN-bilateral acoustic NF)-mutacja ch. 22
- SNN- szwannomatoza
-

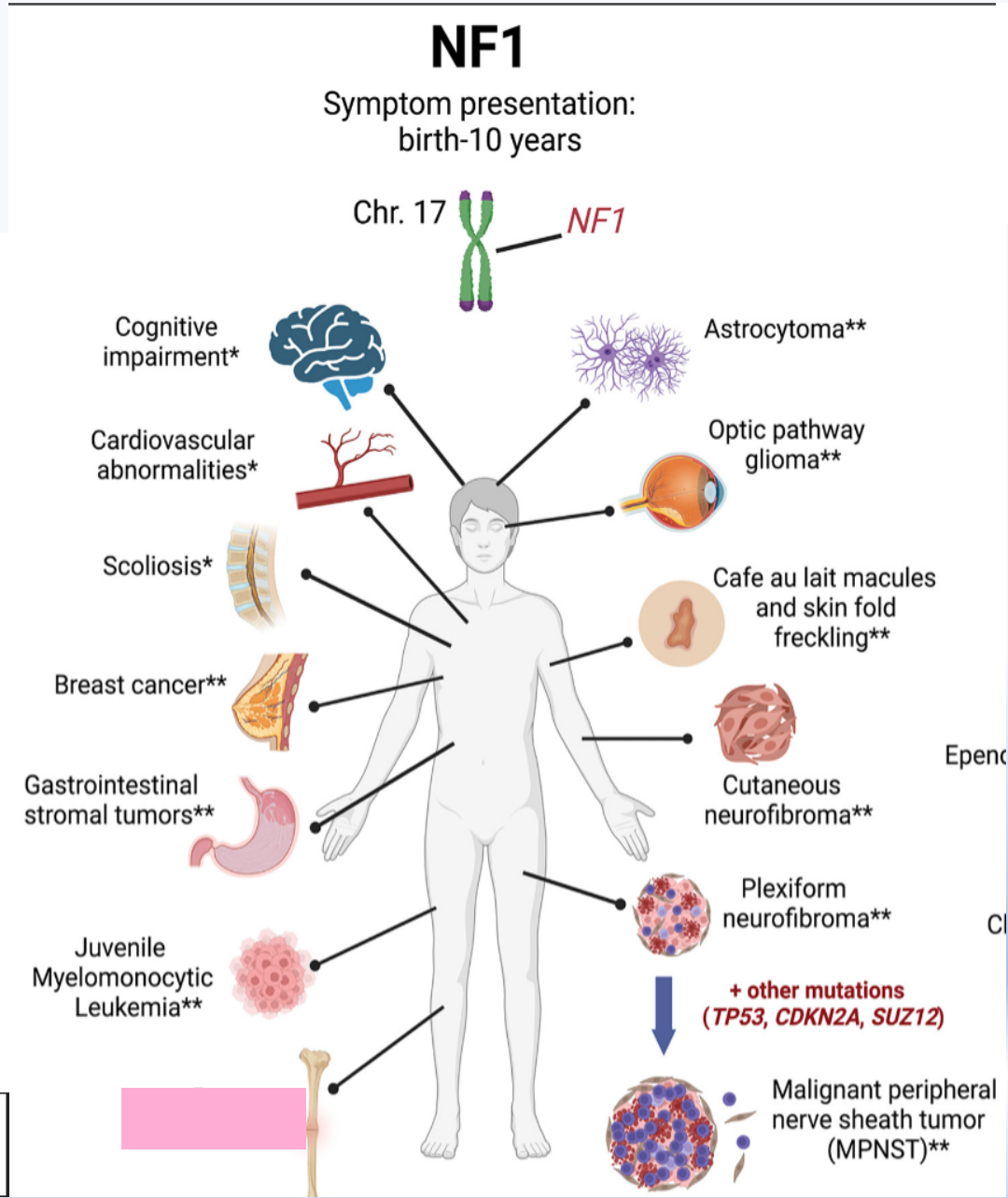
NF1-dziedziczna AD (1:3 tys.), mutacja neurofibrominy

Published online 2022 Feb 18. doi: 10.1242/dmm.049107: 10.1242/dmm.049107

The RASopathies: from pathogenetics to therapeutics

Katie E. Hebron, Edjay Ralph Hernandez, and Marielle E. Yohe*





Gene-targeted therapy for neurofibromatosis and schwannomatosis: The path to clinical trials

Clinical Trials
2024, Vol. 21(1) 51–66

Verena Staedtke[1], Kara Anstett[2], David Bedwell

NF1 a układ kostny i skóra

- **3** gentycznie uwarunkowane choroby**, dziedziczone AD**
- **Mutacja genu NF1 lub NF2 (białko neurofibromina i merlina)**
- Białka te kontrolują rodzinę kinaz protoonkogennych RAS
- Utrata regulacji i kontroli nad układem RAS prowadzi do niekontrolowanej proliferacji komórek
- Skóra, kość, układ nerwowy są głównym obszarem procesów patologicznych
- **Zajęcie układu kostnego jest jednym z 7 kryteriów rozpoznania** (kryterium nr 6)

Poplausky D. at all: Dermatologic manifestations of NF1and emerging treatments. Cancers 2023,15,2770

Kryteria rozpoznania NF1 wg. NIH 2021rok

Table 1 Revised Diagnostic Criteria for NF1, as of 2021

Diagnostic Criteria of NF1	
Two or More of the Following:	**Criteria:**
1	At least six café-au-lait macules (> 5 mm diameter in prepubertal individuals and >15 mm in postpubertal individuals)
2	Freckling in axillary or inguinal regions
3	Optic pathway glioma
4	At least two Lisch nodules (iris hamartomas)
5	At least two neurofibromas of any type, or one plexiform neurofibroma
6	A distinctive osseous lesion (sphenoid dysplasia or tibial pseudoarthrosis)
7	A first-degree relative with NF1

2 lub więcej

Panel: **NIH consensus criteria[14] for diagnosis of neurofibromatosis type 1**

Two or more of the following clinical features are sufficient to establish a diagnosis of neurofibromatosis type 1:

- Six or more café-au-lait macules (>0·5 cm at largest diameter in a prepubertal child or >1·5 cm in post-pubertal individuals)
- Axillary freckling or freckling in inguinal regions
- Two or more neurofibromas of any type or one or more plexiform neurofibromas
- Two or more Lisch nodules (iris hamartomas)
- [redacted]
- An optic pathway glioma
- A first-degree relative with neurofibromatosis type 1 diagnosed by the above criteria

„Marsz” NF1

children

Neurofibromatosis in Children: Actually and Perspectives. *Children* **2022**, *9*, 40. https://doi.org/10.3390/

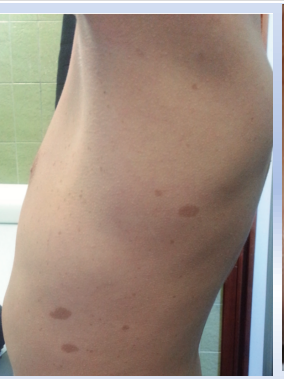
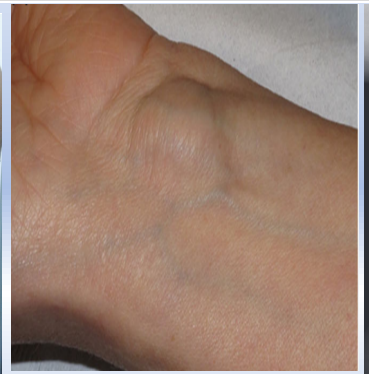
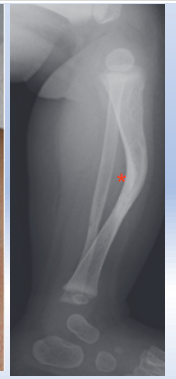
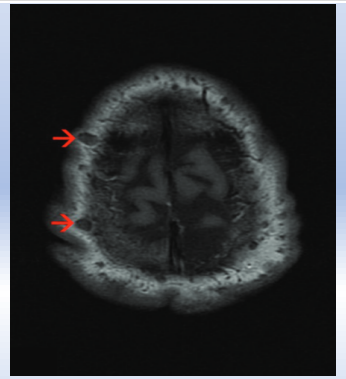
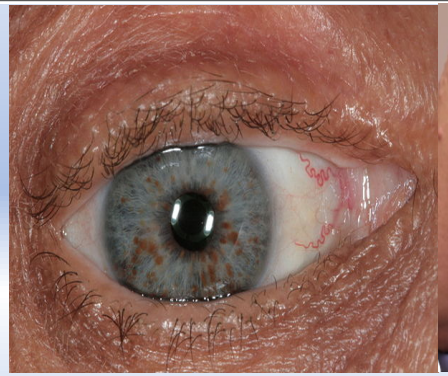
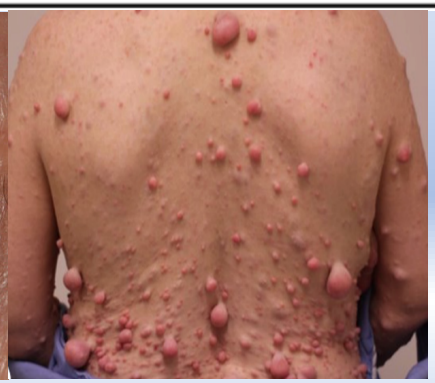
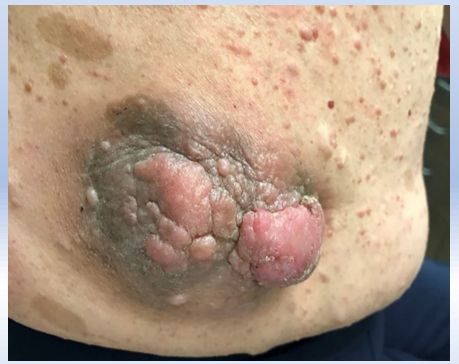
MDPI

Review

Neurofibromatosis in Children: Actually and Perspectives

Table 1. Clinical manifestations for Neurofibromatosis type 1 (adapted after [14]).

Infancy	Early Childhood	Adolescence	Adulthood
[redacted] pseudoarthrosis; Plexiform neurofibroma	Motor/speech delays [redacted] Autism spectrum disorder or attention deficit disorder Difficulties learning	[redacted] Brainstem glioma	[redacted] sheath tumors High-grade glioma Breast cancer

Onkogeneza w NF1

	Lifetime risk
Glioma of the optic pathway	15–20%
Other brain tumour	More than fivefold increase
Malignant peripheral nerve-sheath tumour	8–13%
[illegible]	4–25%
[illegible]	About fivefold increase
Leukaemia	About sevenfold increase
Phaeochromocytoma	0·1–5·7%
[illegible]	1%
[illegible]	1·4–6%

Table: **Lifetime risk of different tumours in children and adults with neurofibromatosis type 1**

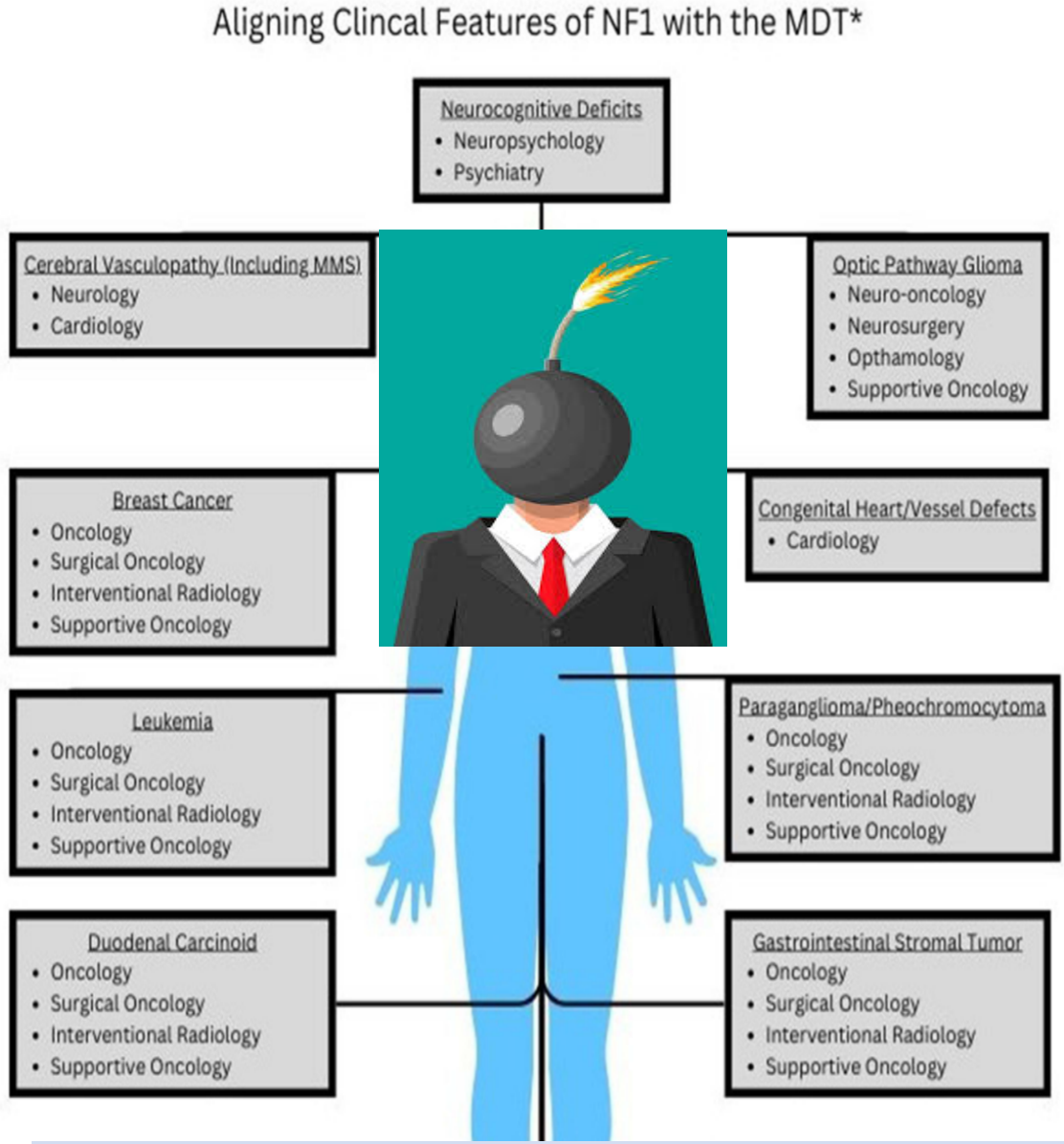
Neurofibromatosis type 1: a multidisciplinary approach to c[illegible]

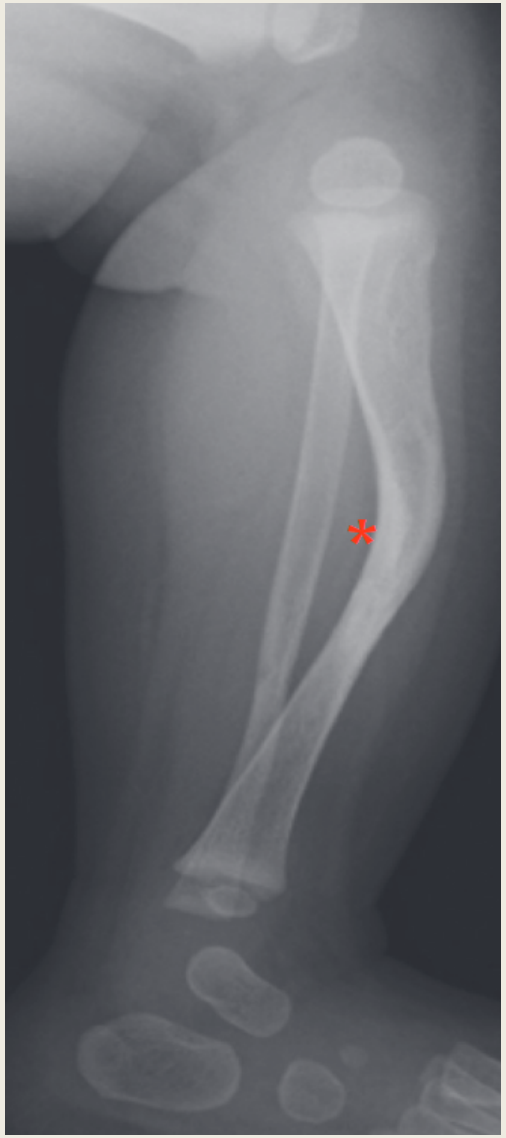
Angela C Hirbe, David H Gutmann

Curr Opin Pediatr. 2015 February ; 27(1): 26–33. doi:10.1097/MOP.0000000000000169.

NEUROFIBROMATOSIS-RELATED TUMORS: EMERGING BIOLOGY AND THERAPIES

Matthias A. Karajannis, MD, MS[a] and **Rosalie E. Ferner, MD, FRCP**[b]





NF1 a narząd ruchu- jakich zmian możemy si spodziewać ?

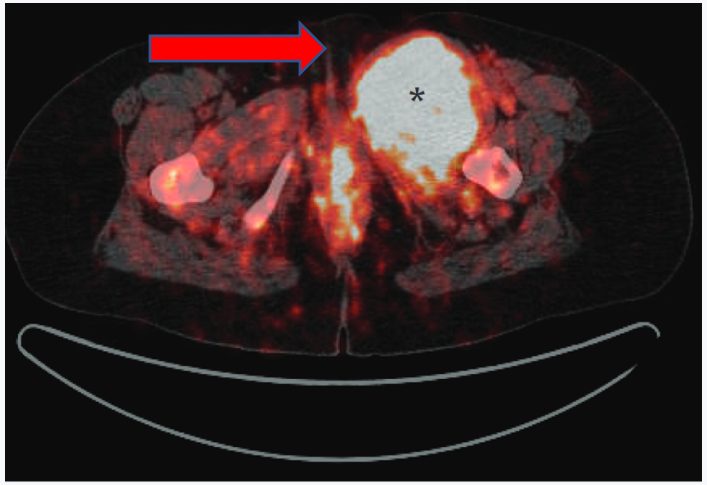
- Sztywność i bóle stawów
- Osteopenia i osteoporoza
- Osteomalacja hipofosfatemiczna
- Dysplazja kości klinowej
- Dysplazja kości długich (udowa, piszczelowa, łokciowa)
- Zniekształcenia kręgosłupa (garb, skoliza, hiperkyfoza)
- Neurofibromy wewnątrzstawowe
- Zaburzenia wzrastania i mineralizacji
- Pseudoartroza-Amputacja !

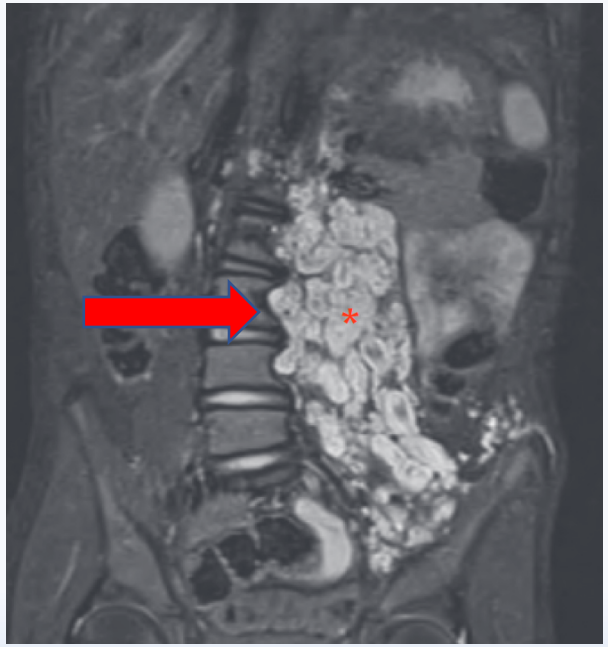
Clin Trials. 2024 February ; 21(1): 29–39. doi:10.1177/17407745231201338.

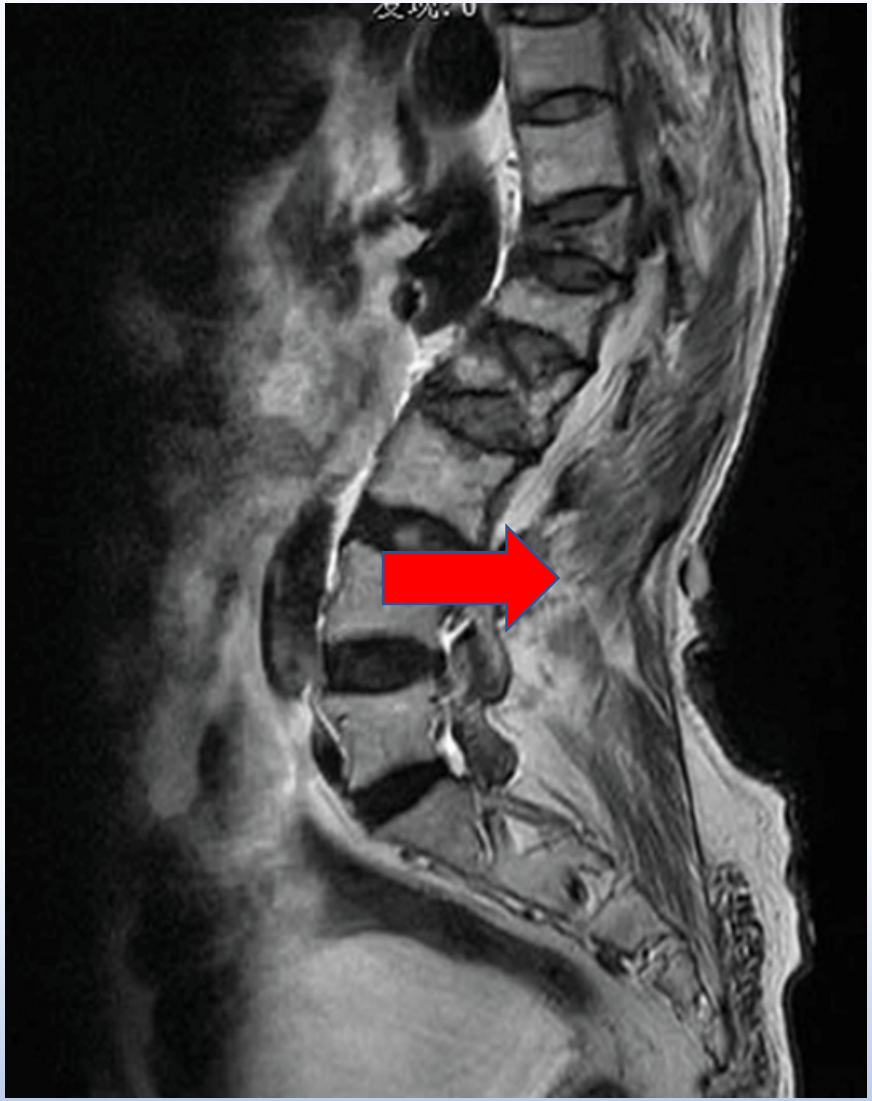
Potential Endpoints for Assessment of Bone Health in Persons with Neurofibromatosis Type 1

Andrea M Gross[1], Scott R Plotkin[2], Nelson B Watts[3], Michael J Fisher[4], Laura J Klesse[5],

Kręgosłup w NF1

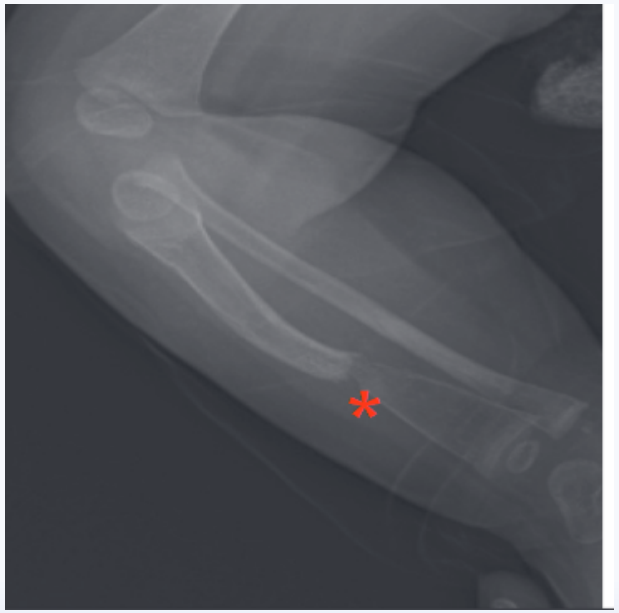






Ferreira JF et all: Kyphoscoliosis: looking beyond the spine. BMJ case report 2015
Hirbe A et all: NF1: a multidisciplinary approach to care. Lancet Neurol 2014

Pseudoartroza w NF1



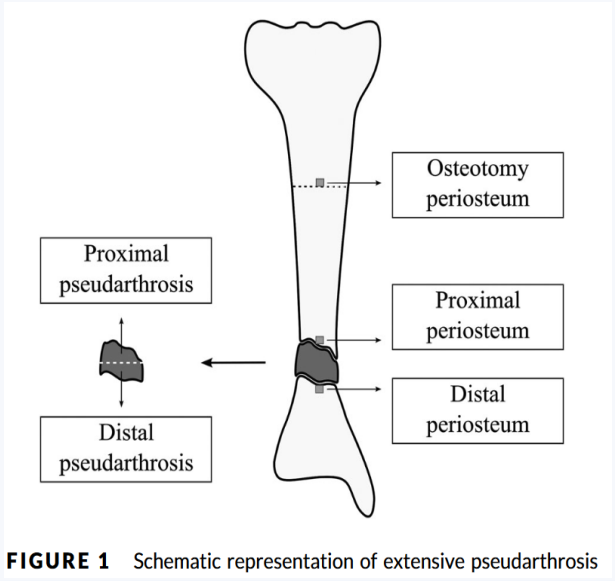
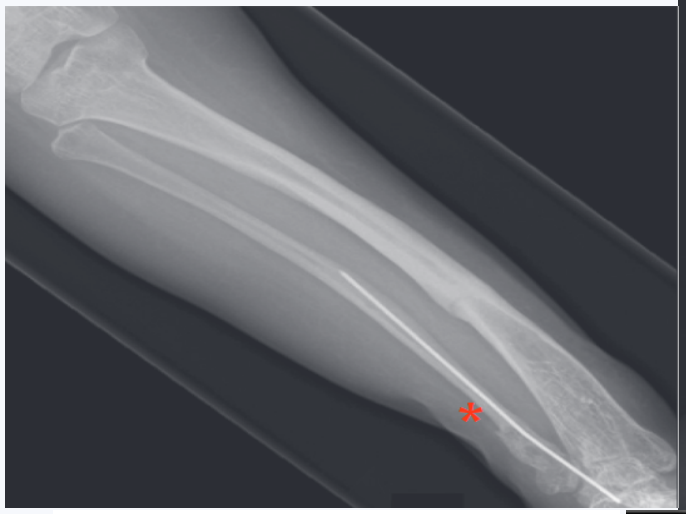
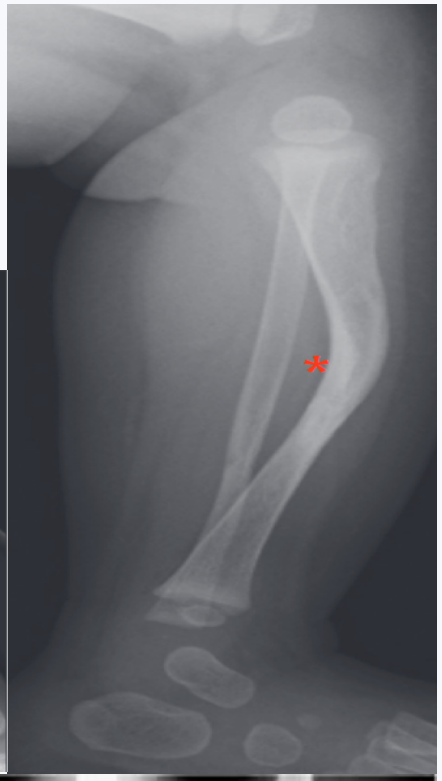
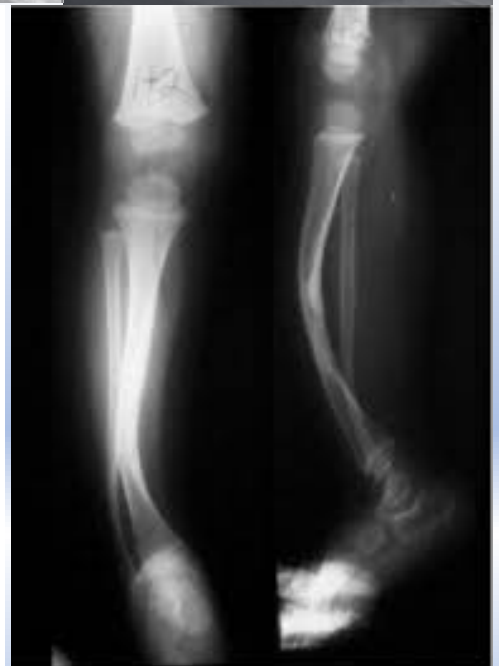


FIGURE 1 Schematic representation of extensive pseudarthrosis







Received: 17 August 2018 | Revised: 3 May 2019 | Accepted: 4 May 2019
DOI: 10.1002/humu.23783

RESEARCH ARTICLE

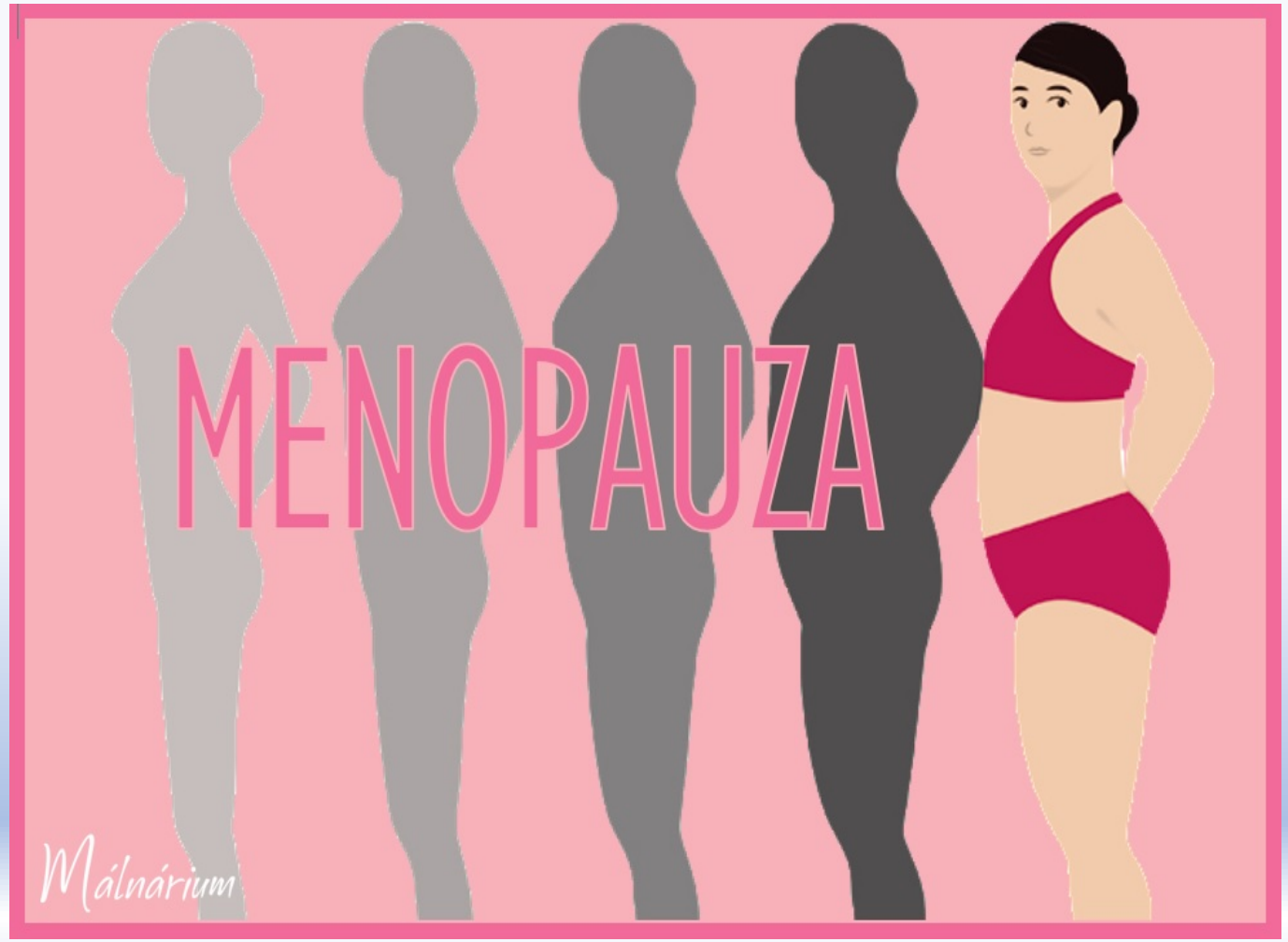
Human Mutation HGVS WILEY

Neurofibromatosis type 1-related pseudarthrosis: Beyond the pseudarthrosis site

Carlijn Brekelmans[1] | Silke Hollants[2] | Caroline De Groote[2] | Natalie Sohier[2] |

Menopauza


Klimakterium
OBJAWY I ZMIANY FIZYCZNE
bóle głowy
uderzenia gorąca
zęby
krwawiące dziąsła
włosy
- wypadanie
- ścieńczenie
piersi
- powiększenie
- ból
serce
kołatanie serca
pęcherz moczowy
- częstomocz
- nietrzymanie moczu
skóra
- suchość
- świąd
kości
- kruchość
- zmniejszenie masy kostnej
narząd rodny
- krótsze lub dłuższe cykle
- suchość pochwy
- swędzenie, pieczenie
OBJAWY PSYCHOLOGICZNE:
- ZAWROTY GŁOWY
- POGORSZENIE PAMIĘCI
- NIEPOKÓJ
- WAHANIA NASTROJU
- SPADEK LIBIDO
OBJAWY OGÓLNE:
- WZROST MASY CIAŁA
- NOCNE POCENIE SIĘ


MENOPAUZA
Málnárium

Objawy menopauzy

Contents lists available at ScienceDirect

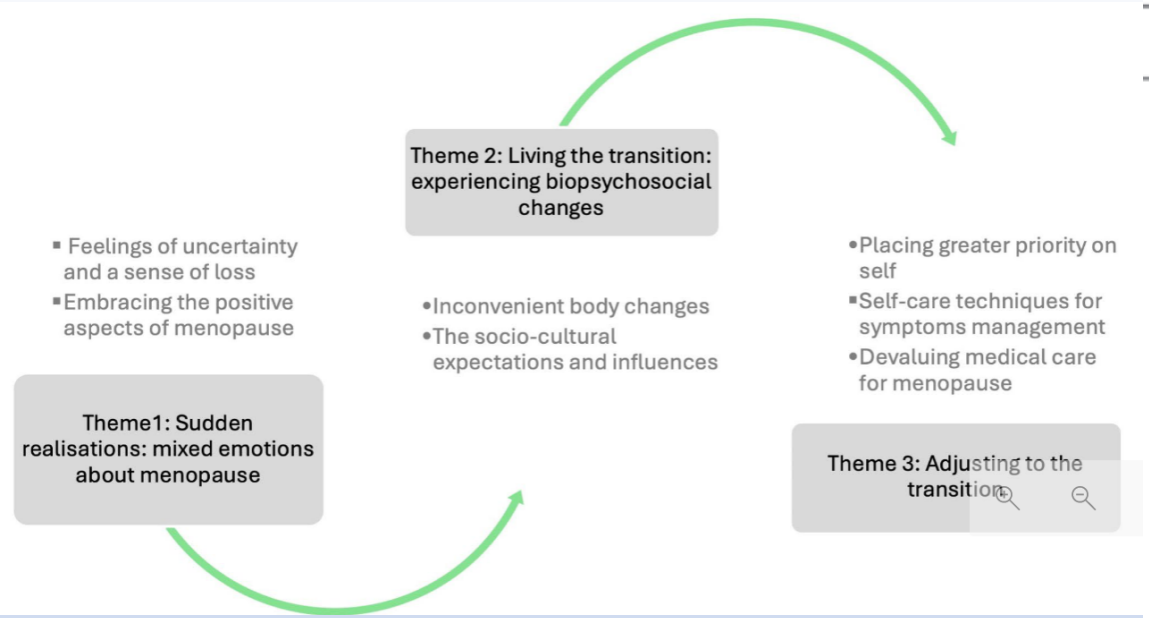
Maturitas

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

Menopause and work: An electronic survey of employees' attitudes in the UK

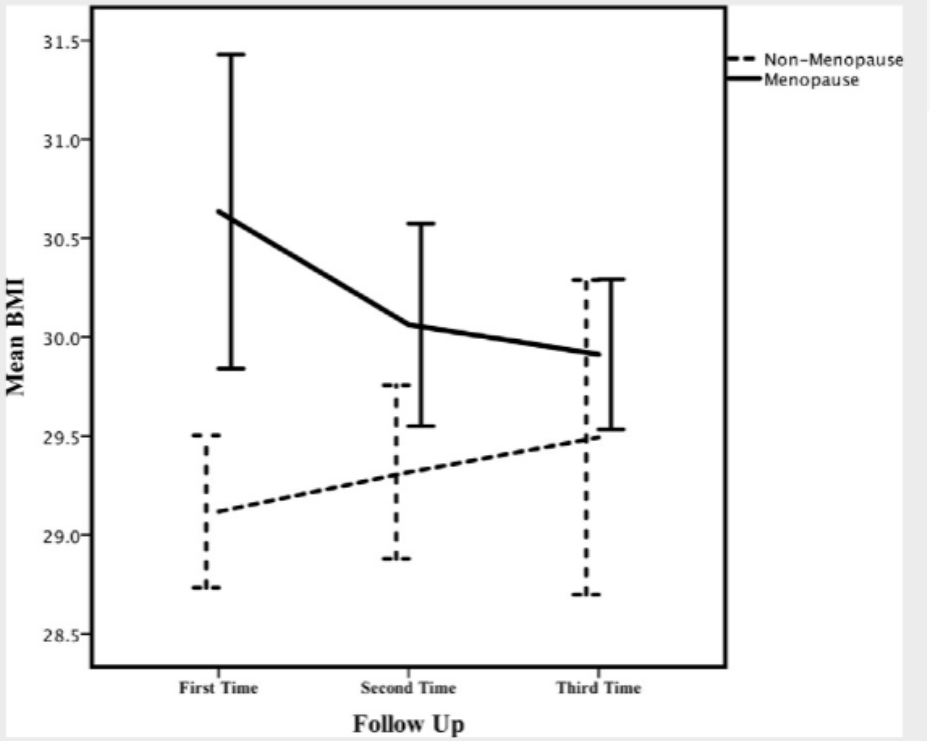
Amanda Griffiths*[,3], Sara Jane MacLennan[1,3], Juliet Hassard[2,3]

Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Yang Fujia Building, Jubilee Campus, Wollaton Road,



Symptom	Work (%)	Life in general (%)
Poor concentration	50.9	34.9
Tiredness	50.7	53.4
Poor memory	50.5	42.1
Feeling low/depressed	41.9	39.7
Lowered confidence	38.9	21.9
Sleep disturbances	37.3	56.5
Irritability	35.6	37.8
Hot flushes	35.1	40.4
Joint and muscular aches and discomfort	31.3	41.5
Mood swings	29.0	35.5
Anxiety/panic attacks	25.3	21.2
Tearfulness	23.7	25.4
Frequent visits to the toilet	23.3	32.8
Heavy periods/flooding	22.4	24.0
Clumsiness	17.4	24.4
Palpitations/irregular or racing heart	15.0	19.9
Weight gain	10.6	38.3
Night sweats	8.3	43.1
Changes in skin/dryness	6.4	27.0

Menopauza a BMI



Mean and confidence interval for observed BMI by menopause status at first, second, and third follow-up sessions.

Montazeri. Age at natural menopause and BMI. Fertil Steril 2018.

Effect of aging, menopause, and age at natural menopause on the trend in body mass index: a 15-year population-based cohort

Seyed Ali Montazeri, M.D., M.P.H.,[a] Fahimeh Ramezani Tehrani, M.D.,[a] Razieh Bidhendi Yarandi, M.Sc.,[a,b]

Descriptive characteristics of the study participants.

Characteristic	Baseline	1st follow-up		2nd follow-up		3rd follow-up		4th follow-up
	No	No	Yes	No	Yes	No	Yes	Yes
No. of participants	929	752	177	511	394	174	685	929
Age (y)	43 ± 5	45 ± 4	51 ± 5[a]	46 ± 4	52 ± 5[b]	48 ± 4	54 ± 4[c]	54 ± 4
BMI (kg/m^2)	28.8 ± 4.6	29.1 ± 4.5	30.6 ± 4.7[a]	29.3 ± 4.8	30.1 ± 4.8[b]	29.5 ± 4.8	29.9 ± 5.1	29.9 ± 4.6
HC (cm)	106 ± 9.1	106 ± 9	109 ± 10[a]	106 ± 9.5	107 ± 10.1	103 ± 8.5	104 ± 9.2[c]	103 ± 9.8
Weight (kg)	70 ± 12	71 ± 12	74 ± 12[a]	73 ± 12	73 ± 12	72 ± 12	73 ± 12	73 ± 13
WC (cm)	90 ± 11.3	92 ± 11.5	99 ± 11[a]	92 ± 11.7	96 ± 12.2[b]	96 ± 10.7	98 ± 11.5[c]	98 ± 12.4
Waist/hip ratio	0.8 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	1.0 ± 0.3
Waist/height ratio	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0.1
Systolic blood pressure (mm Hg)	119 ± 18	115 ± 16	122 ± 20[a]	118 ± 18	121 ± 19[b]	118 ± 15	122 ± 19[c]	117 ± 16
Diastolic blood pressure (mm Hg)	79.3 ± 10	76 ± 9	77 ± 11[a]	78 ± 11	79 ± 11[b]	78 ± 10	80 ± 11[c]	79 ± 10
FPG (mg/dL)	99 ± 34	110 ± 41	109 ± 40[a]	99 ± 25	109 ± 29[b]	81 ± 29	81 ± 29	90 ± 29
HDL-c (mg/dL)	53 ± 12	45 ± 11	45 ± 12	41 ± 10	42 ± 11[b]	44 ± 11	44 ± 11	48 ± 12
LDL-c (mg/dL)	122 ± 37	131 ± 35	139 ± 34[a]	123 ± 31	133 ± 33[b]	116 ± 32	130 ± 31[c]	122 ± 34
Triglycerides (mg/dL)	164 ± 89	163 ± 95	189 ± 144[a]	164 ± 108	175 ± 97[b]	150 ± 81	177 ± 100[c]	162 ± 92
Total cholesterol (mg/dL)	207 ± 41	207 ± 40	221 ± 46[a]	195 ± 36	209 ± 39[b]	190 ± 37	208 ± 38[c]	203 ± 39
Overall characteristics								
Age at menarche (y)					14 ± 2			
Age at natural menopause (y)					49 ± 4			
Parity (IQR)					3 (2%)			
No. of children (IQR)					2 (0)			
Ever smoking					63 (7%)			
Education[d]					361 (41%)			

Witamina D a NF1

metabolites

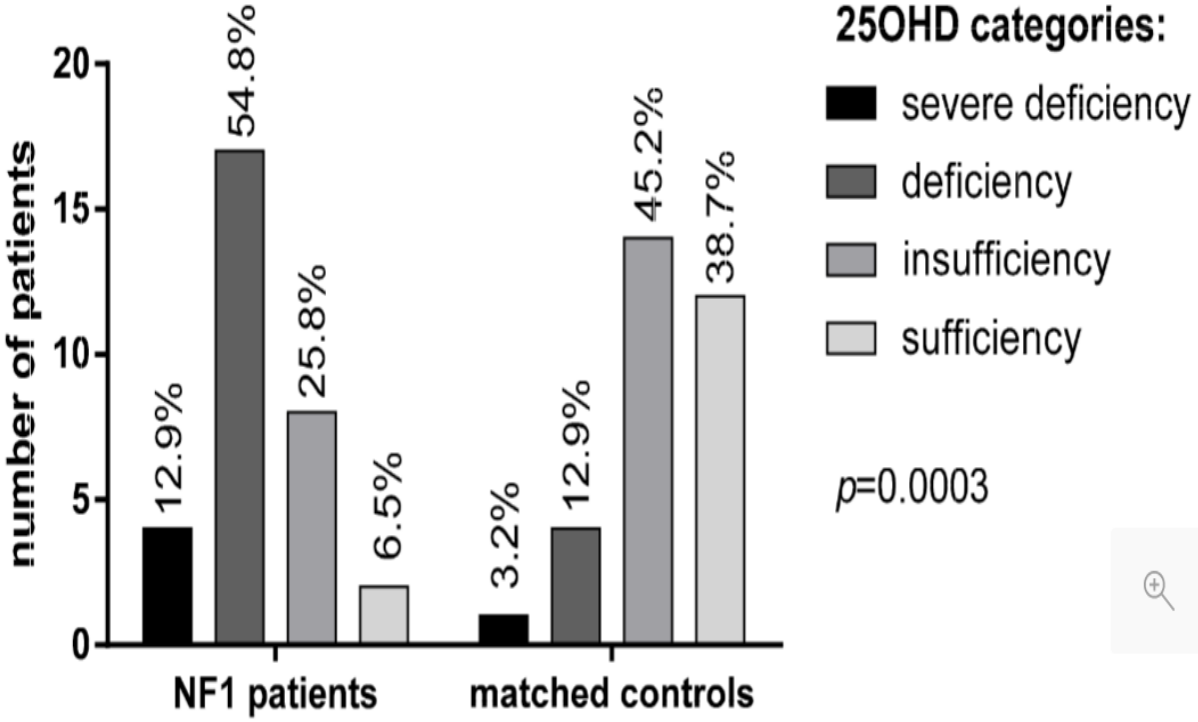
MDPI

Article

Vitamin D and Bone Metabolism in Adult Patients with Neurofibromatosis Type 1

Roberta Modica [1,*], Barbara Altieri [2], Francesco D'Aniello [3], Elio Benevento [1], Giuseppe Cannavale [1],

Metabolites **2023**, *13*, 255. https://doi.org/10.3390/metabo13020255



Parameters	NF1 Patients	Controls	*p*-Value
Age at time of the study, years	41 ± 11.4	43.8 ± 7.2	0.106
BMI, kg/m^2	27 ± 5.8	25.5 ± 4.2	0.406
25OHD, ng/mL	16.4 ± 6	27.2 ± 9.2	<0.0001
Albumin-corrected serum calcium, mg/dL	9.4 ± 0.4	9.3 ± 0.4	0.423
Phosphorus, mg/dL	3.6 ± 0.5	3.9 ± 0.5	0.035
PTH, pg/mL	42.3 ± 31.9	23.8 ± 15.5	0.077

Witamina D a menopauza

Table: Vitamin D And Menopause: Clinical Links

Organ system	Effect of menopause	Link with Vitamin D
Bio-metabolism	Increased total body fat mass, hypertriglyceridaemia, weight gain. Increased risk of metabolic syndrome and cardiovascular disease.	Increased risk of VD deficiency with weight gain.VD Supplementation reduces central fat deposition, lowers risk of Metabolic syndrome and cardiovascular disease.
Insulin action	Decreased Insulin action and sensitivity.	VD Supplementation reduces progression to T2DM.
Musculoskeletal system	Decreased bone density, musculoskeletal pain.	VD Increases bone density, Fracture prevention.
Neuropsychiatric health	Cognitive decline and mood disorders.	VD has positive effect on memory and cognition, reduced risk of dementia.
Malignancy	Increased susceptibility to breast and colon cancer.	High VD levels lower mortality rates in breast and colon cancer.
Genitourinary health	Genitourinary syndrome of menopause (GSM).	VD produces positive changes in vulvovaginal health.

Gęstość piersi a NF1

Familial Cancer (2024) 23:35–40
https://doi.org/10.1007/s10689-023-00355-y

ORIGINAL ARTICLE

Breast density in NF1 women: a retrospective study

R. De Santis[1] · G. Cagnoli[2] · B. Rinaldi[2] · D. Consonni[3] · Beatrice Conti[2] · M. Eoli[4] · A. Liguori[1] · M. Cosentino[1] ·

Table 1 Considered variables in the population with Neurofibromatosis 1 (NF1) and in the control cohort (Healthy)

Variable	NF1		Healthy controls		P-value
	N	%	N	%	
Total	**98**	100	**300**	100	<0.001
Age (years), mean (DS)	**52.1 (7.9)**		**58.0 (10.6)**		<0.001
Age					<0.001
<50	**43**	43.9	**74**	24.7	
50–59	**34**	34.7	**105**	35.0	
60–69	**19**	19.4	**73**	24.3	
70+	**2**	2.0	**48**	16.0	
BMI (kg/m2), mean (DS)	23.9 (4.4)		**23.8 (4.1)**		0.96

Conclusion

The results of this study demonstrate that women with NF1 have a breast density comparable to that of the general population, allowing us to hypothesise that the increased BC risk in NF1 does not rely on a higher breast density. These results confirm the adequateness of the screening program proposed in the recent GENTURIS Guidelines, aimed at guarantee early breast cancer diagnosis in this high-risk population.

Metabolizm kostny a NF1

	Patients	Controls	p
Phenotype			
Calcium mg/dl	9.6 ± 0.88	9.9 ± 0.4	0.009
Calcitonin pg/ml	3.4 ± 2.7	9.6 ± 2	p < 0.01
Osteocalcin ng/ml	121 ± 15	67 ± 5	p < 0.01
CTX ng/ml	1.64 ± 0.04	0.42 ± 0.005	p < 0.01
Vitamin D ng/ml	21 ± 7.3	45 ± 15	p < 0.01
z-score	− 1.1 ± 1	0.1 ± 0.9	p < 0.01
Mild			
Calcitonin pg/ml	3.5 ± 2	9.2 ± 1.4	p < 0.01
Vitamin D ng/ml	19.5 ± 7	44.3 ± 12	p < 0.01
z-score	− 1 ± 0.8	0.2 ± 0.9	0.02
Moderate			
Calcitonin pg/ml	3.15 ± 2.3	9.3 ± 2.1	p < 0.01
Vitamin D ng/ml	25.6 ± 17	47.4 ± 15	p < 0.01
z-score	− 0.9 ± 1.2	0.04 ± 0.9	0.0005
Severe			
Calcitonin pg/ml	4.8 ± 3	10 ± 2	p < 0.01
Vitamin D ng/ml	15.2 ± 6	43.9 ± 15	p < 0.01
z-score	− 0.6 ± 1.4	0.16 ± 0.9	0.01

Table 3. Biochemical markers of bone metabolism a

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Bone metabolism in patients with type 1 neurofibromatosis: key role of sun exposure and physical activity

Ursula Pia Ferrara[1], Cristina Tortora[2], Carmen Rosano[1], Antonia Assunto[1],

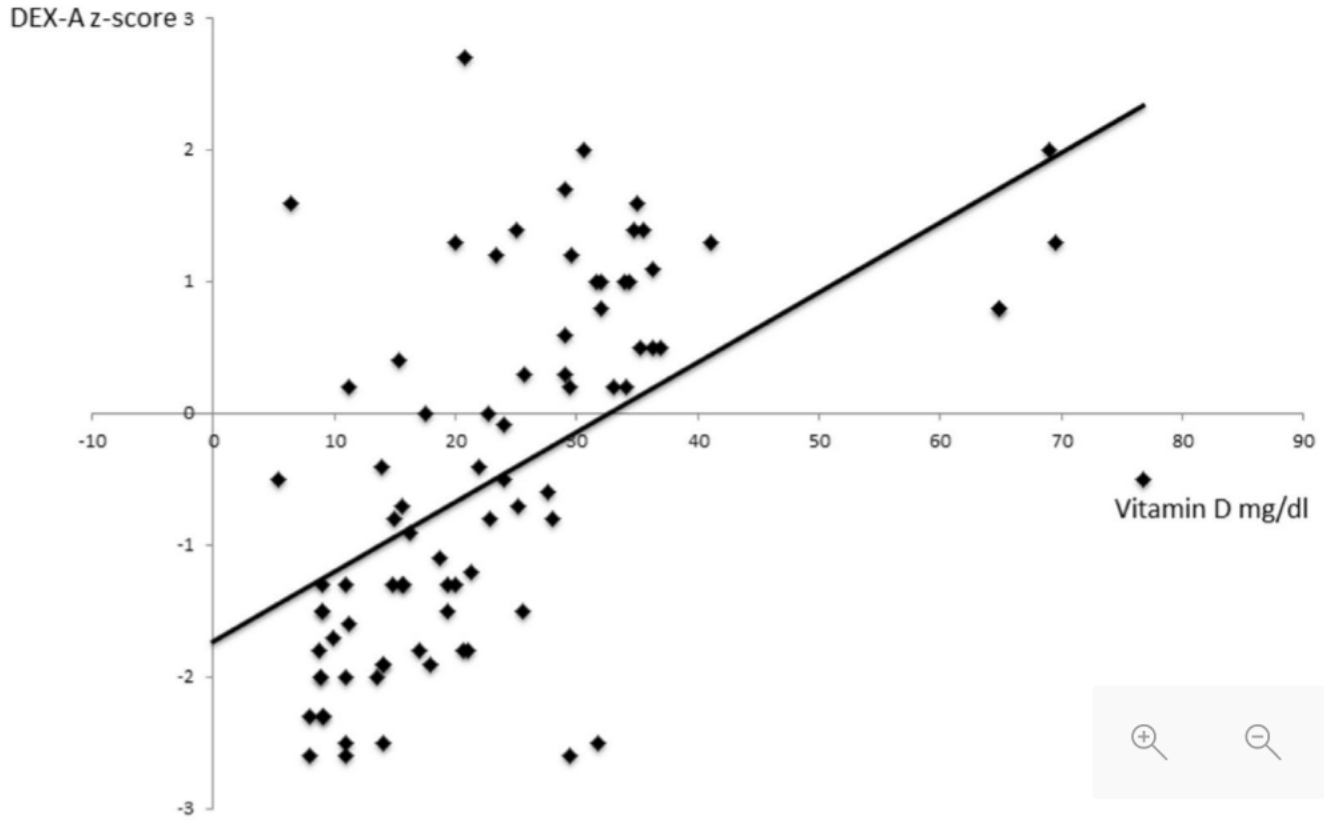

Figure 1. Correlation between vitamin D serum levels and bone mineral density values.

NF1-leczenie

Drug (ClinicalTrials. gov identifier)	Mode of action
Prospective therapeutic studies for NF2 patients with progressive VS	
Lapatinib [55]*	Dual EGFR/ErbB2 inhibitor
Everolimus [56]*	mTORC1 inhibitor
Bevacizumab (NCT01207687)	VEGF-A inhibitor
Bevacizumab (NCT01767792)	VEGF-A inhibitor
Axitinib (NCT02129647)	Multi-kinase inhibitor (VEGFR2, PDGFR, c-kit)
Phase 0 (pharmacokinetic/pharmacodynamic, non-therapeutic) studies for NF2 VS/m	
Lapatinib (NCT00863122)	Dual EGFR/ErbB2 inhibitor
Everolimus (NCT01880749)	mTORC1 inhibitor

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REVIEW

Neurofibromatosis Type 1: Optimizing Management with a Multidisciplinary Approach

Shaan Lalvani, Rebecca M Brown

Novel therapies for NF1 associated tumors – recently publish

Drug	Mode of action
Inoperable or progressive plexiform neurofibromas (≥20% volume increas	
Tipifarnib [15]*	Farnesyltransferase inhibitor
Pirfenidone [16]	Anti-fibrotic anti-inflammatory ↓ collagen, ↓ fibroblasts
Sorafenib [17]	Multi-kinase inhibitor (BRAF, VEGFR2, PDGFR, c-kit)
Sirolimus [18]	mTORC1 inhibitor
Optic pathway glioma and low grade glioma	
Bevacizumab [19]	VEGF-A inhibitor
Rapamycin and erlotinib [20]	mTORC1 inhibitor EGFR inhibitor
Sorafenib [21]	Multi-kinase inhibitor (BRAF, VEGFR2, PDGFR, c-kit)

Farmakoterapia menopauzy

Making choices at menopause

Karen Magraith, Bronwyn Stuckey

Box 1. Contraindications to menopausal hormone therapy

Contraindications to menopausal hormone therapy (MHT):

- breast, endometrial and other hormone-dependent cancers (current or previous)
- undiagnosed vaginal bleeding.

Conditions that are relative contraindications when transdermal MHT is preferred:

- established cardiovascular disease
- venous thromboembolic disease[13]
- active liver disease
- possibly migraine with aura.

Note that treated hypertension is not a contraindication.

Table 1. Non-hormonal medications for treatment of menopausal vasomotor symptoms[21]

Medication	Suggested dosage	Common adverse effects
SSRIs and SNRIs		
Escitalopram	10–20 mg/day	Nausea, drowsiness, sexual dysfunction*
Paroxetine†	10–20 mg/day	
Venlafaxine	37.5–150 mg/day	
Desvenlafaxine	25–150 mg/day	
Other medications		
Gabapentin	100 mg at night, slowly titrating to maximum 300 mg three times per day	Dizziness, drowsiness
Pregabalin	75 mg at night, slowly titrating to maximum 150 mg twice daily	Dizziness, drowsiness, nausea, headache
Clonidine	25 mcg twice daily, slowly titrating to maximum 75 mcg twice daily	Dry mouth, drowsiness, visual disturbance

NF1- podsumowanie

- **NF1 to wrodzona choroba proliferacyjna dziedziczona AD (RASopatia/ fakomatoza)**
- ***Pseudoartoza, patologiczne złamania, dysplazaja kości klinowej i piszczelowej (tibial bowing)*** to charakterystyczna triada w układzie ruchu
- ***Cafe au lait, lentigines axiliares, neurofibromy*** to charakterystyczna triada skórna
- Guzy nienowotworowe, przednowotworowe, i nowotworowe skóry, nerwów i narządów wewnętrznych wpisane w naturę choroby
- Bardzo wysokie ryzyko onkologiczne (realne scenariusze kliniczne)

  - uznawane za choroby pierwotnie nowotworowe, **ostrożnie z HTZ!**
- Aktualne leczenie kompleksowe: chirurgia, laseroterapia, elektrodyssekcja,
- **Selumetynib** (doustny inhibitor multi kinaz aktywowanych mitogenami MEK1& MEK2)- także nadzieją dla pacjentów dorosłych!
- Profilaktyka osteoporozy
- Suplementacja witaminy D3