Paediatric Rheumatology

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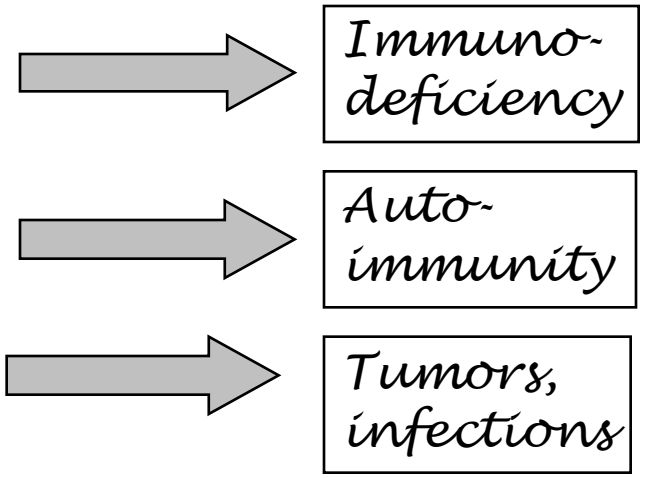
Functions of the immune system

AIM : protection against „parazites”

- external: microbes
- internal: tumorous cells

IDEALLY:

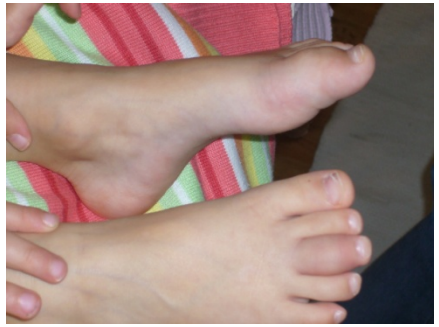
- Covers the whole body
- Distinguish well „danger”” sign
- Eliminate “danger” effectively



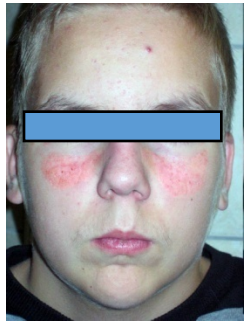
Parts:

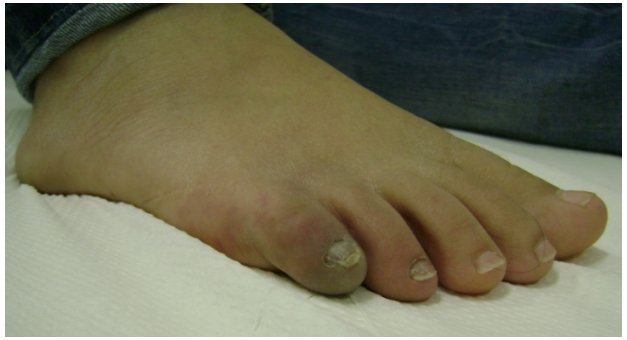
- Innate immunity(Neu, Mo/Ma, Il-1, Il-6, TNF)
- adaptive immunity (B-cells, T-cells, spec. Abs)

Paediatric rheumatology

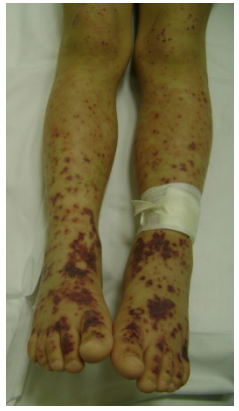


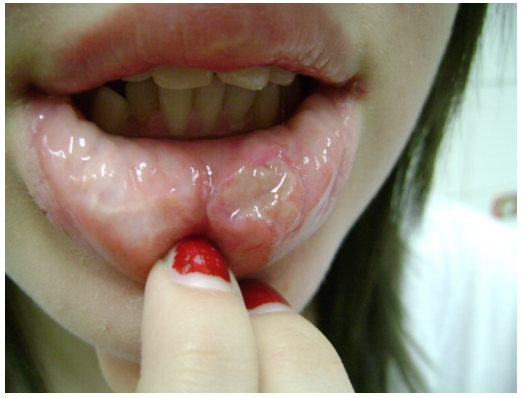
JUVENILIS IDIOPATHIAS ARTHRITIS





Systemic autoimmune diseases





Vasculitidies

Autoinflammatory disorders

- Disease of the innate immunity
- First diease during evolution, but only identified in the late 1990s
- Better understanding of pathology –

– adequate treatment

Heterogenous, monogenic fever syndromes

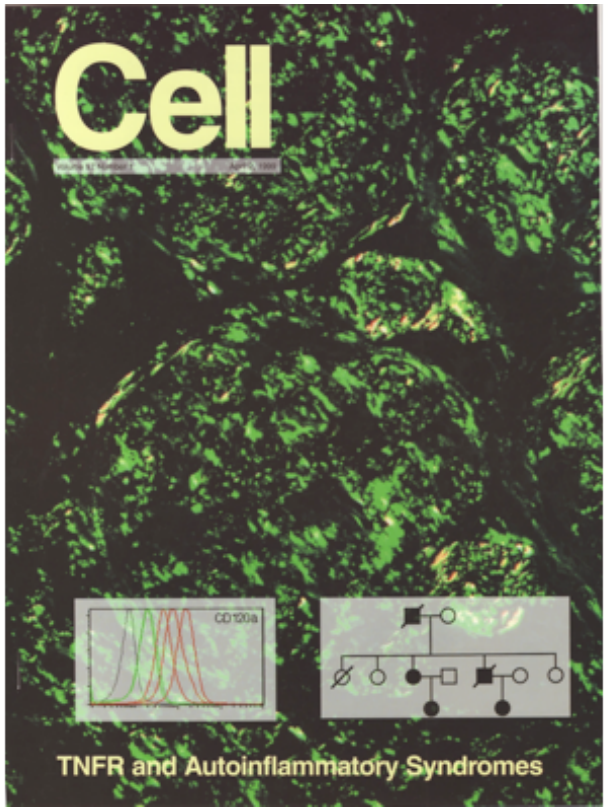
↓

and many other „complex” disorders...

Terminology of „Autoinflammation“

TRAPS (TNF receptor associated pediatric syndromes):

- Perodic fever+ peritonitis, pleuritis, arthritis, erythema
- amyloidosis → renal failure
- *Mutation of TNF receptor gene*

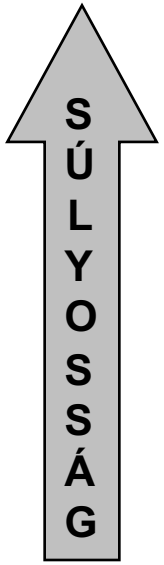


FMF: familiar mediterrae

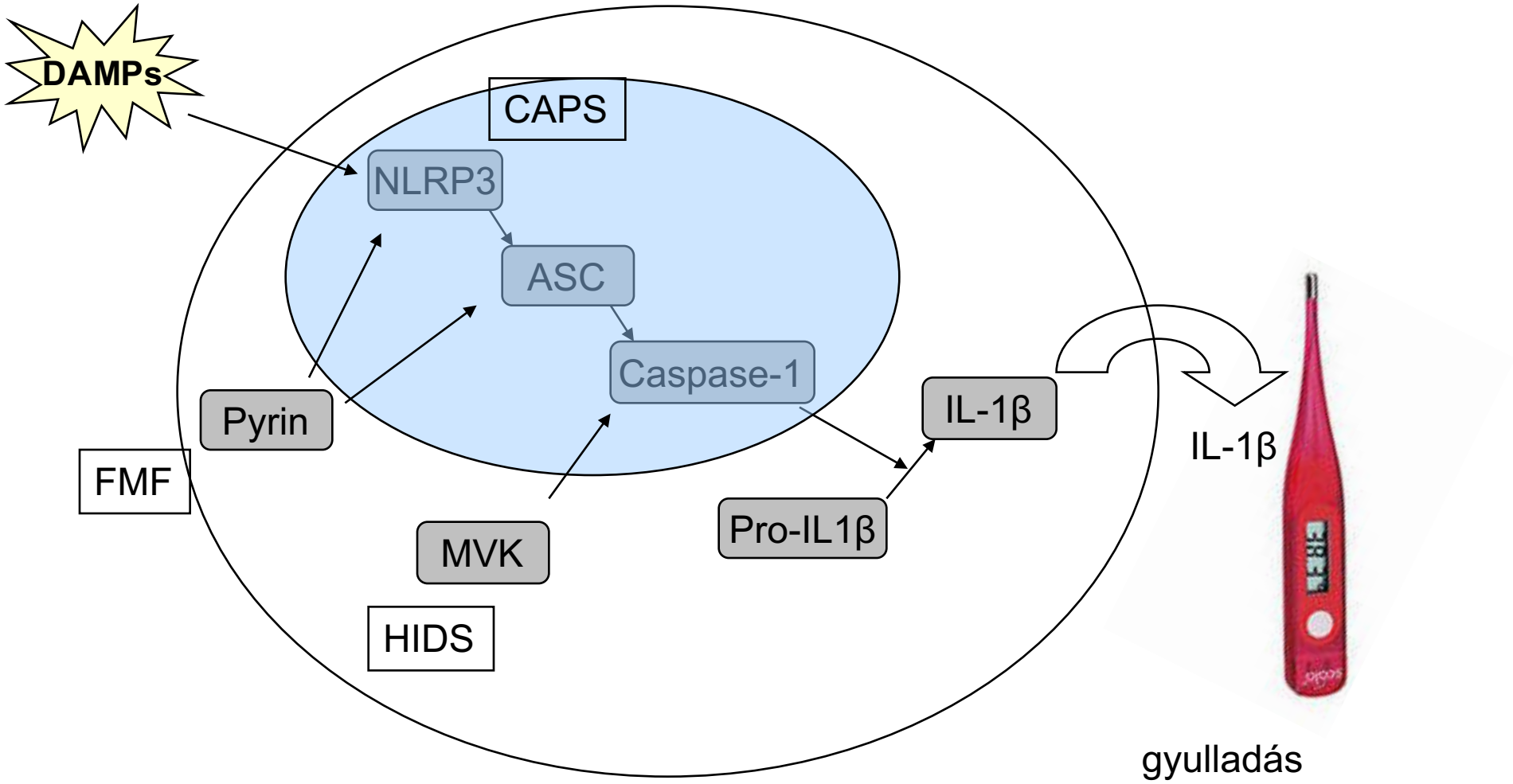
- Fever + inflammation (serositis, synovitis, dermatitis)
- No autoimmune feature
- *MEFV gene* (Mediterranean Fever): pyrin
- AR

2000s:

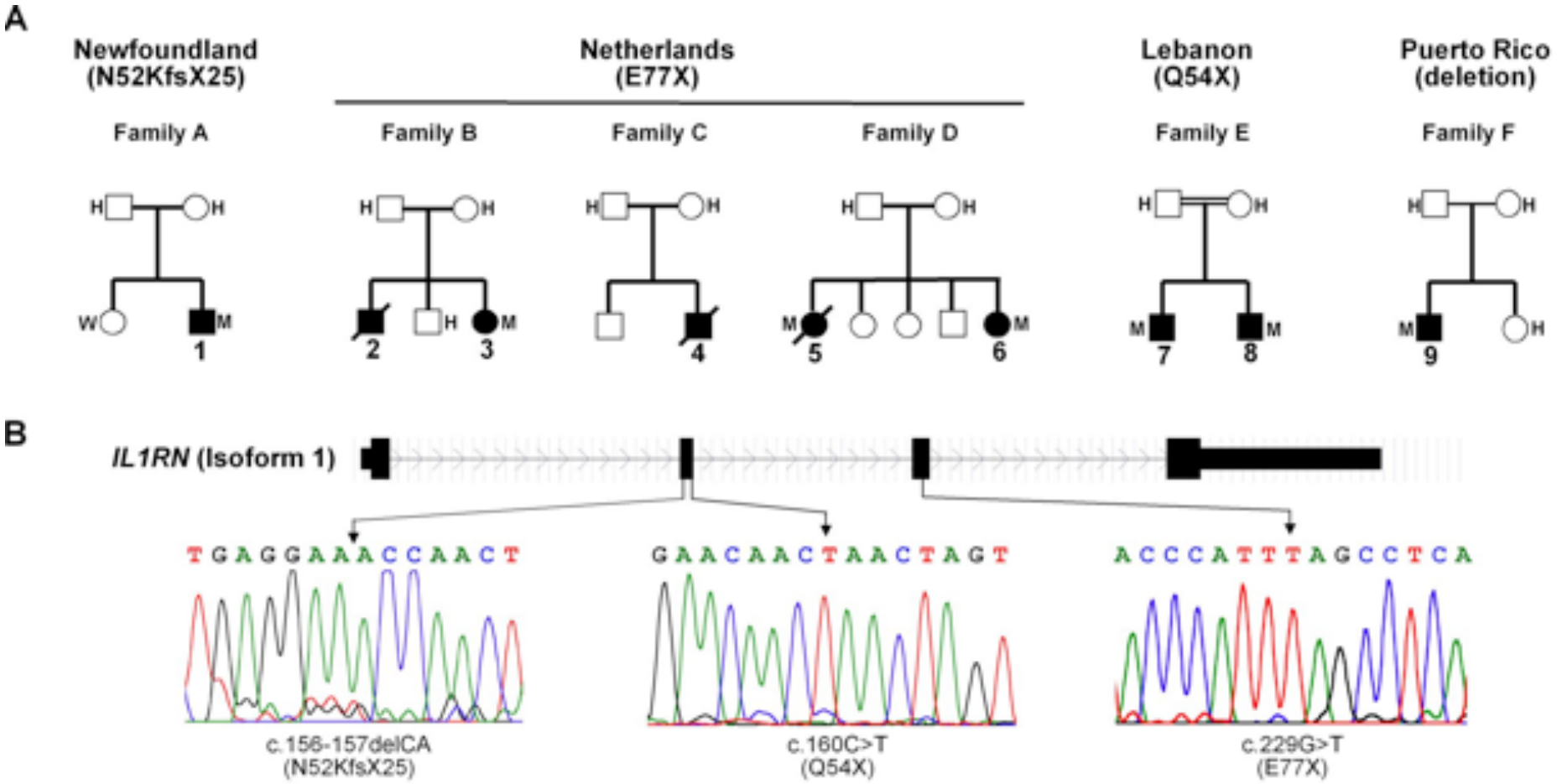
- HIDS (hyperimmunoglobulinemia D with periodic fever syndrome) – *MVK gén*
- *NLRP3/CIAS1 gén* – cryopyrin (IL-1β aktivátora) – cryopyrinopathiák (CAPS), AD
  - CINCA (chronic infantile neurologic cutaneous and articular syndrome)
  - MWS (Muckle-Wells syndrome)
  - FCAS (familial cold autoinflammatory syndrome)



Inflammasome – ‘molecular engine of innate immunity’



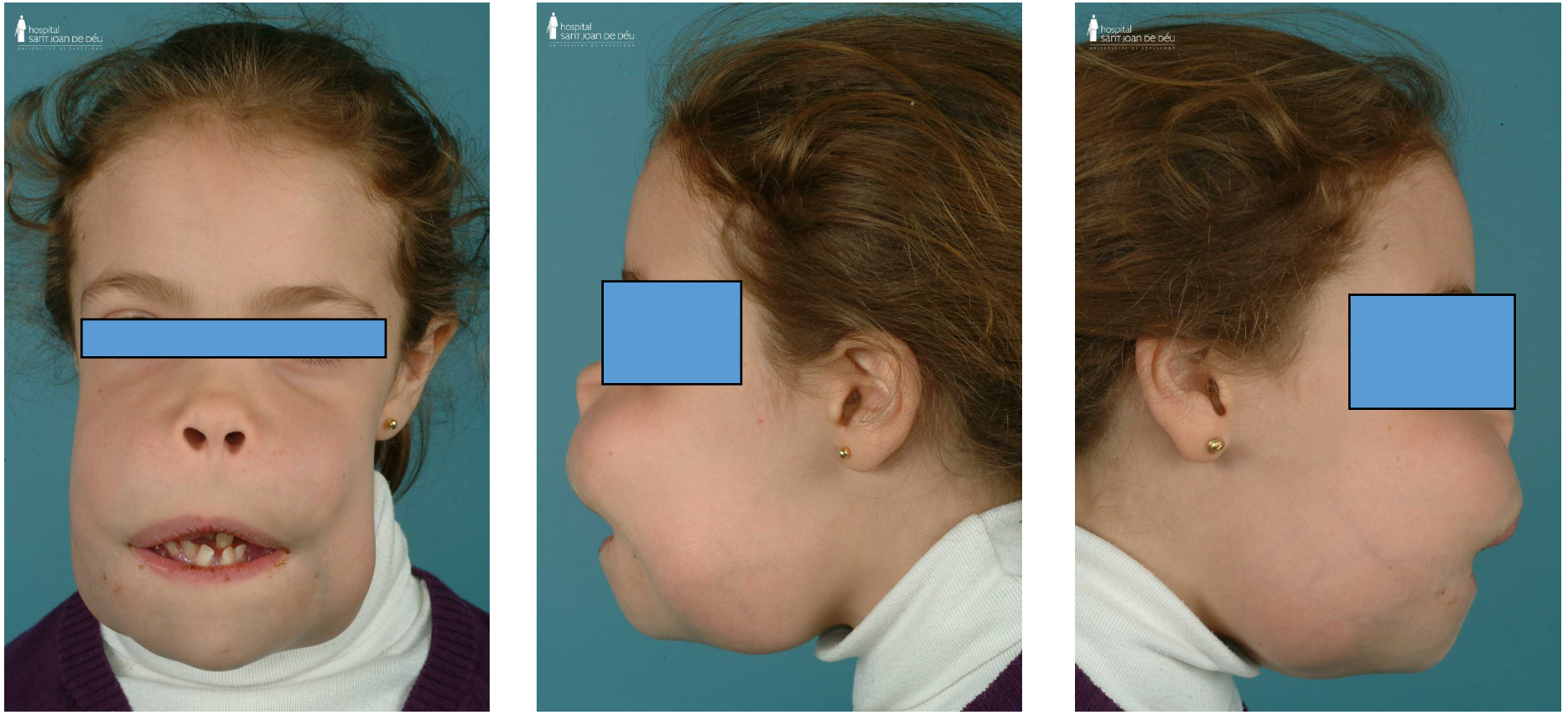
Deficiency of the IL-1 Receptor Antagonist (DIRA)



The NEW ENGLAND JOURNAL of MEDICINE

Aksentijevich I et al. *N Engl J Med,* 2009

Rare?



@ Jordi Antón Lopez, MD, PhD

PReS, Valencia, 2010

Inherited autoinflammatory disorders

AR:

FMF (familiáris mediterrán láz)

HIDS (hyperimmunoglobulinaemia D szindróma)

AD:

TRAPS (tumor nekrózis faktor receptor-asszociált periodikus szindróma)

Cryopyrinopathiák:

- MWS (Muckle Wells szindróma)
- FCAS (familiáris hideg autoinflammatoricus szindróma)
- CINCA/NOMID (krónikus csecsemőkori neurológiai cutan és artikularis szindróma)

Blau szindróma (familiáris juvenilis granulomatosus arthritis)

PAPA (pyogén steril arthritis, pyoderma gangrenosum, acne)

Toplak et al. Pediatric Rheumatology 2010, 8:29
http://www.ped-rheum.com/content/8/1/29

PEDIATRIC
RHEUMATOLOGY

SHORT REPORT Open Access

Periodic fever syndromes in Eastern and Central European countries: results of a pediatric multinational survey

Nataša Toplak[1*], Pavla Dolezalovà[2], Tamas Constantin[3], Anna Sedivà[4], Srdjan Pašić[5], Peter Čižnar[6], Beata Wolska-Kuśnierz[7], Miroslav Harjaček[8], Mariana Stefan[9], Nicolino Ruperto[10], Marco Gattorno[10†], Tadej Avčin[1†], Eastern/Central European autoinflammatory collaborating group for the Paediatric Rheumatology International Trials Organization (PRINTO) and Eurofever Project[10]

Autoinflammatory disorders are underdiagnosed

Magyar – Szlovén kétoldalú Tudományos és Technológiai (TéT) Együttműködés 2011- 2012:

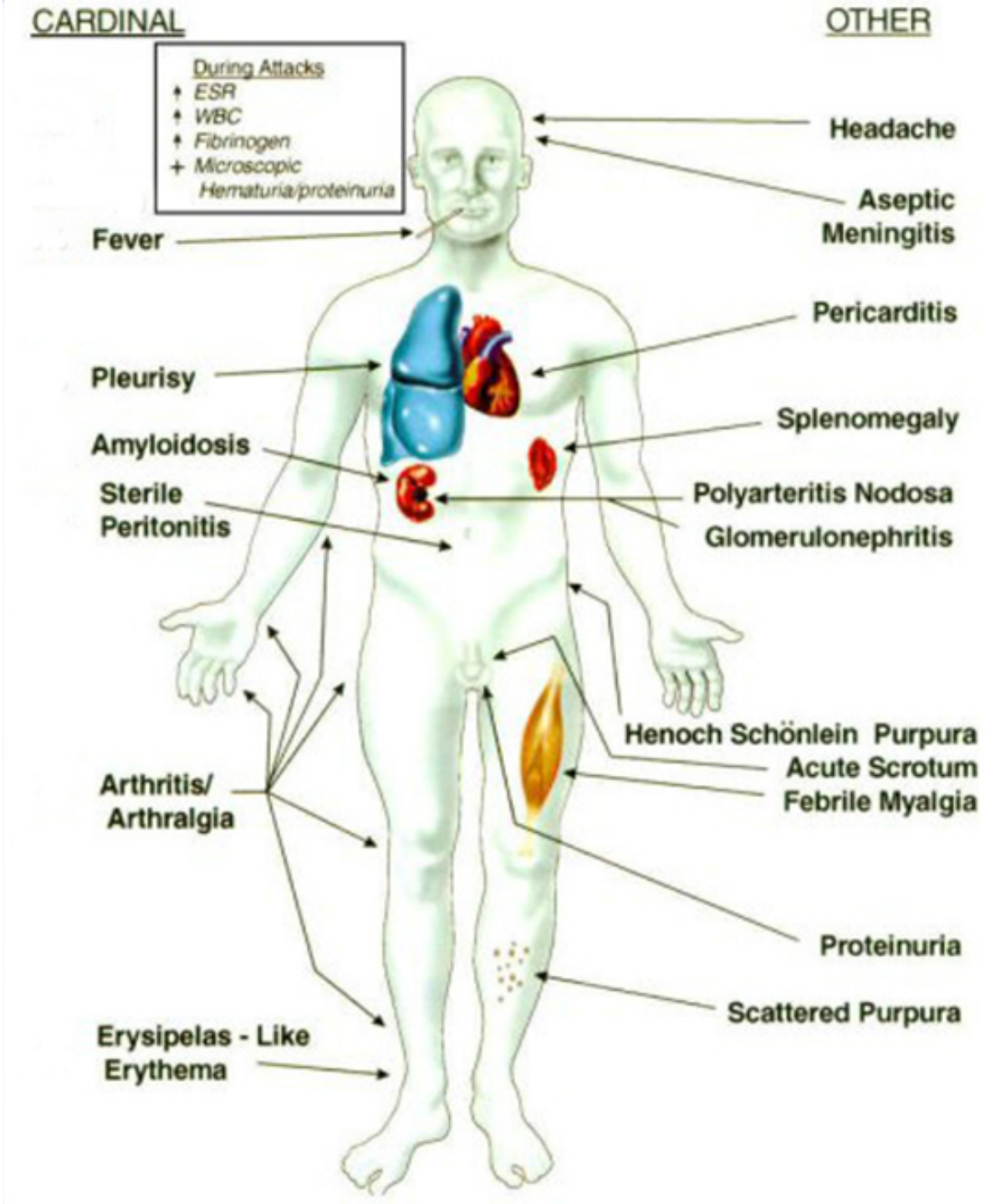
A periódikus láz szindrómák epidemiológiájának és genetikai hátterének vizsgálata Szlovéniában és Magyarországon

univerzitetni klinični center ljubljana

NIH NEMZETI INNOVÁCIÓS HIVATAL

UNIVERSITAS BUDAPESTINENSIS DE SEMMELWEIS NOMINATA • 1769 •

Symptoms of FMF



Hungary **5%**

Slovenia **7%**

Bosnia and Herzegovina **8%**

Macedonia **16%**

Pediatric rheumatology - diseases

- **Juvenile idiopathic arthritis, JIA.**

  Incidence 10/100.000 children. Prevalence 15-150/100.000 children.
- **Infectious musculoskeletal diseases**
  - Septic arthritis
  - Reactive arthritis
  - Lyme arthritis
  - Acute rheumatic fever and post-streptococcal arthritis
- **Connective tissue diseases**
  - SLE. Incidence 0.3-0.9/100.000
  - JDM. Incidence 0.4-1.1/100.000
  - Scleroderma and systemic sclerosis
  - Overlap diseases
- **Vasculitides**
  - Henoch-Schönlein purpura. Incidence 13.5/100.000
  - Kawasaki disease
  - Polyarteritis nodosa
  - Wegener granulomatosis
- **Autoinflammatory syndromes** rare!
- **Non-inflammatory mechanical pain syndromes**

JIA categories

	Frequency	Onset age	Sex ratio
Systemic arthritis 4–17%		Throughout	F=M
Oligoarthritis	27–56%	Peak at 2–4 ys	F>>>M
RF+ polyarthritis 2–7%		Adolescence	F>>M
RF- polyarthritis 11–28%	Biphasic	F>>M	
Enthesitis-related a.	3–11%	Adolescence	M>>F
Psoriatic arthritis 2–11%		Biphasic	F>M
Undifferentiated a.	11–21%		

Medical history - present illness

Chief complaint? Pain? Swelling? Limping?

SIGNS OF INFLAMMATION:

PAIN, WARMTH, REDNESS, SWELLING, LOSS OF FUNCTION

- **Location** of pain?
- Details of **onset**: acute, gradual, traumatic?
- **Duration** of pain? **Severity** of pain: Getting better or worse?
- **Quality** of pain: Stabbing, burning, freezing, aching, spasms, crushing?
- **Particular time of day** that it is worse or better? Specifically, morning, evening, or nocturnal pain?
- Does it radiate, migrate, or is it episodic?
- It is hot or cold to the touch?
- Does it look different or **swollen**?
- Does it **interfere with functioning**? School attendance, activities of daily living?
- Does anything make it better or worse? Medications, rubbing, ice, heat, activity, rest, distraction?
- Between 0 and 10, how much does it hurt?
- **Associated symptoms**? Fever, rash, weight change, weakness, sleep disturbance, depression, anxiety, behavior change, cough, vision or hearing changes, headache, abdominal pain, diarrhea, dizziness, unable to concentrate?
- Medications?

Physical examination - Joint examination

- Particularly for young children, completing a thorough physical examination may require more than one attempt
- Sometimes engage the child to play
- Little children: on parent's lap
- Physical exam begins with general appearance and growth chart
- Pay special attention to the skin and eye

Joint examination:
look, feel, move

- INSPECTION
  - observe symmetry at rest
  - loss of normal contour and landmarks
  - distention and fullness - surface anatomy
  - erythema
  - atrophy
  - angulations
  - deformities
  - limb length
  - muscle bulk

Joint examination:
look, feel, move

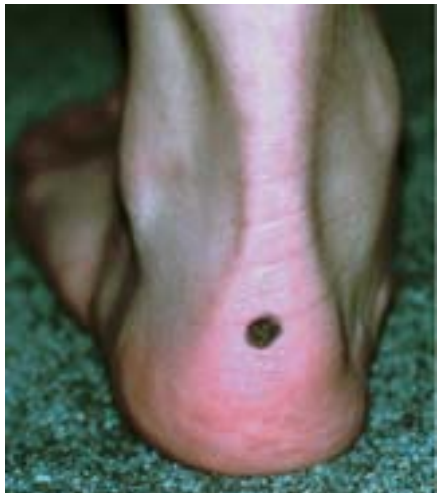
- PALPATION:
  - palpate for joint swelling: Is it effusion (fluid), soft tissue or bone?
  - skin warmth (compare with the other side)
  - presence of enthesitis?
  - joint tenderness?
  - effusions in the knees are generally easily felt and may be balloted

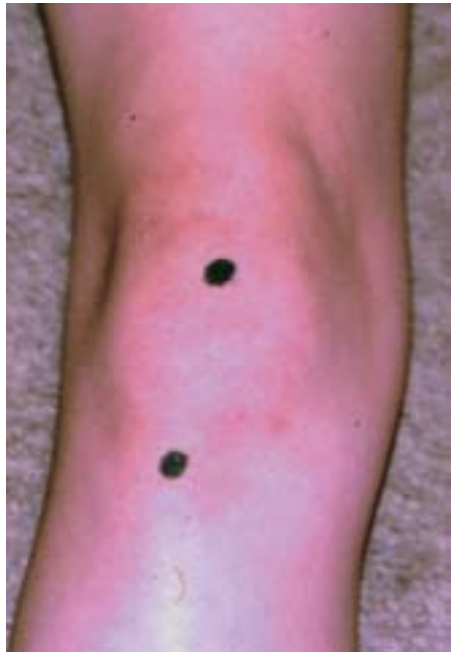
Feel

Examination of the elbow - An effusion would be felt under the middle finger of the examiner’s hand when the elbow is extended.

Feel - enthesitis

The enthesis is where tendons attach to bone. The sites that are the most commonly involved entheses in enthesitis-related arthritis are shown with arrows.



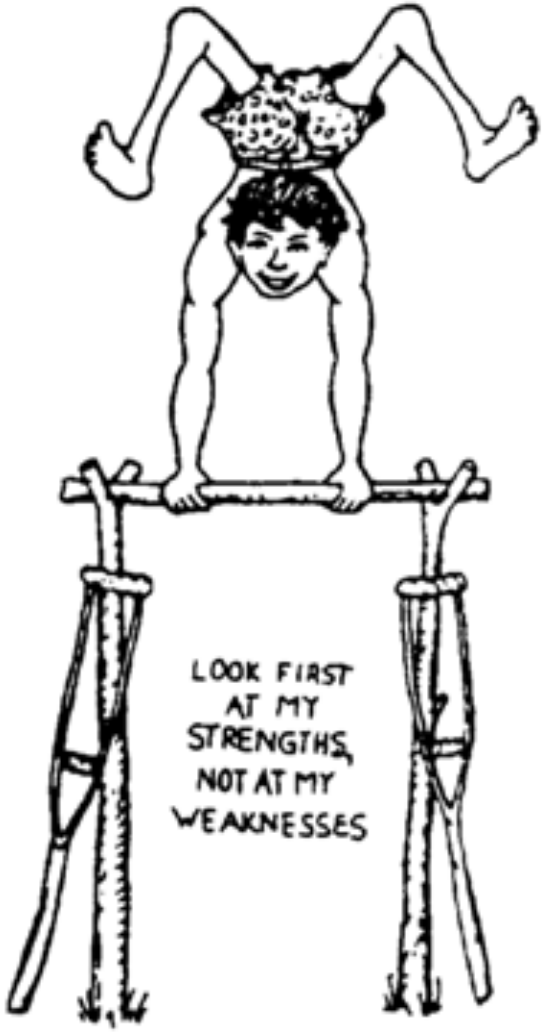


Joint examination:
look, feel, move

- RANGE OF MOTION in all directions
  - Active = by the patient
  - Passive = by the examiner
  - flexion contractures are a hallmark of JIA !

FINALLY: It is extremely important to perform an examination of **all joints** and not limit the examination to the area of complaint. It is common in examining children with arthritis to discover significantly reduced range of motion, especially in the wrists, elbows, and hips, even though the child has no complaints referable to those areas.

Examination of the ped rheum patient – look, feel, move: muscle power



Muscles or
muscle groups

On a 5- or 10 point scale
- No contractions felt
- Holds test position against strong pressure

Muscle power

SITTING POSITION

- M. trapezius: shoulder elevation. Shrug your shoulder up! I'm try to push your shoulder – you hold it, dont't let me push your shoulder!
- M. deltoideus: shoulder abduction. Hold your arm up. I'm going to push down – don't let me push it down.
- M. biceps brachii: elbow flexion. Bend your elbow. I'm try to pull down it.
- M. iliopsoas: hip flexion. Bring your knee up. I try to push it down.
- M. qudriceps femoris: knee extension. Kick your leg out. I try to bend it.
- Wrist extensors: wrist dorsiflexion. Bring your hand back. I try to straighten it.
- Wrist flexors: wrist volarflexion
- Ankle dorsiflexors: Bring your foot up like this. I try to push it down.

SUPINE POSITION

- Neck flexors: head raise. Bring your head off the table. Hold it up.

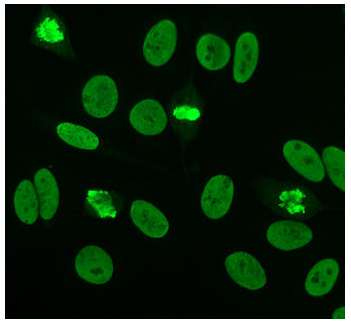
SIDE-LYING

- M. gluteus medius: hip abduction. Lift your leg. I try to push down.

PRONE

- Neck extensors: raise your head
- M. gluteus maximus: hip extension. Lift your leg. I try to push down.
- Hamstrings: knee flexion. Bend your knee. I try to pull it down.
- Ankle plantarflexors

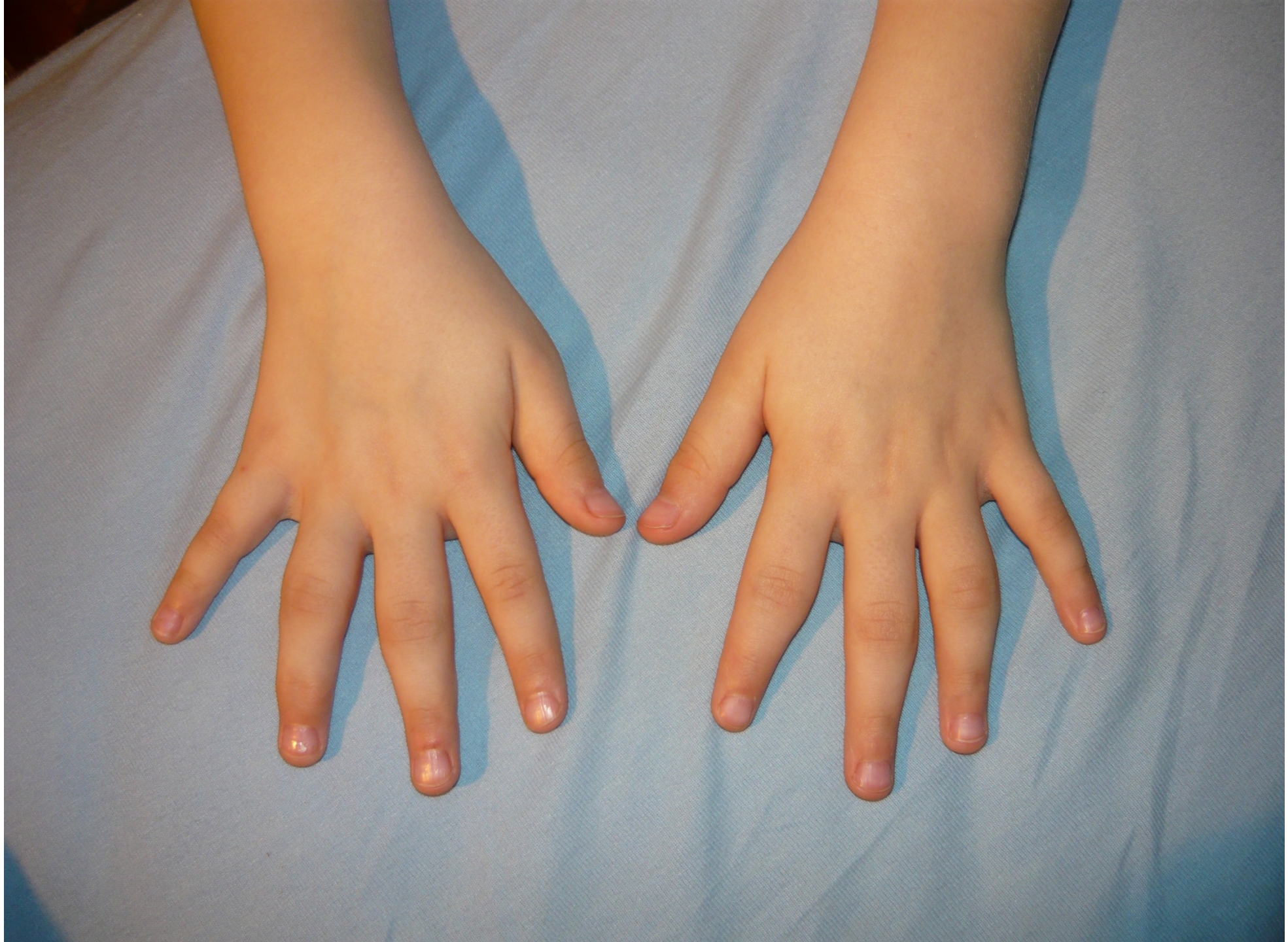
Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis

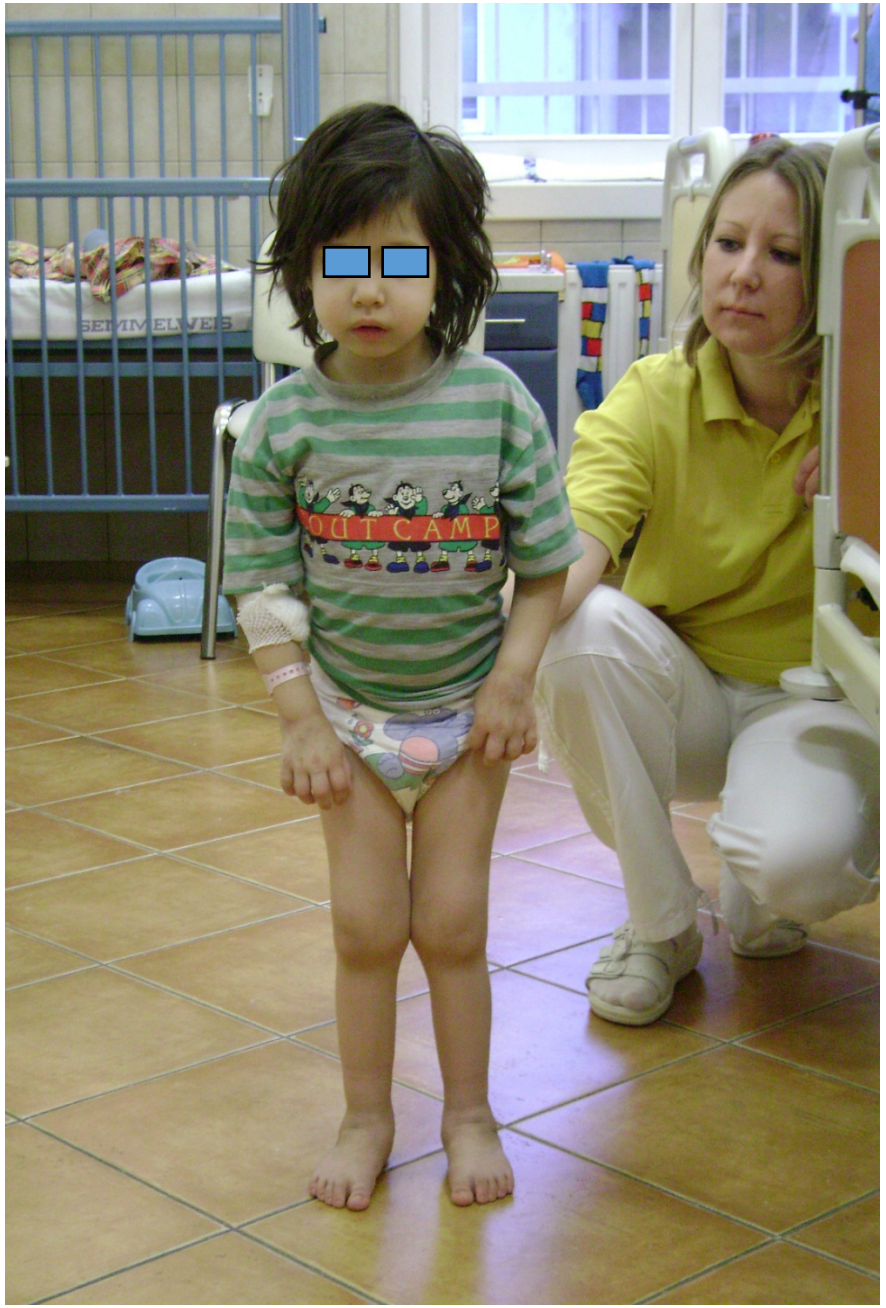


- close relationship between the presence of ANAs and
- younger age at disease presentation,
- female predominance,
- asymmetric arthritis,
- development of iridocyclitis,
- lower number of affected joints over time,
- and lack of hip involvement

Arthritis Rheum. 2011 Jan;63(1):267-75.

Monoarthritis

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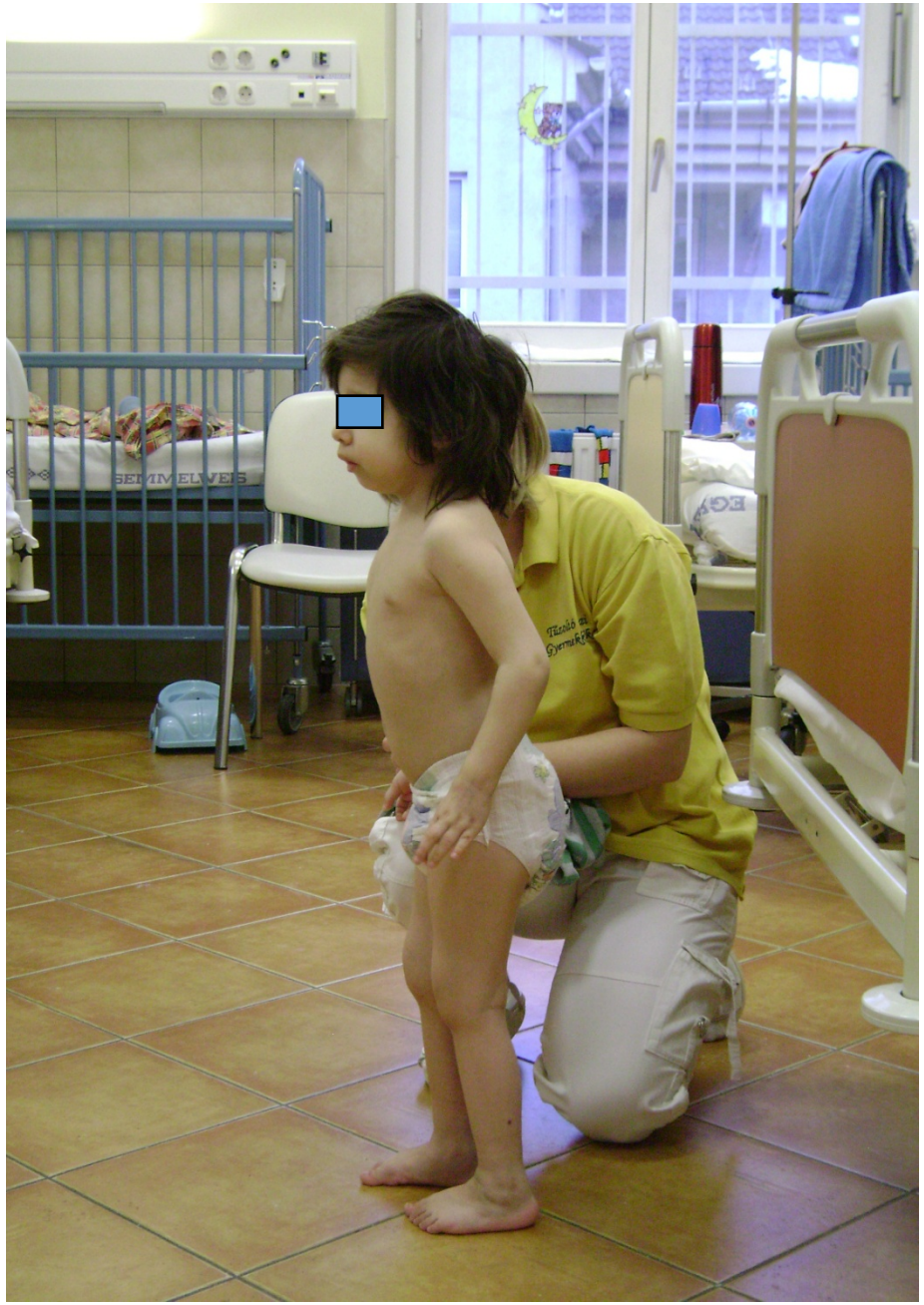
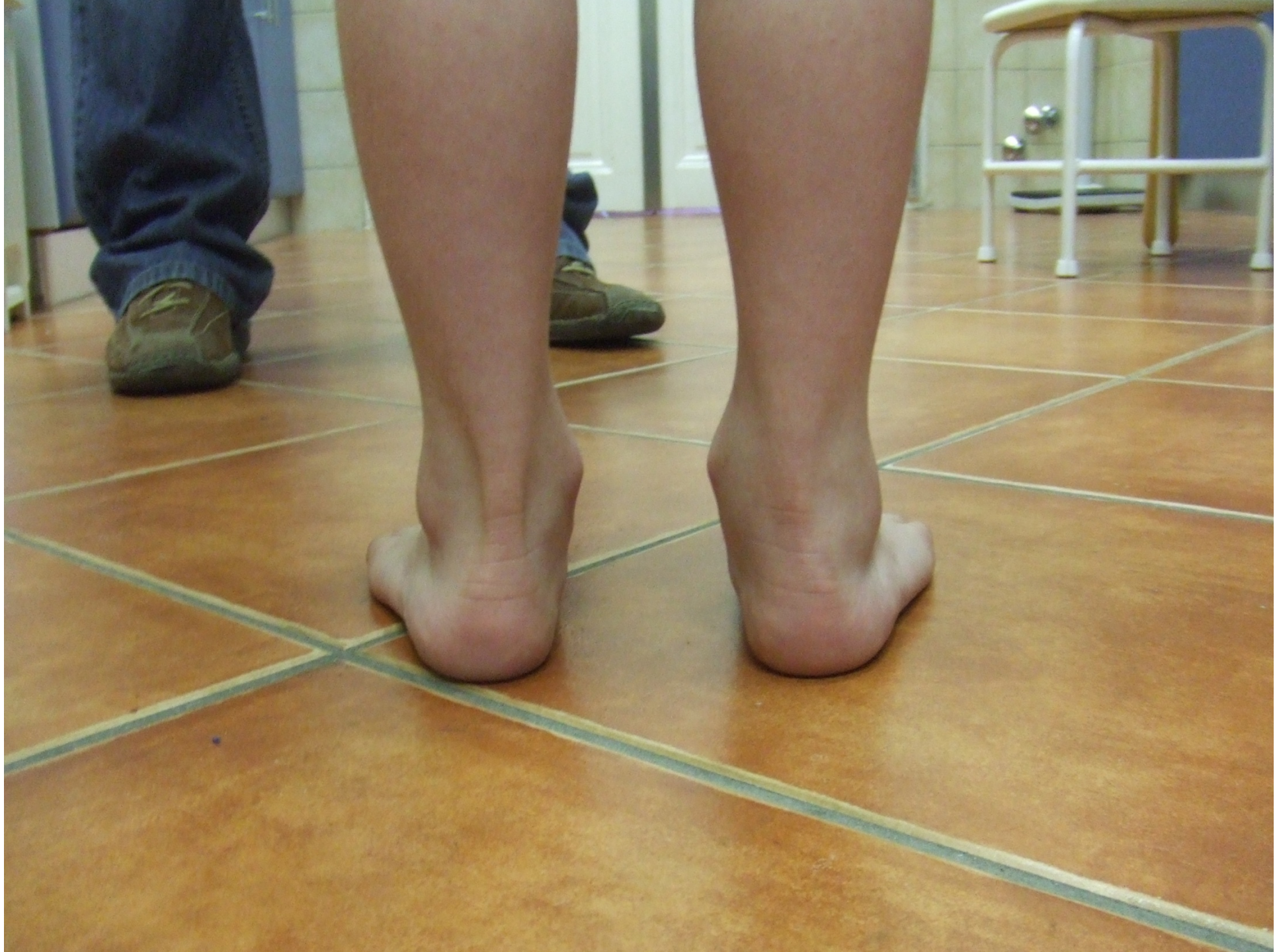
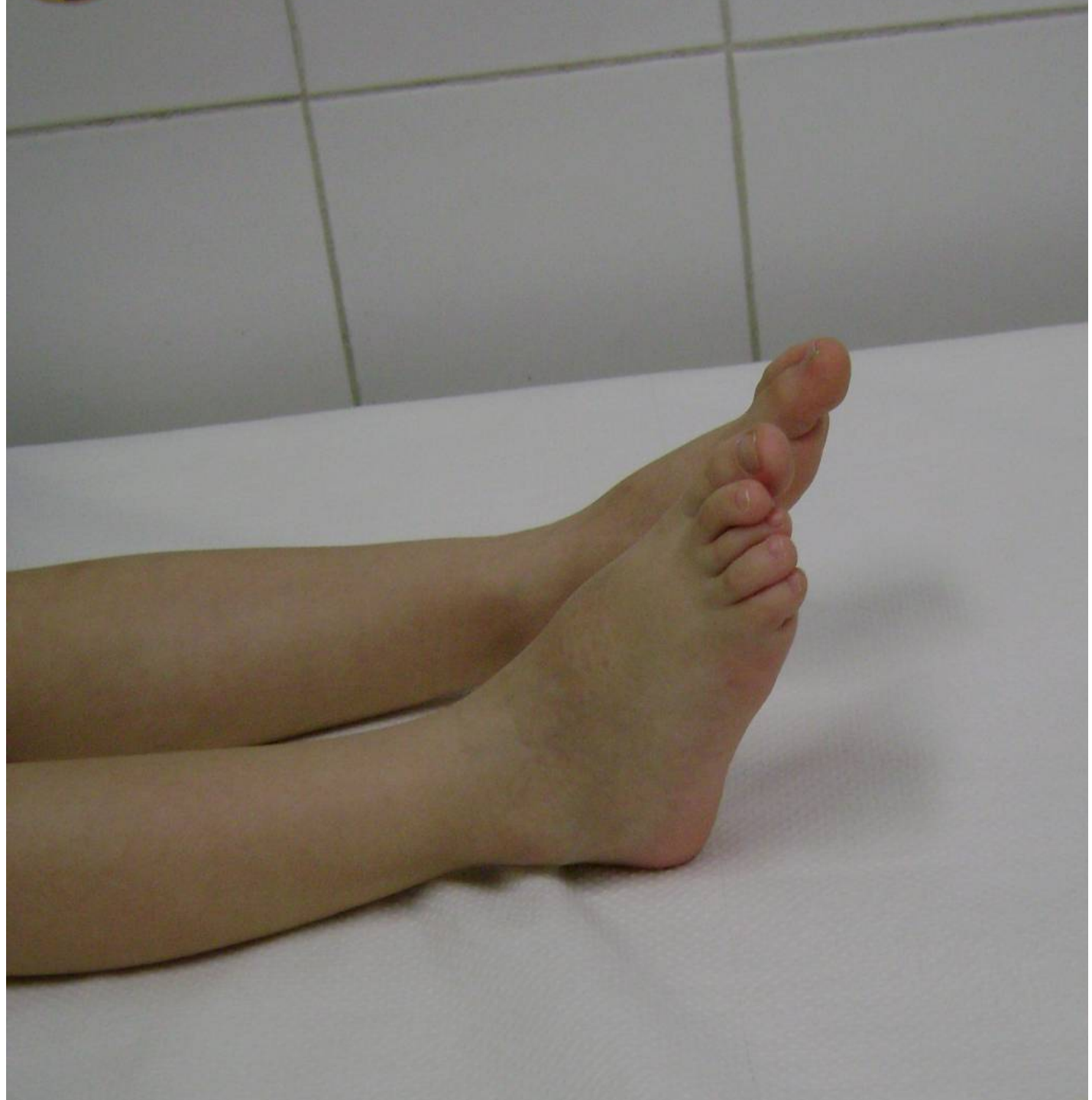
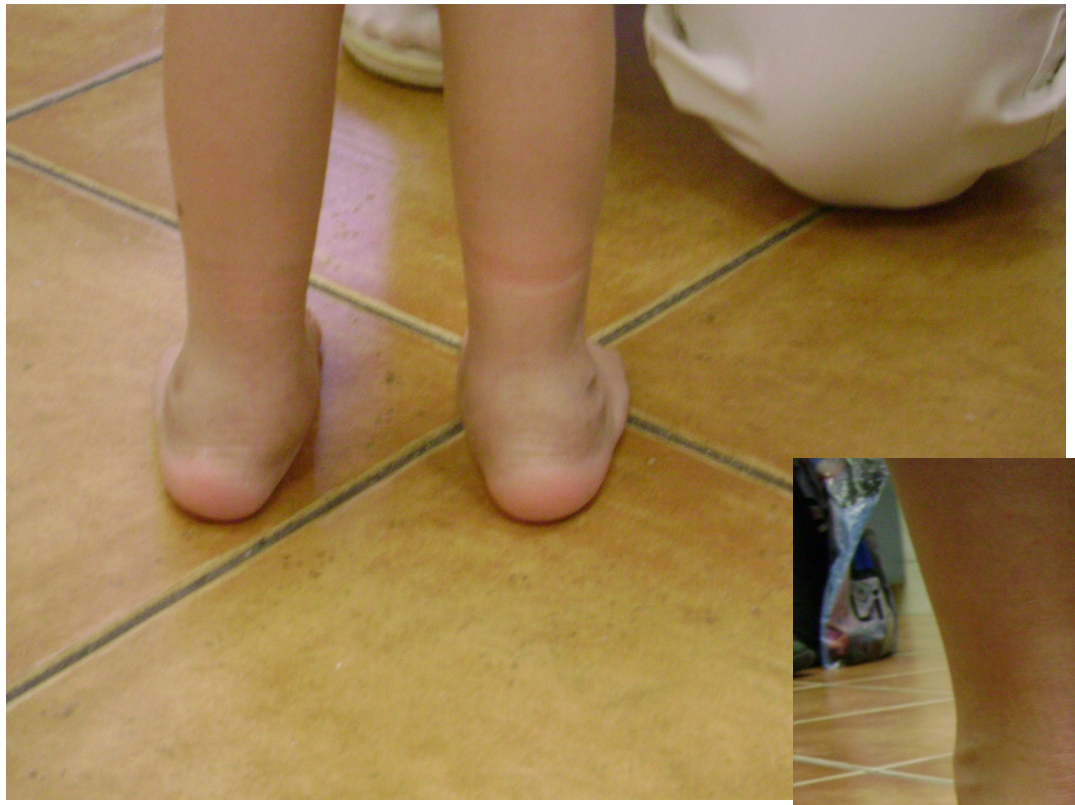
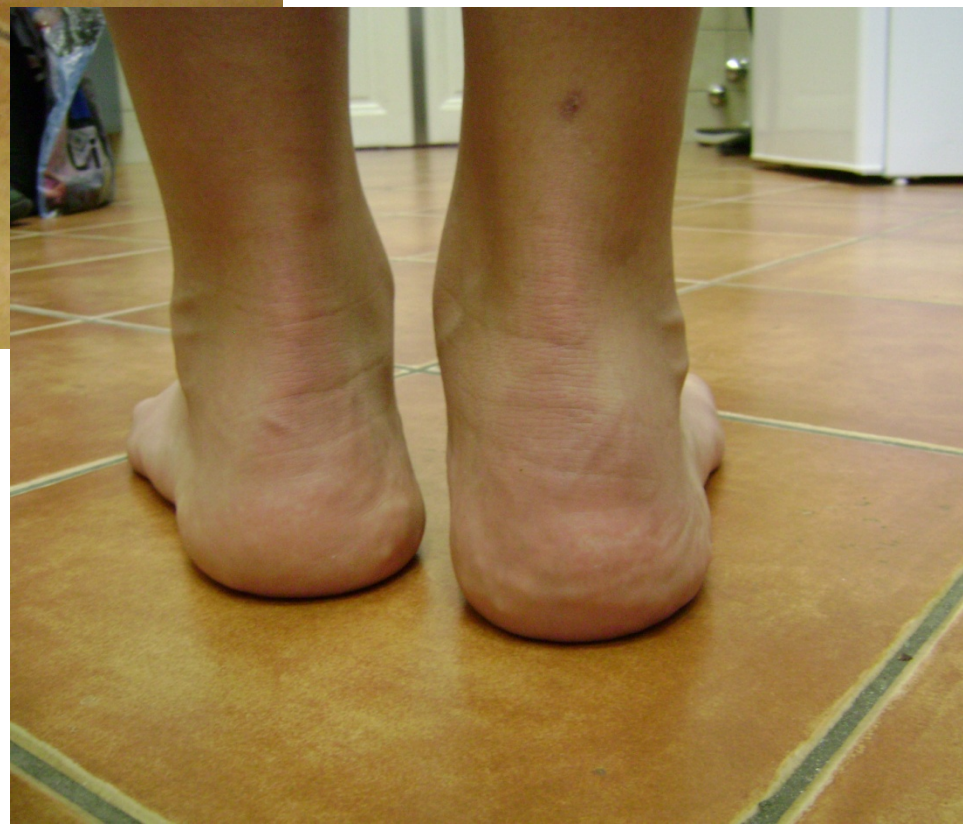
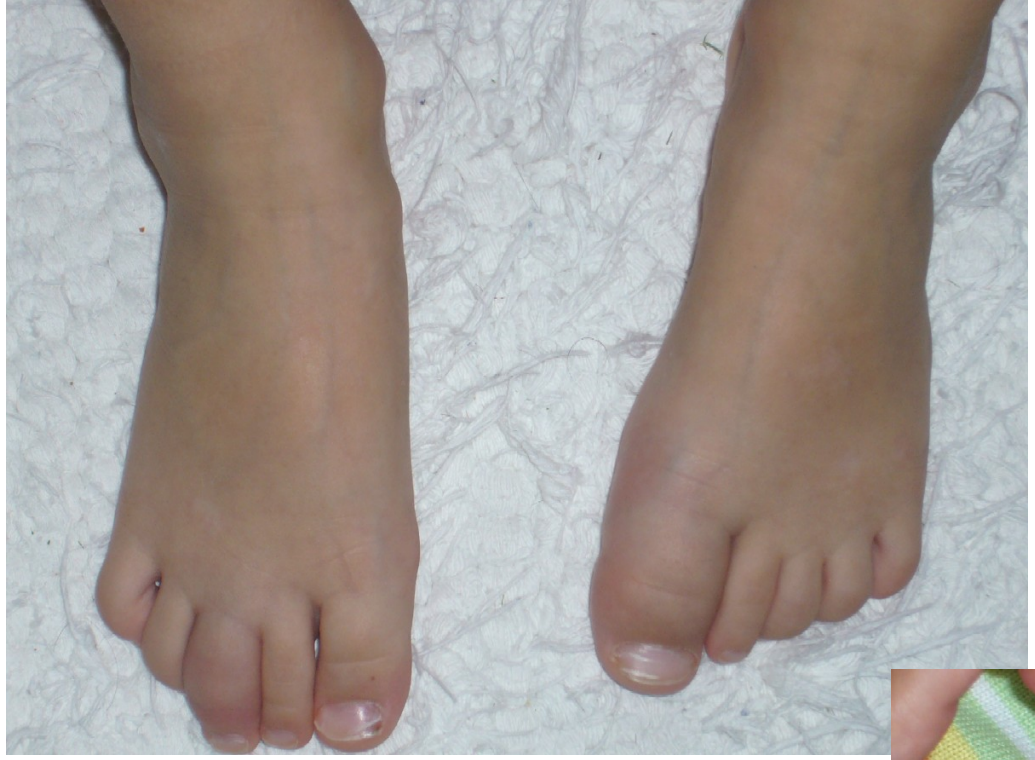


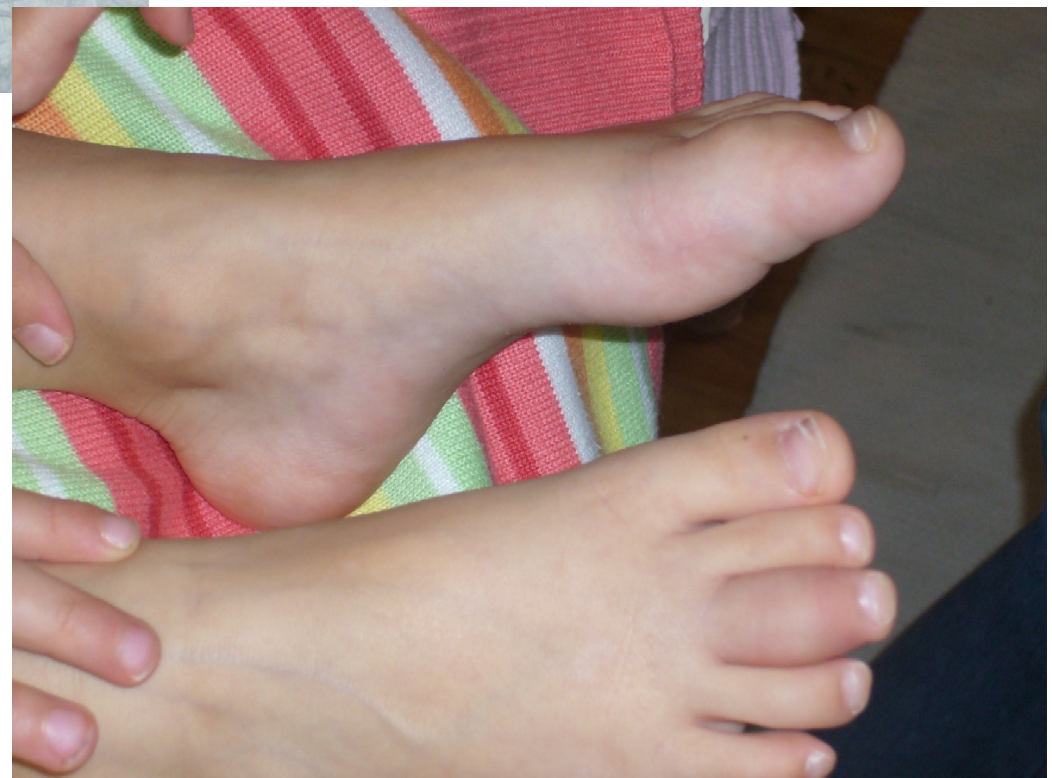


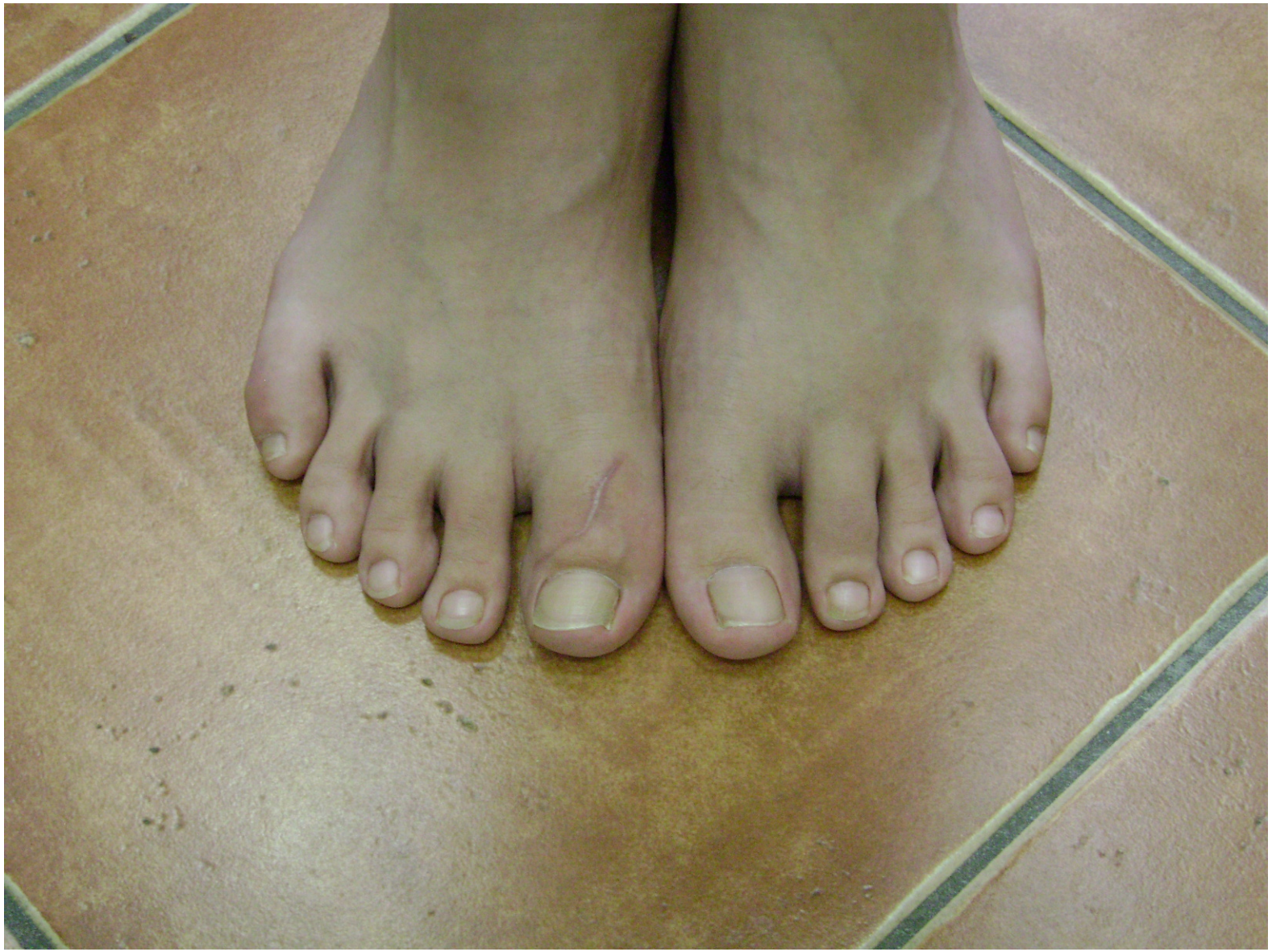


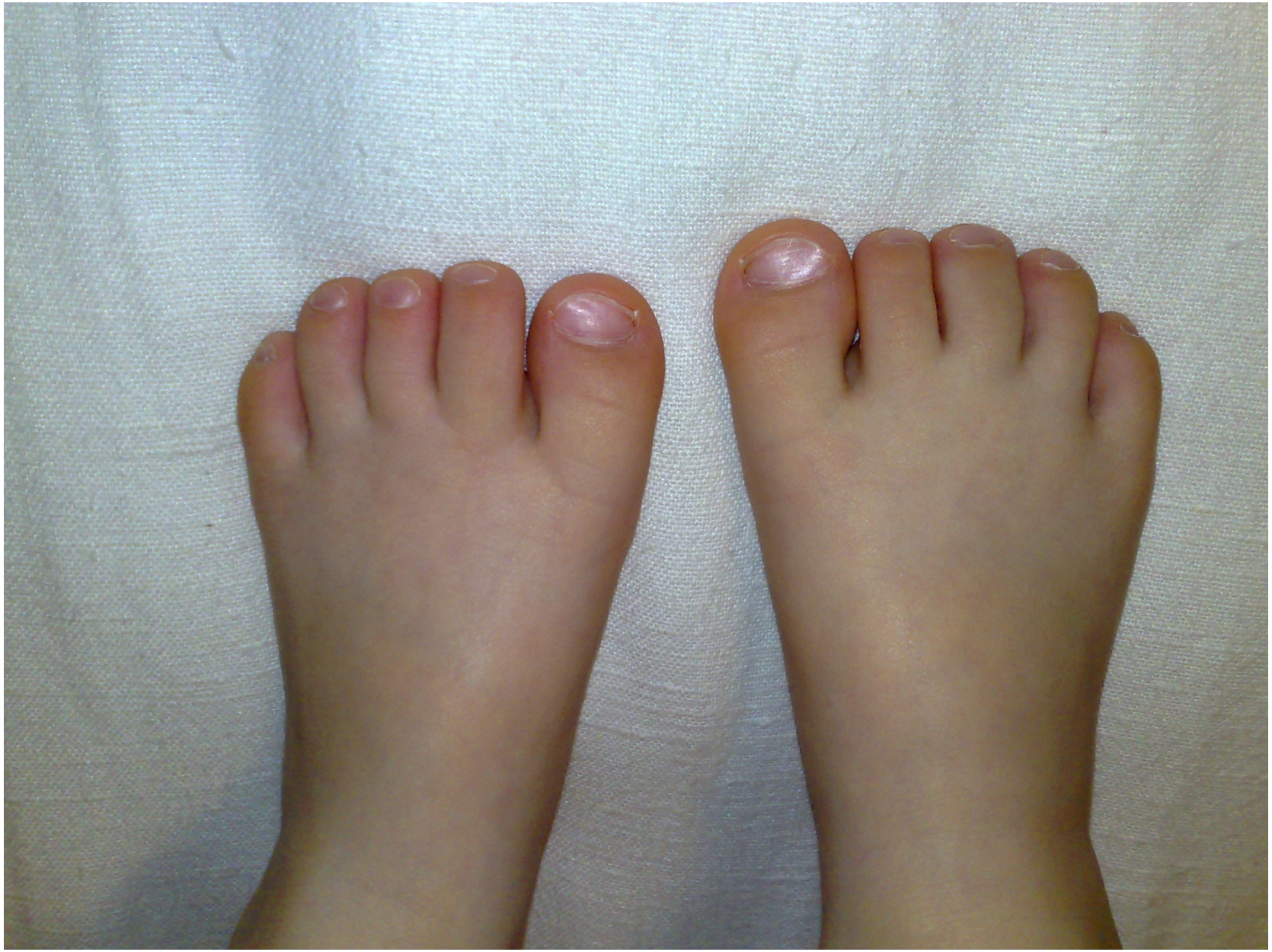


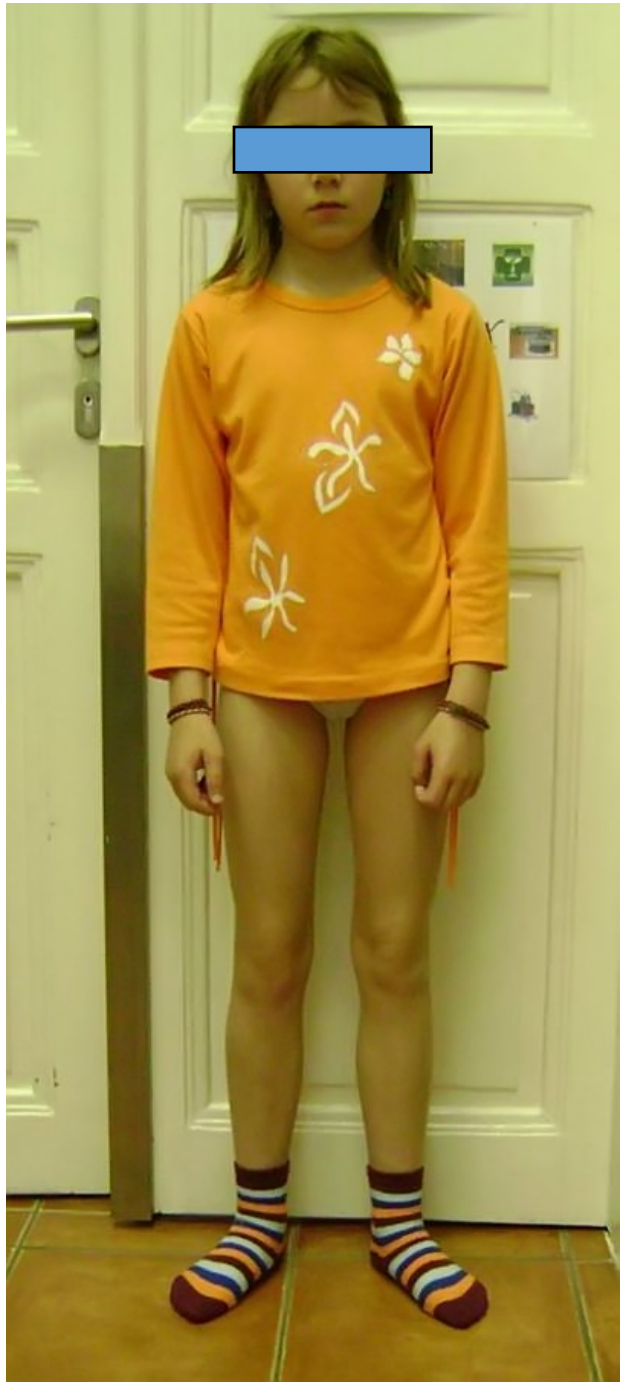


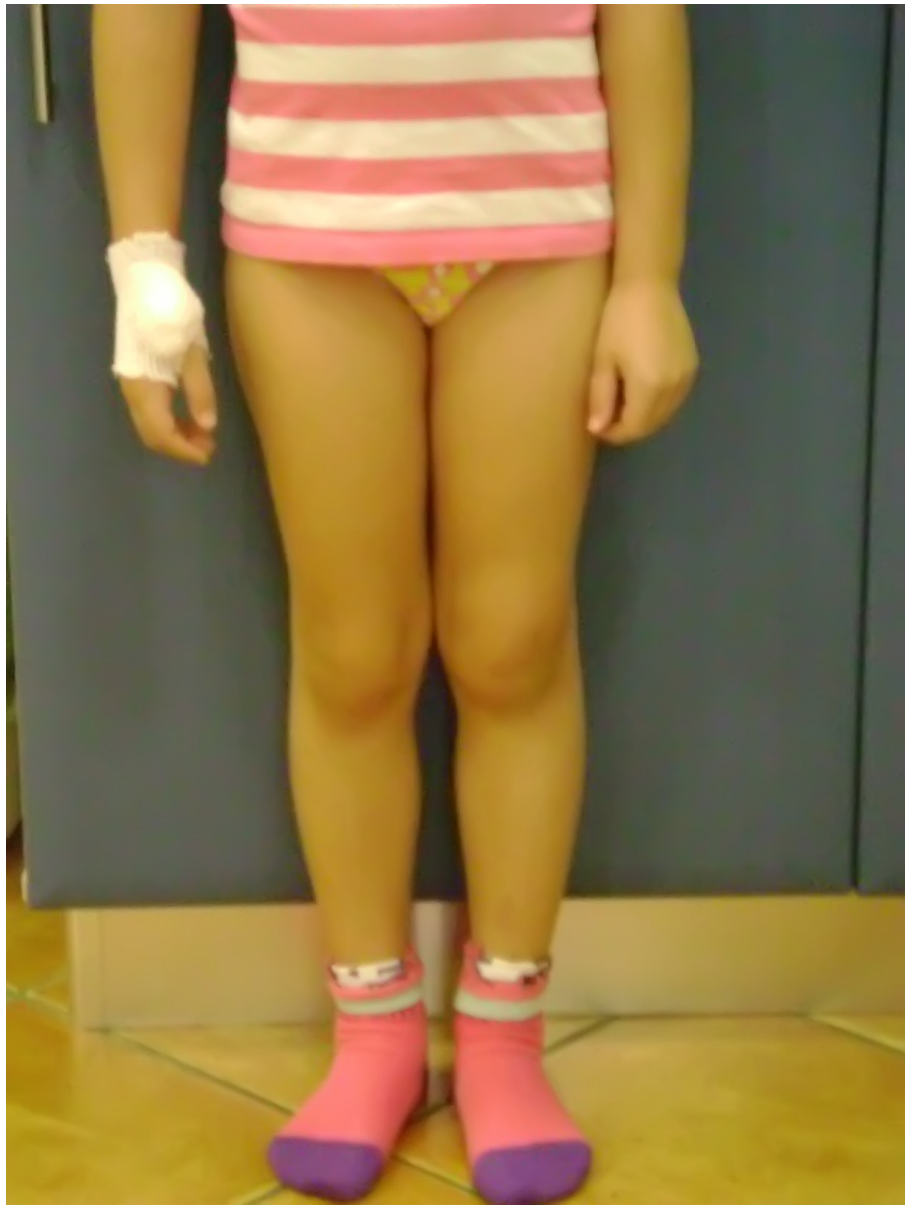


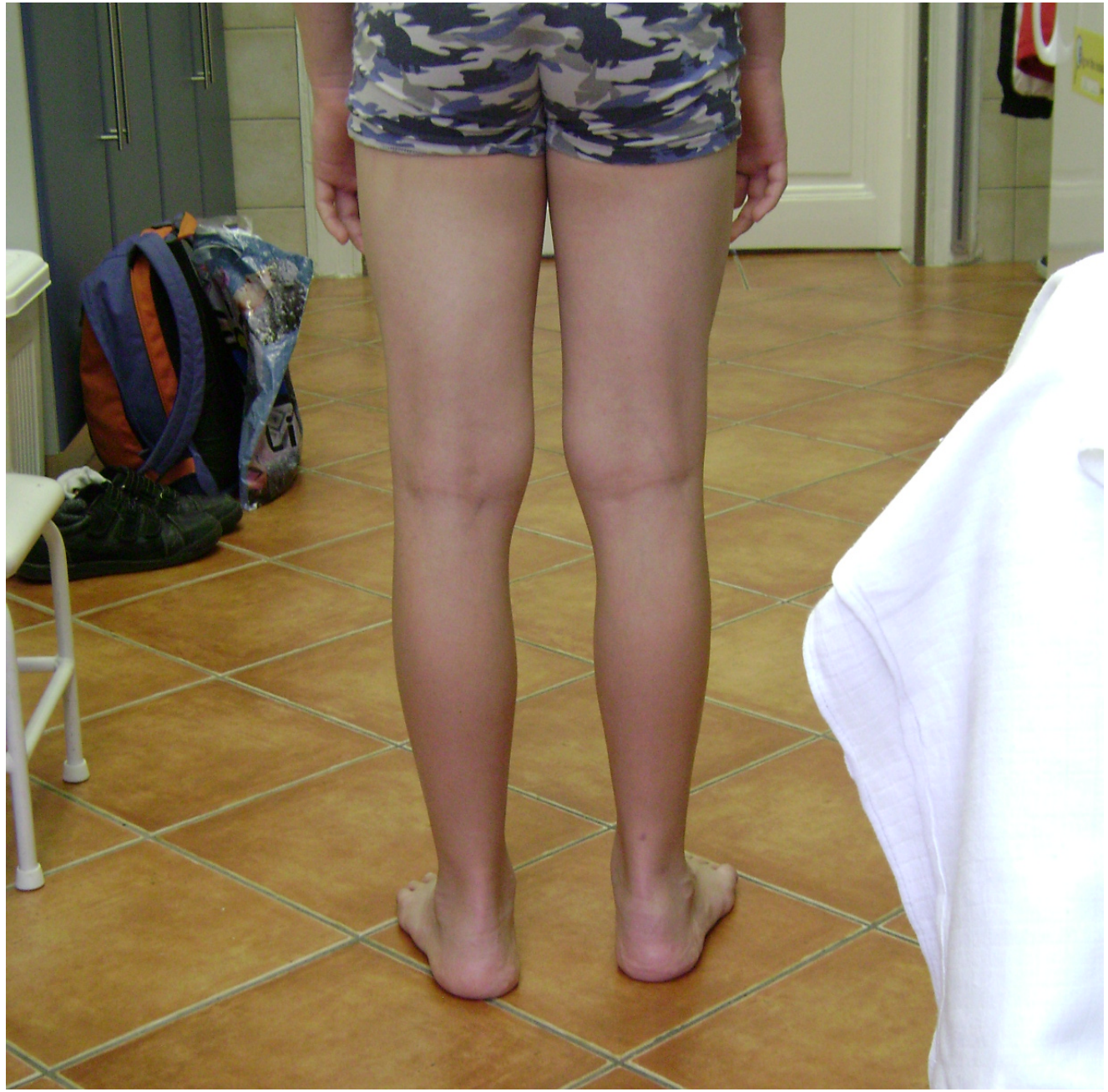


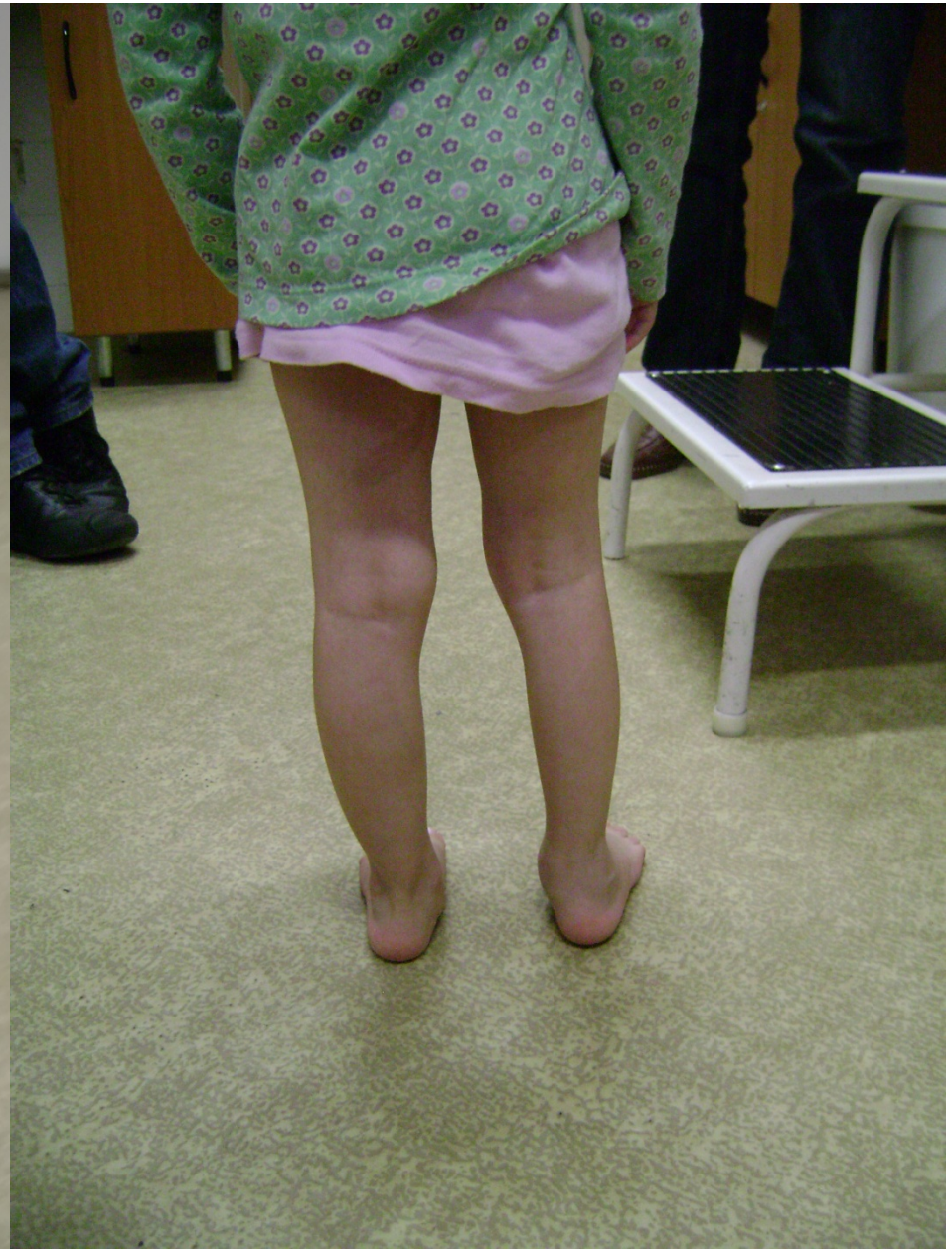


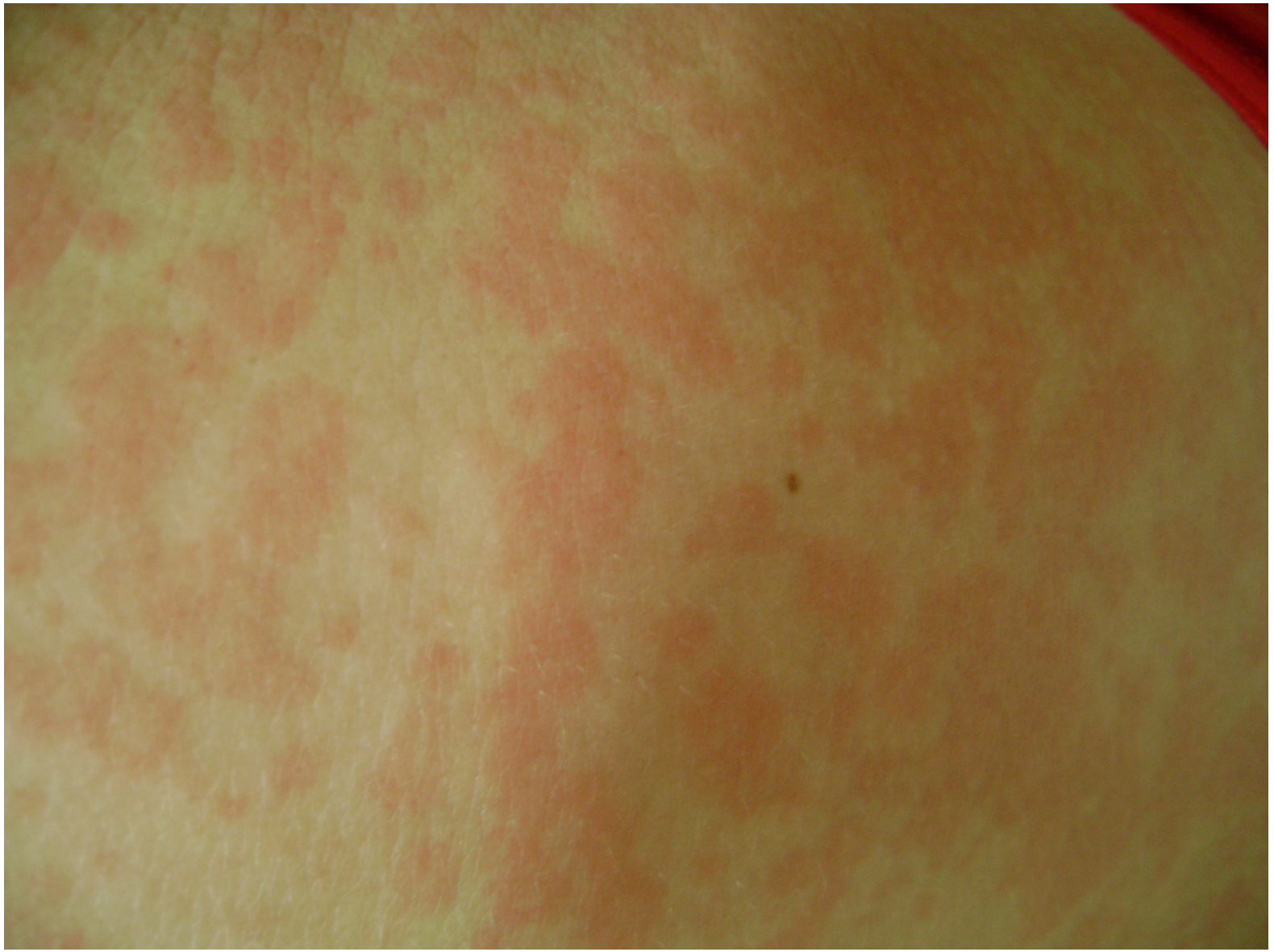


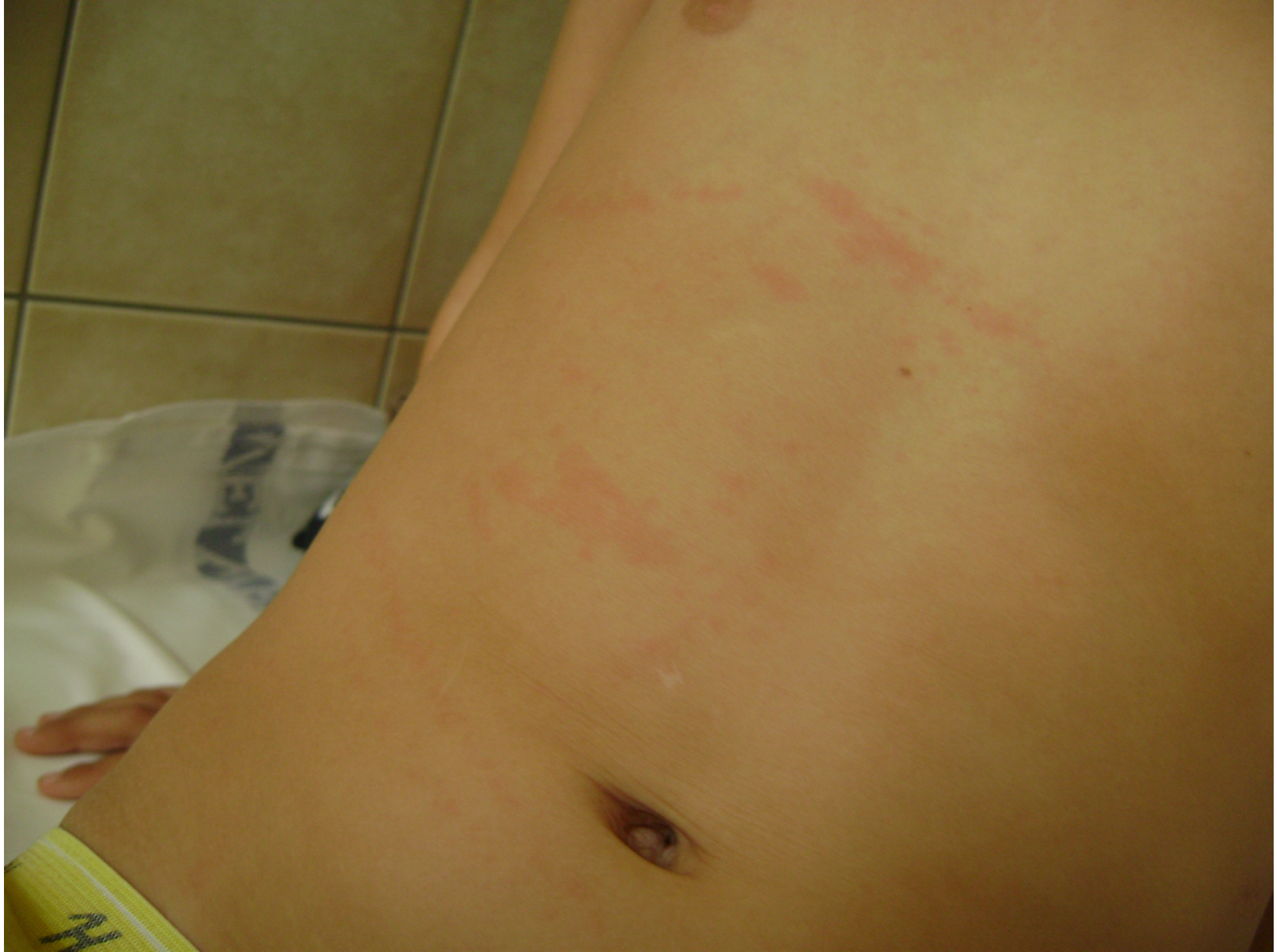


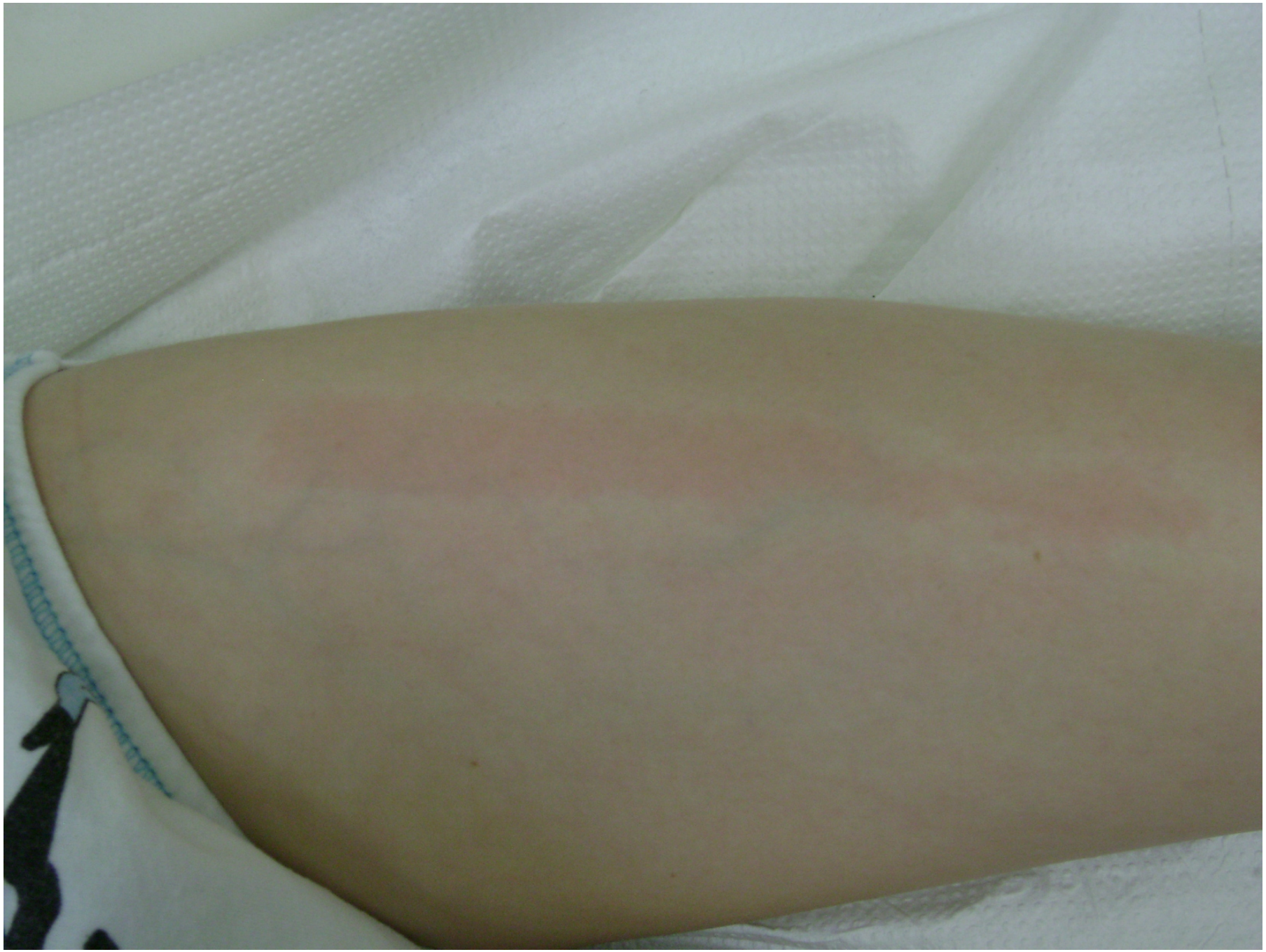


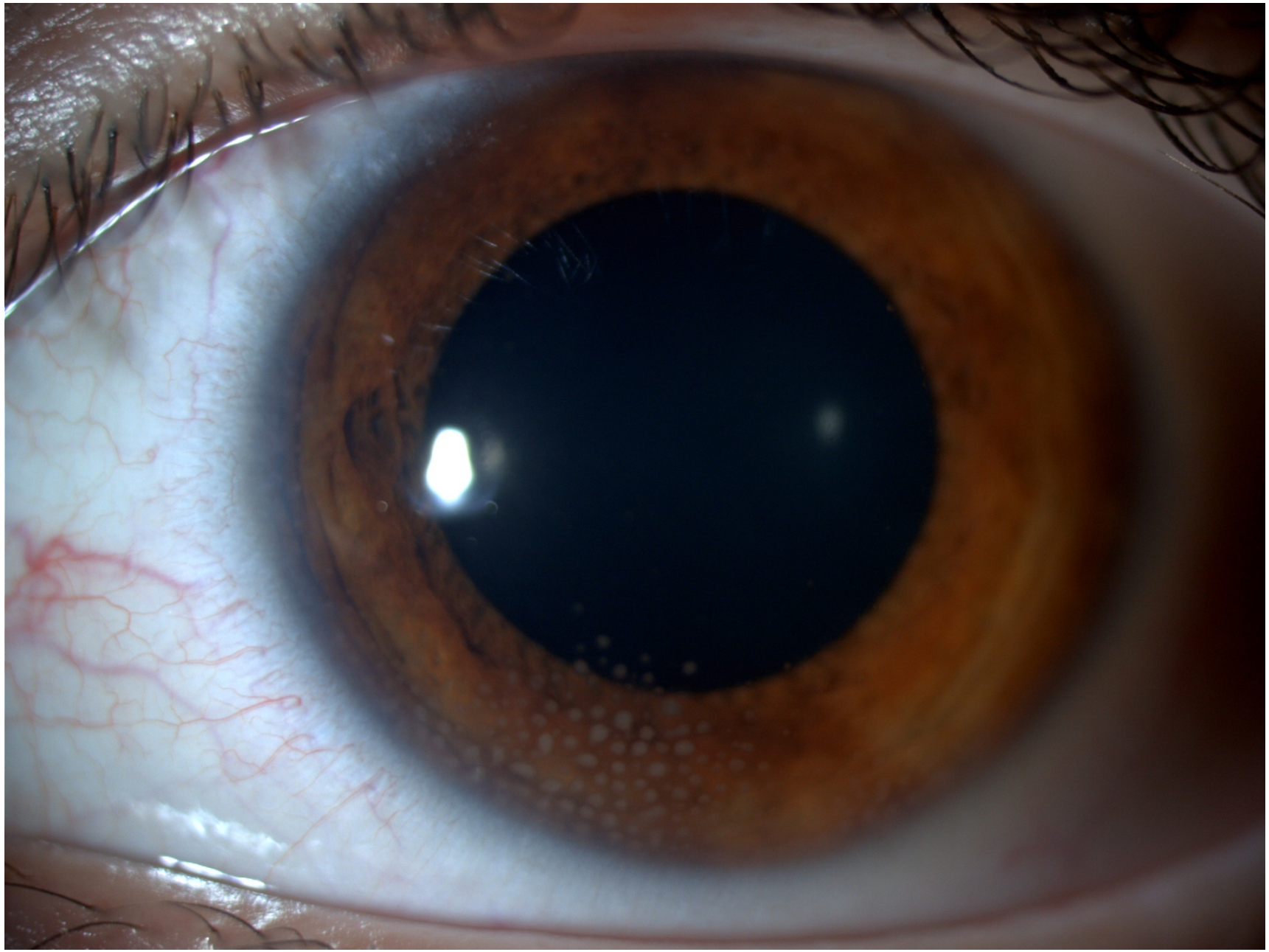


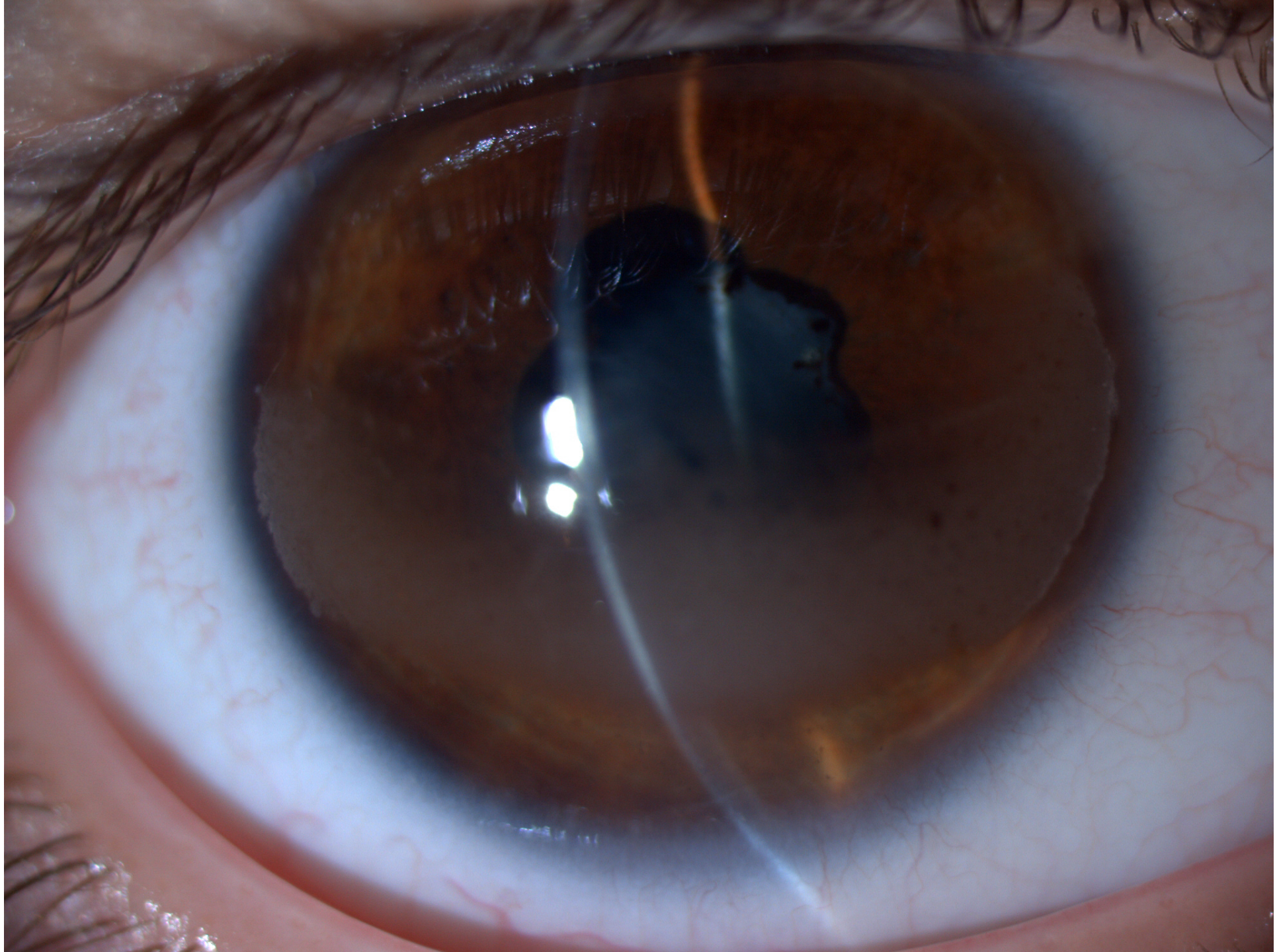


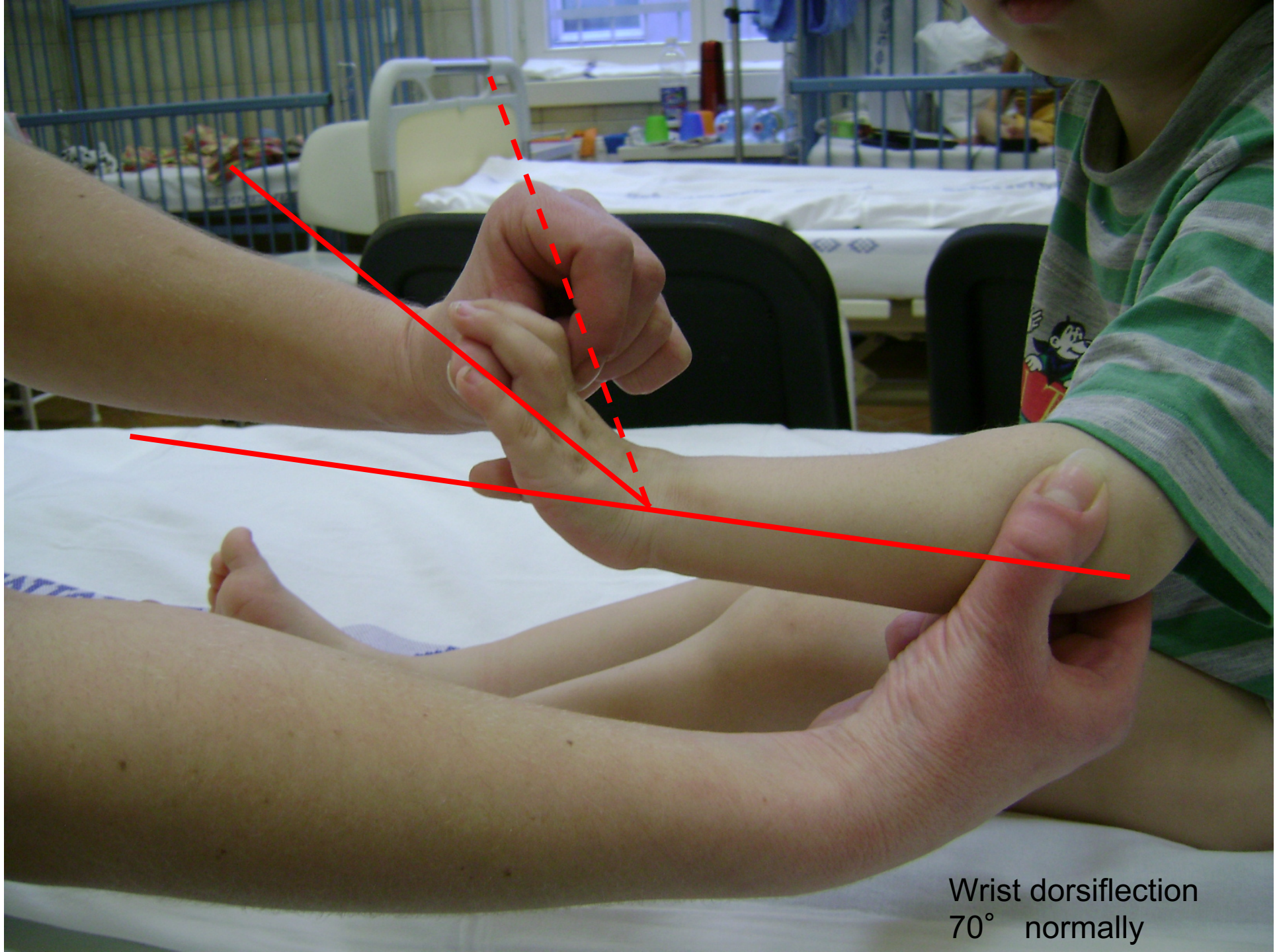


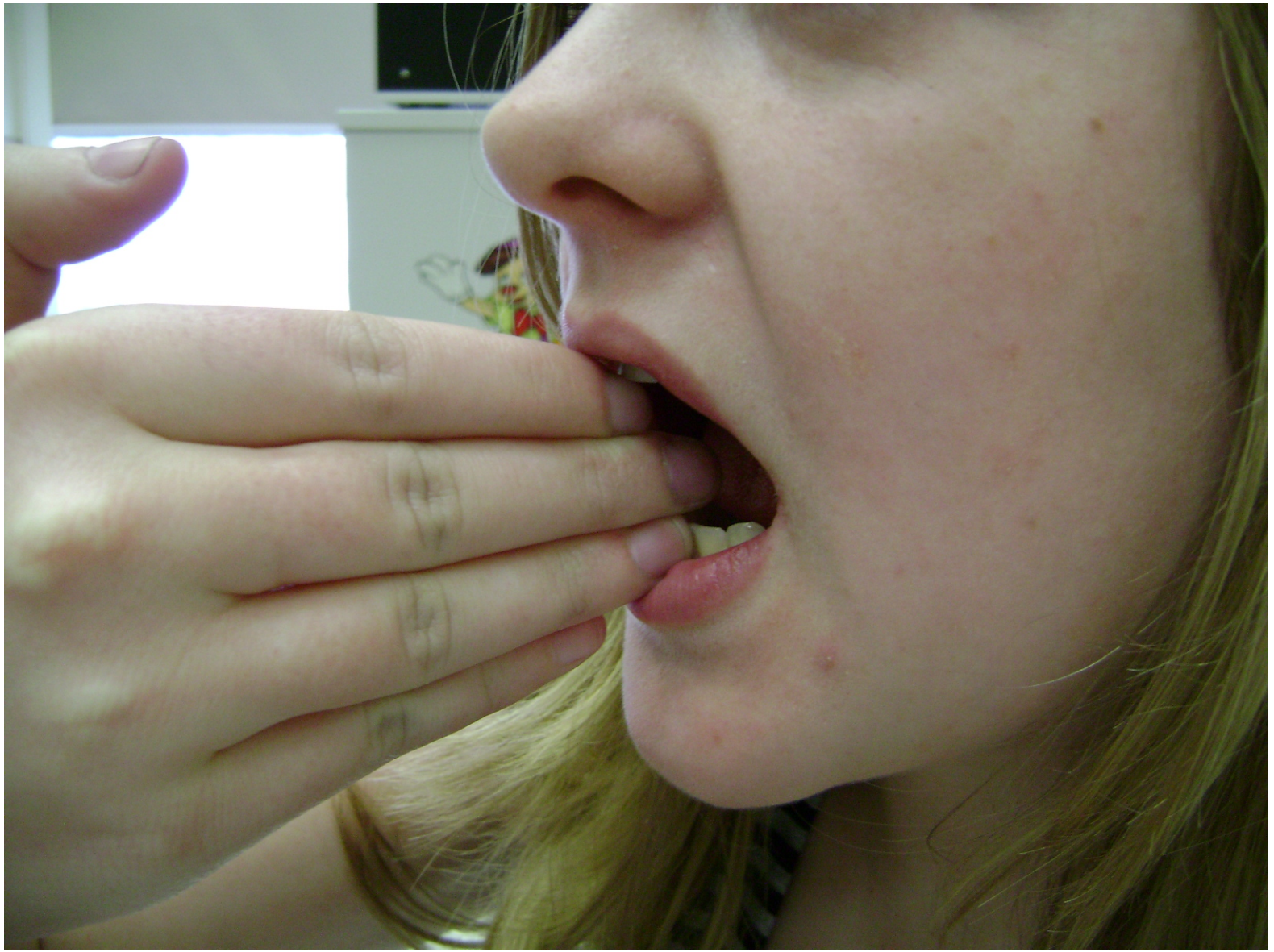









Wrist dorsiflection
70° normally



Auto-antibodies in JIA

Antibodies

- ANA
- IgM RF
- Anti-CCP
- Anti-RA 33

ANA

- Prevalencia JIA-ban
  - Oligoarticularis JIA 38-85%
  - Polyarticularis JIA 30-50%
  - Szisztémás JIA 0-17%
  - Psoriasoshoz társuló JIA 41% [11]
  - Enthesitis asszociált JIA 19% [11]

- High risk for developing uveitis especially in patients with oligoarthitis
- Poor prognosis and risk for having longer period of active disease

ANA

- Group of ANA positive patients represents a more homogenous group of patients than JIA cathegories:
    - Yonger age disease onset
    - Oligoarthritis
    - Girls
    - Assymetric arthritis
    - Uveitis
- Low specificity

Rheumatoid faktor

- Prevalence in JIA-ban [4,5]
  - Polyarticularis 21%
  - Oligoarticularis 9%
  - Szisztémás 0-15%

- Predominantly in girls
- Small and large joints
- Usually polyarthitis
- More frequent in adolescents
- Sometimes the diease is „similar” to adult RA
- Poor prognosis: more damage, erosion, lack of remission

Citrullinált peptidek elleni antitestek (anti-CCP)

- Filaggrin ellen termelődő antitest
- Rheumatoid arthritisben már igen magas specificitású (87-96%) és szenzitivitású (69-77%), a RA korai markere
- RF-pozitív polyarthritisben 73 ill. 57%-ban találták pozitívnak, míg más altípusban 2-3%-ban, ami szignifikáns különbséget jelent [17,18]
- Kedvezőtlen prognosztikai faktornak tekinthető, a kórlefolyás különösen gyors és destruktív [17]

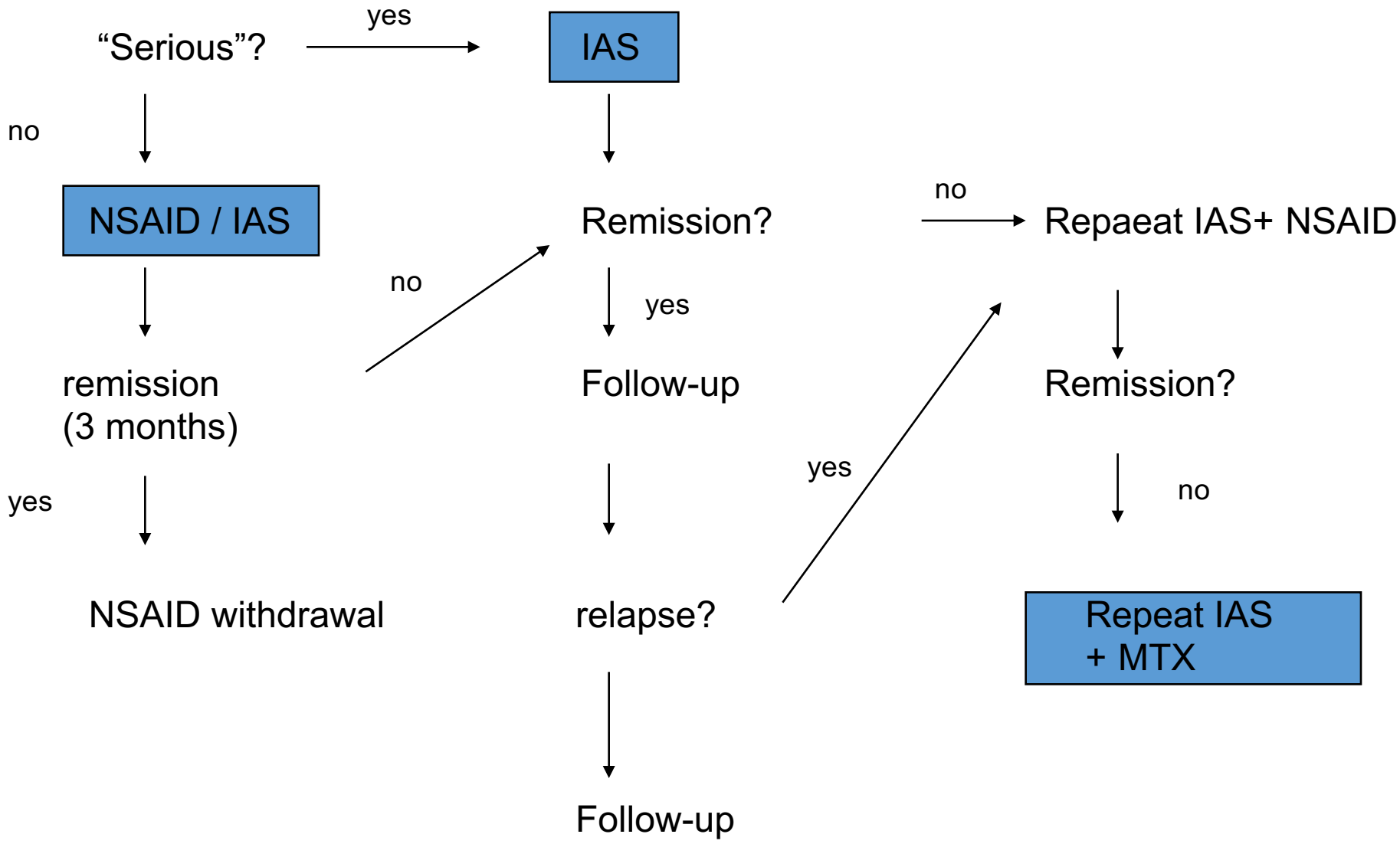
Anti-RA 33

- Heterogeneous nuclear ribonucleoprotein A2, 33 kDa tömegű antigén ellen termelődő antitest
- Előfordulása felnőttkori autoimmun betegségekben [19]
  - Rheumatoid arthritis 35%
  - Szisztémás lupus erythematosus 23%
  - Kevert kötőszöveti betegség 38%
  - Nem autoimmun etiológiájú arthritisekben ritka, vagy hiányzik
- A rheumatoid arthritis már igen korai fázisában pozitívvá válik, így segít elkülöníteni más arthritis formáktól [20]
- RF-negatív esetekben, más autoantitestekkel egyetemben (AKA, APF, ANA) 51,7%-ban bizonyultak pozitívnak, ill. kezelt RA-s betegeknél perzisztáltak, míg az RF ekkor már 58%-ban eltűnt [21]
- Míg RF $\geqq$ 50U/ml mellett az anti-CCP a súlyos, addig az anti-RA 33 az enyhébb lefolyás prediktora [22]

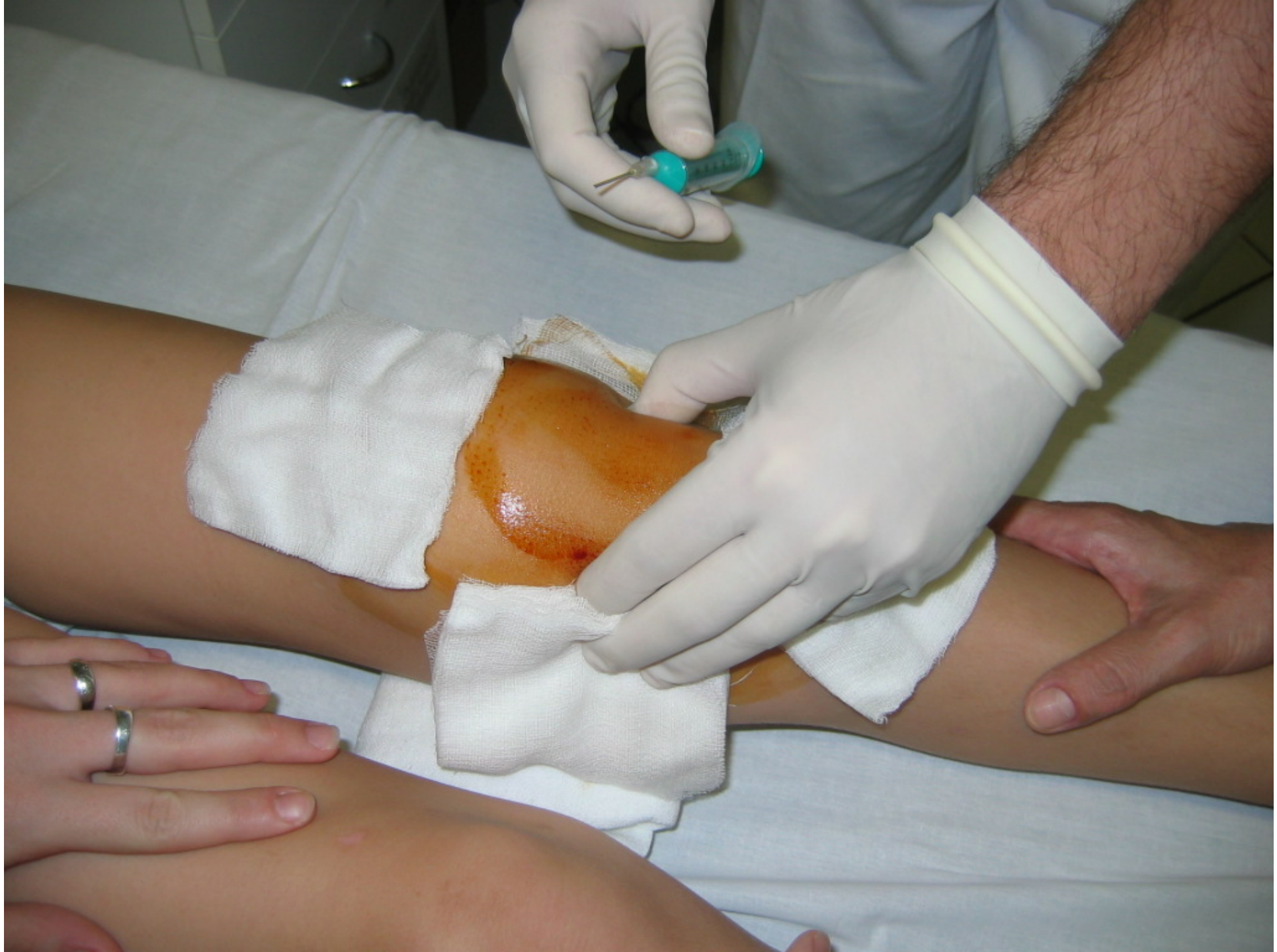
Anti-RA 33 JIA-ban [23]

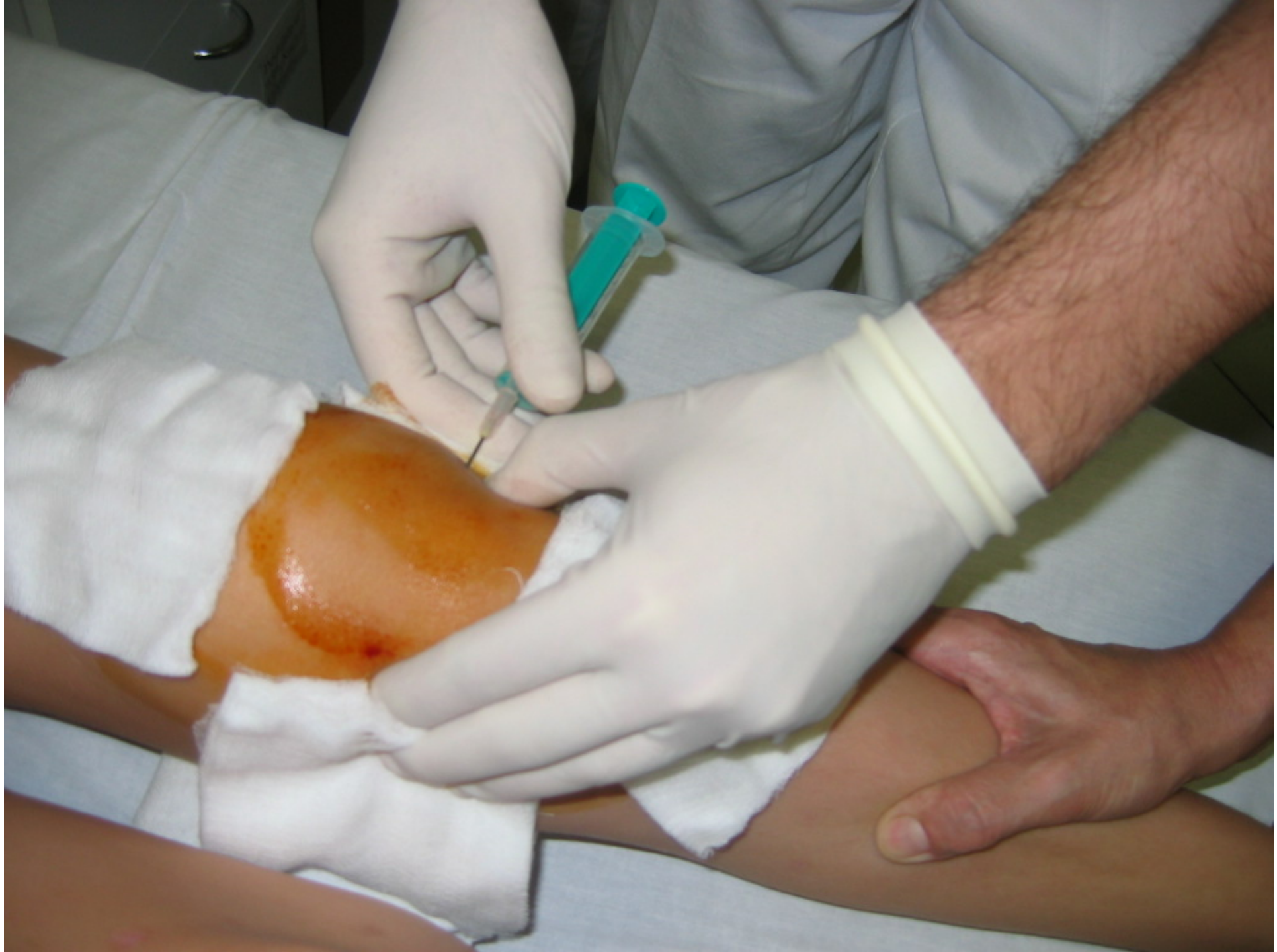
- A betegségben - mind a korai, mind a késői fázisban - magasabbnak találták az autoantitest szintjét, mint az egészséges kontroll csoport esetében
- A vizsgált, JIA-ban szenvedő gyermekek 66,7%-a pozitív volt anti-RA33-ra nézve, ill. hasonló értéket kaptak korai, 6 hétnél rövidebb ideje fennálló arthritises betegeknél, akik később már kimerítették a JIA kritériumait
- Az értékek korreláltak a betegség klinikai ill. laboratóriumi aktivitásával és a radiológiai progresszióval

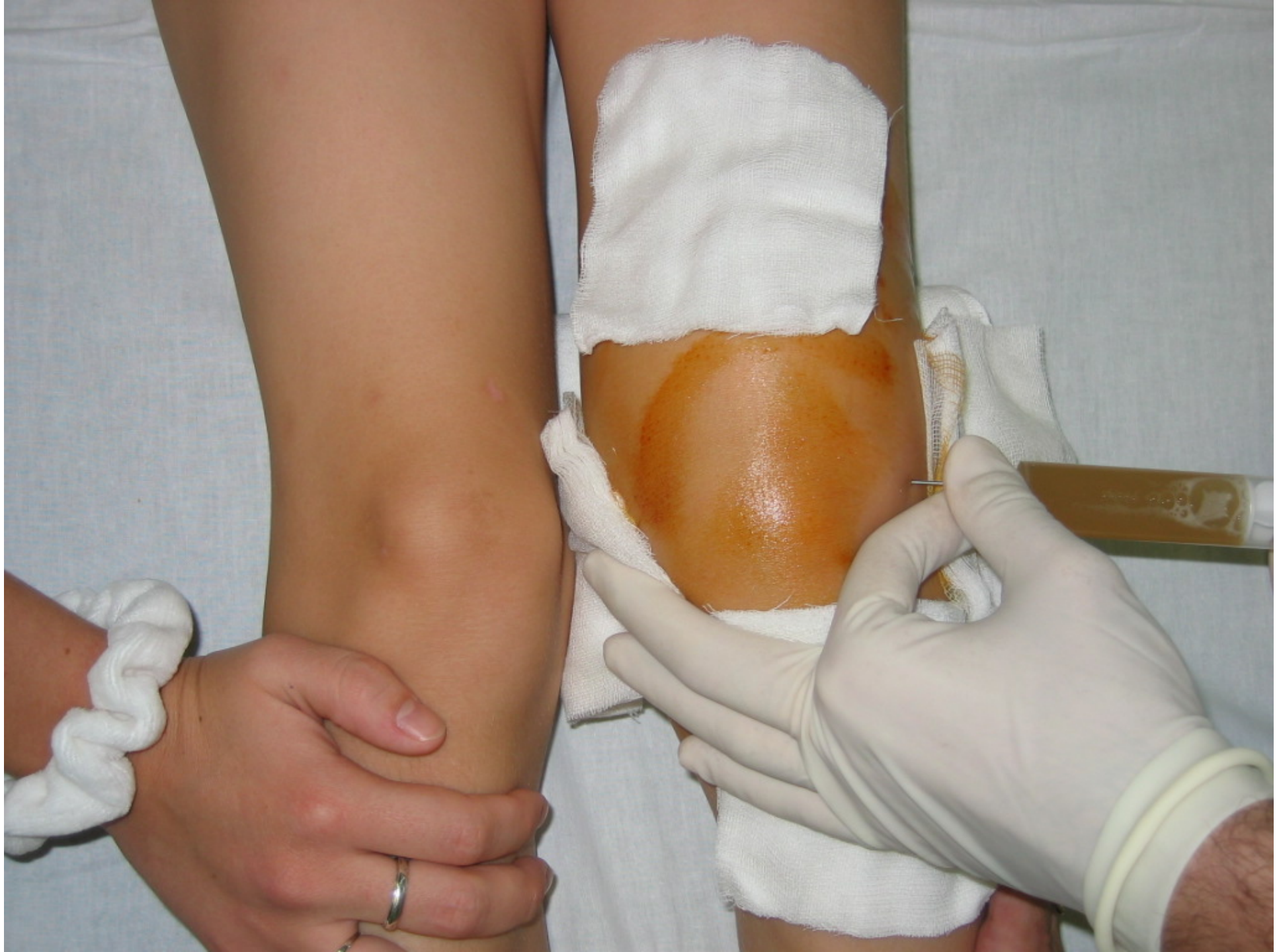
Oligoarthritis treatment



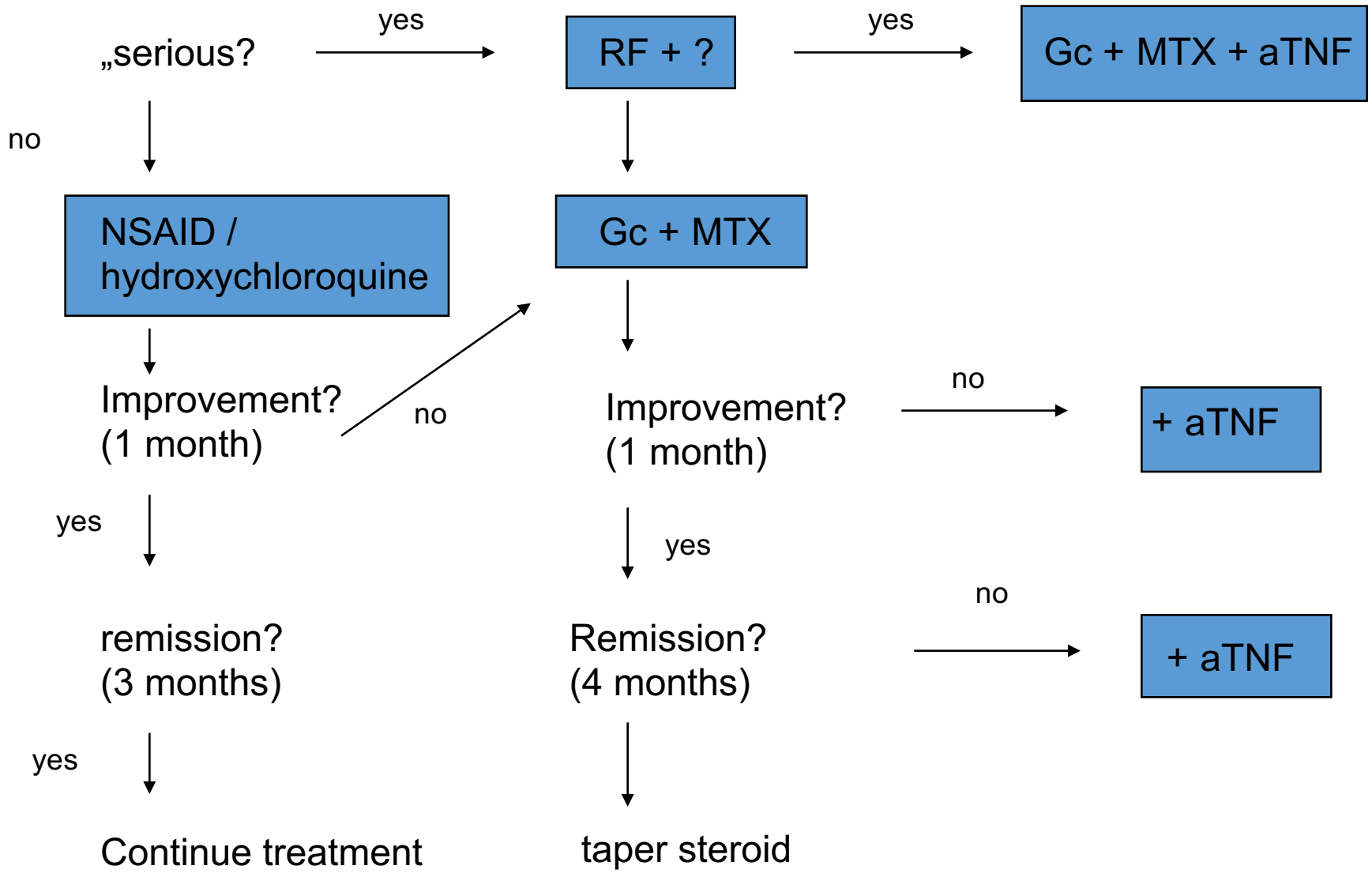
CA Wallace: Current management JIA, 2006







Polyarthritis treatment



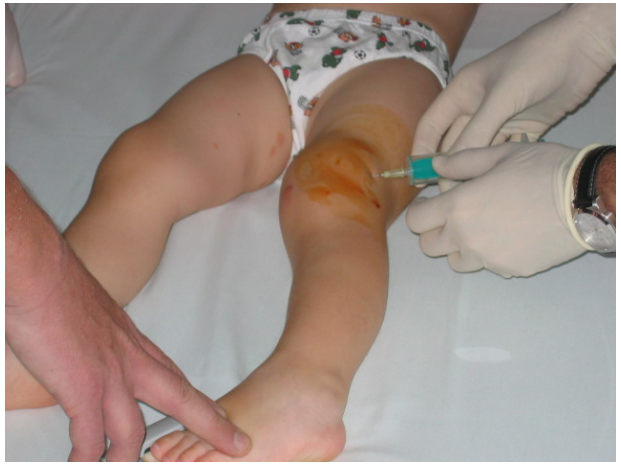
CA Wallace: Current management JIA, 2006

„Evidence - based use of MTX in children with rheumatic diseases”

- When: 6 week NSAID, or IAC
- Usual dose: 10-15 mg/m2
- Maximum dose: 20 mg/m2
- ≥ 15 mg/m2 sc / im

- Folát supplementation

Rheumatology Int 2005

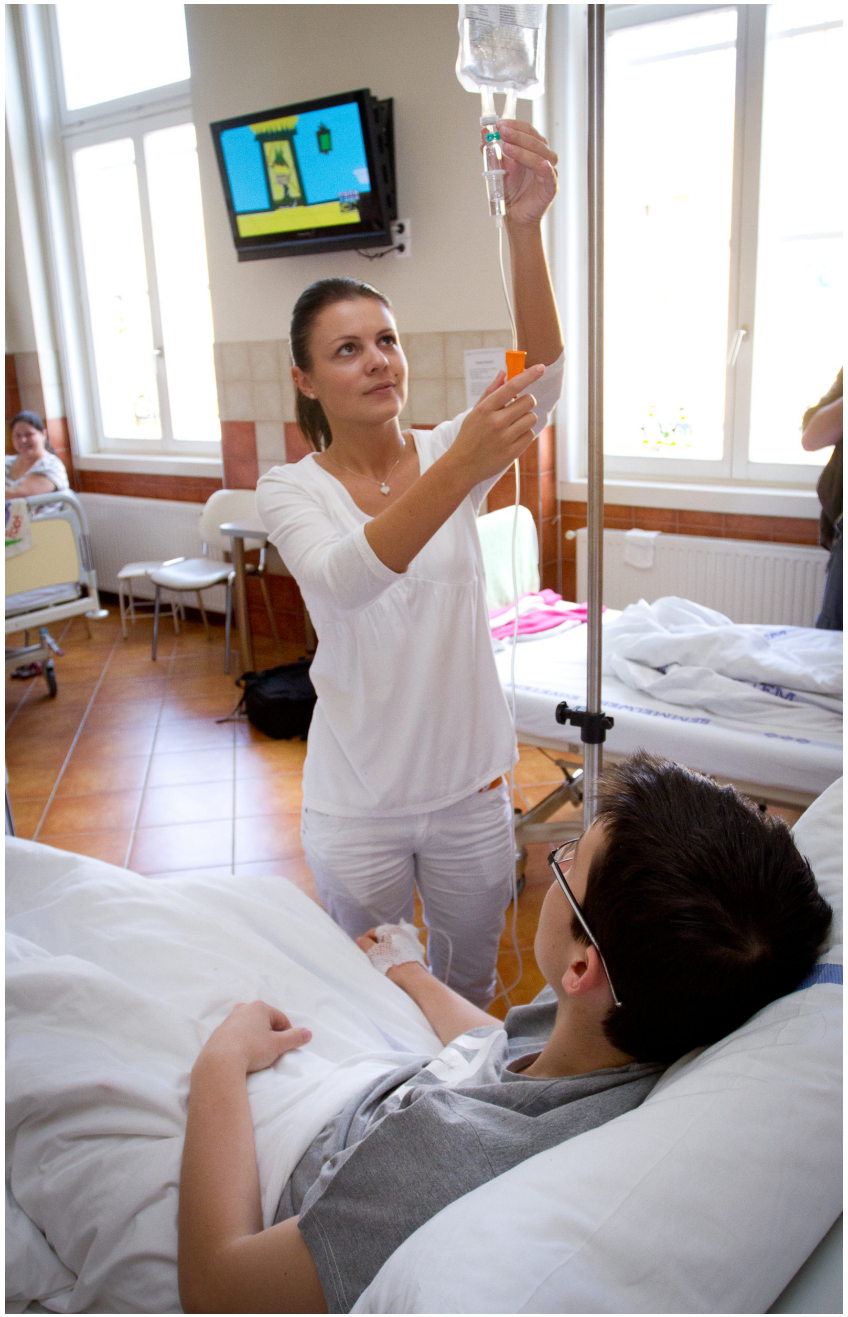



TREXAN 2,5 mg tabletta
100 db
METHOTREXATE
Hatóanyag: 2,5 mg vízmentes methotrexát (2,78 mg metotrexát formájában) tablettánként
Segédanyagként (42,0 mg) laktózt is tartalmaz
Orvosi rendelvényre kiadható gyógyszer (Sz)


Enbrel 25 mg

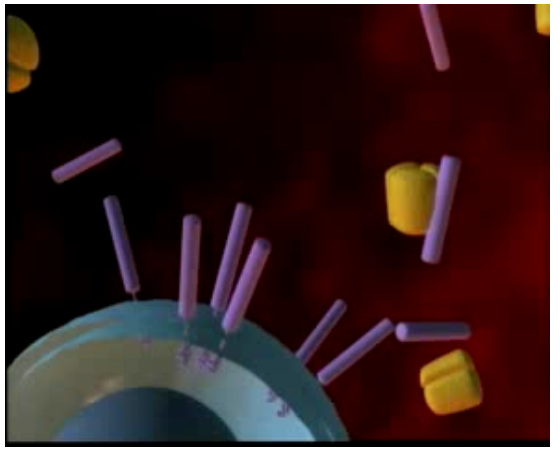
Tocilizumab (RoActemra), Remicade (infliximab)

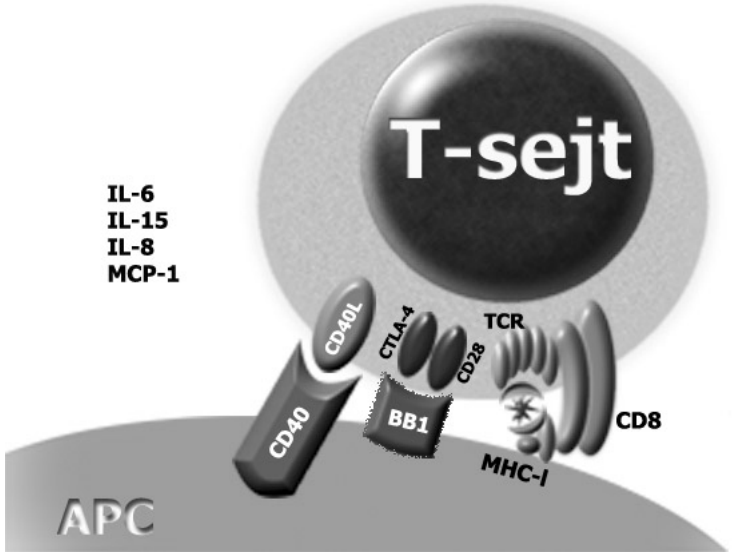
Infusion treatments

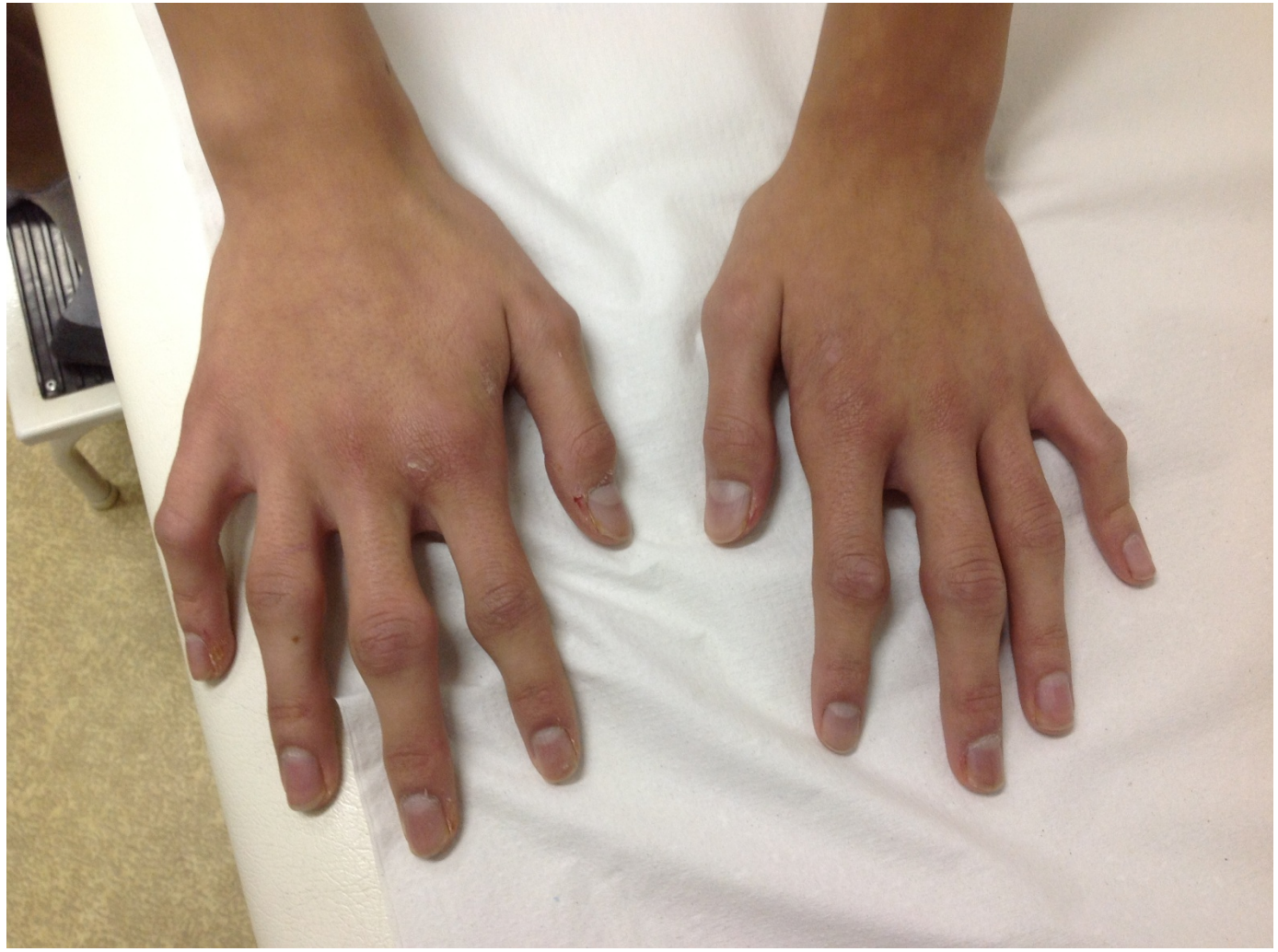


Biologicals

- **TNF antagonisits**
  - Etanercept (solubile receptor)
  - Adalimumab (humán aB)
  - Infliximab (chimera aB)
- **Il-1 antagonists**
  - Anakinra (IL-1Ra at)
  - Canakinumab (human IL-1b aB)
- **CD20 antagonists (B cells)**
  - Rituximab (anti-CD20 McAb)
- **CTLA-4 antagonists**
  - Abatacept (CTLA-4 on Ig)
- **Il-6 antagonists**
  - Tocilizumab (IL-6Ra aB)

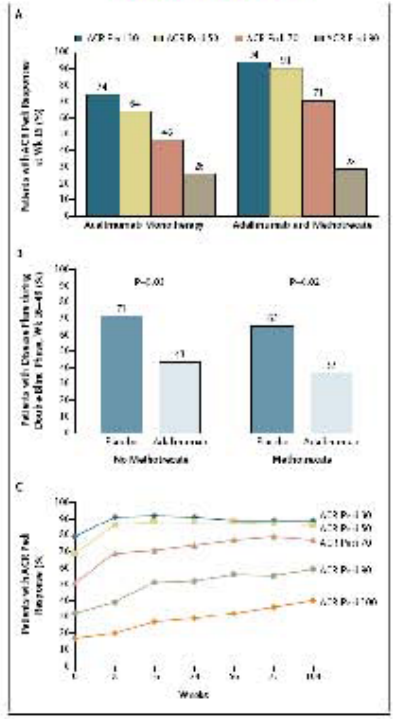






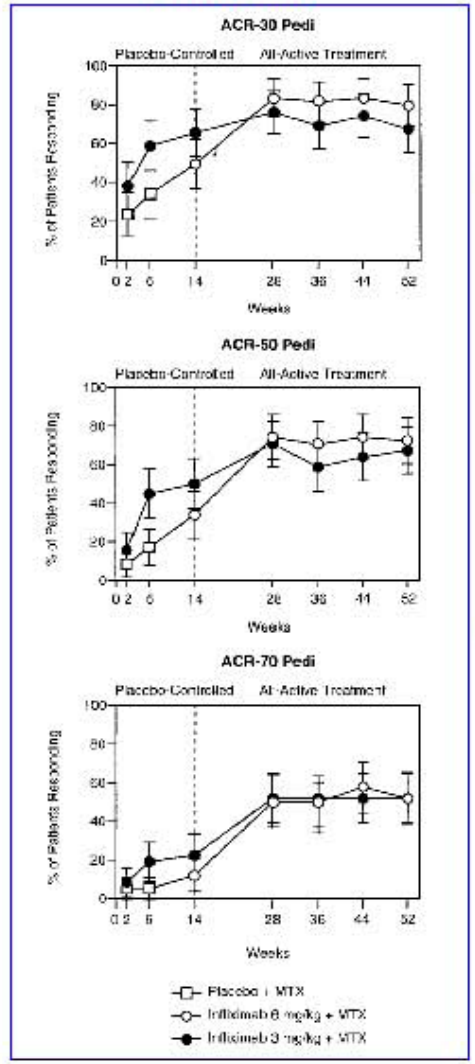
Etanercept, adalimumab, tocilizumab, abatacept: licensed for JIA

Adalimumab



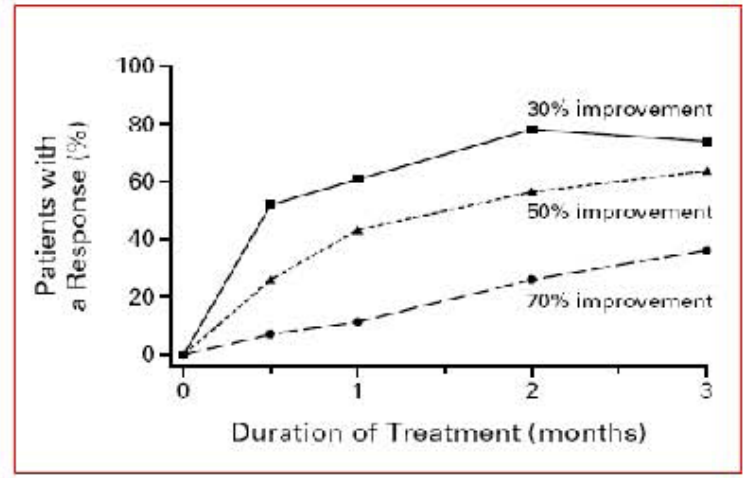
Lovell DJ et al. NEJM 2008;359:810-20

Infliximab



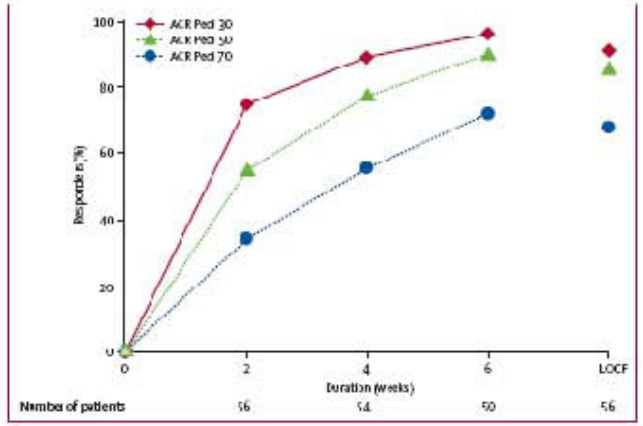
Ruperto N et al. A&R 2007;56:3096-106

Etanercept



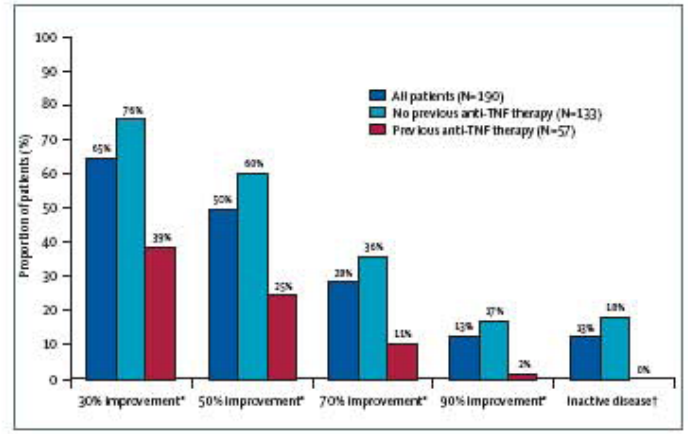
Lovell DJ et al. NEJM 2000;342:763-9

Tocilizumab



Yokota S et al. Lancet 2008;371:998-1006

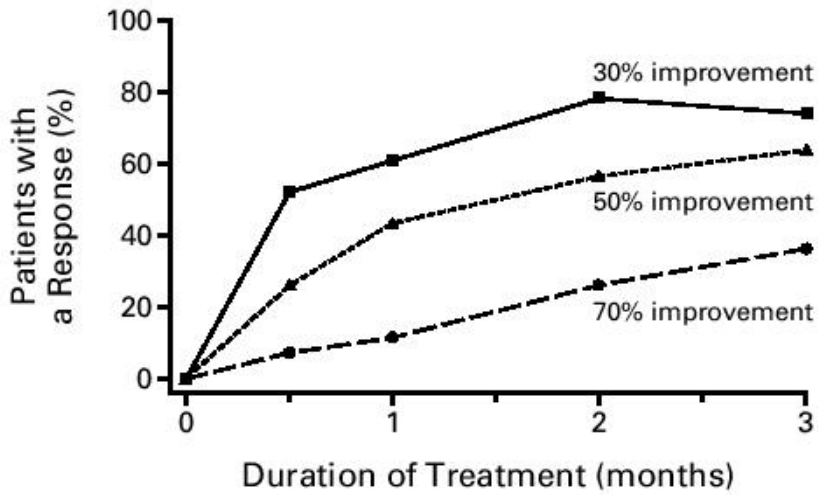
Abatacept

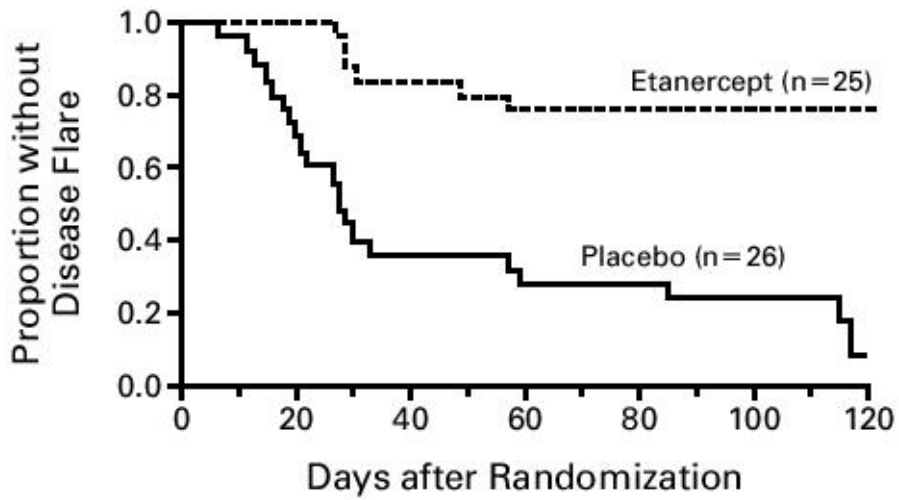


Ruperto N et al. Lancet 2008;372(9636):383-91

ETANERCEPT IN CHILDREN WITH POLYARTICULAR JUVENILE RHEUMATOID ARTHRITIS

DANIEL J. LOVELL, M.D., M.P.H., EDWARD H. GIANNINI, M.SC., DR.P.H., ANDREAS REIFF, M.D., GAIL D. CAWKWELL, M.D., PH.D., EARL D. SILVERMAN, M.D., JAMES J. NOCTON, M.D., LEONARD D. STEIN, M.D., ABRAHAM GEDALIA, M.D., NORMAN T. ILOWITE, M.D., CAROL A. WALLACE, M.D., JAMES WHITMORE, PH.D., AND BARBARA K. FINCK, M.D., FOR THE PEDIATRIC RHEUMATOLOGY COLLABORATIVE STUDY GROUP



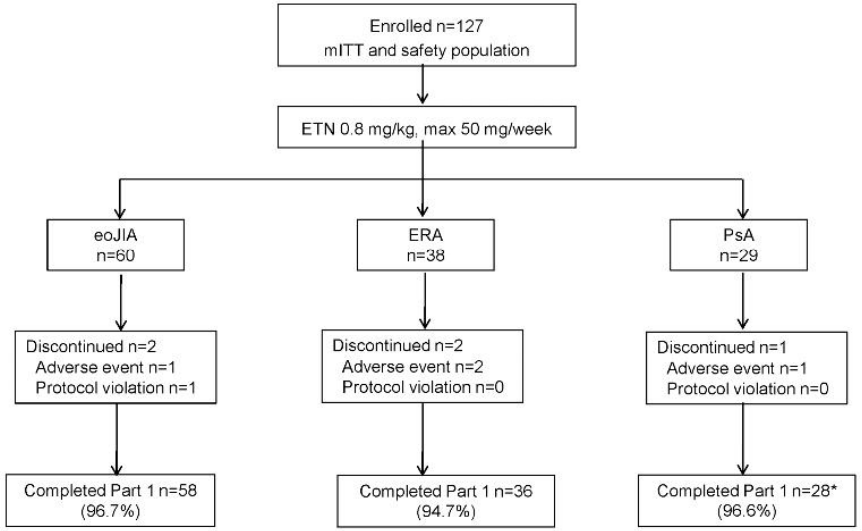


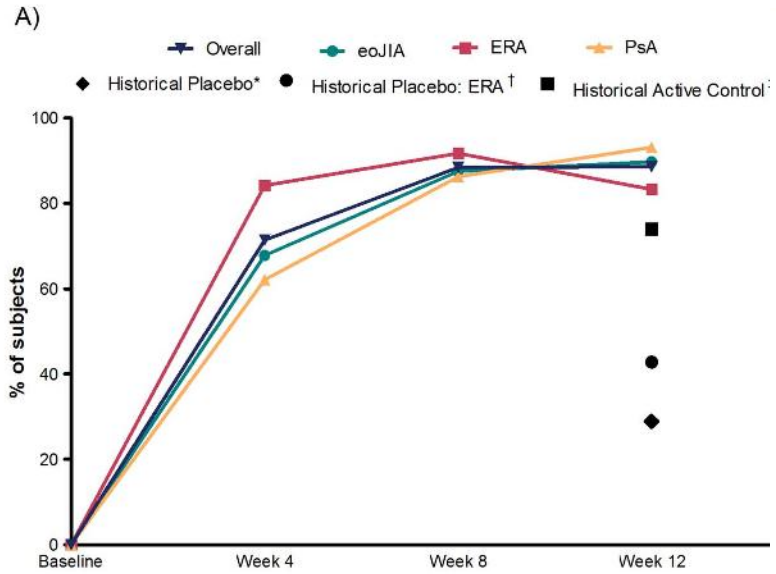
N Engl J Med

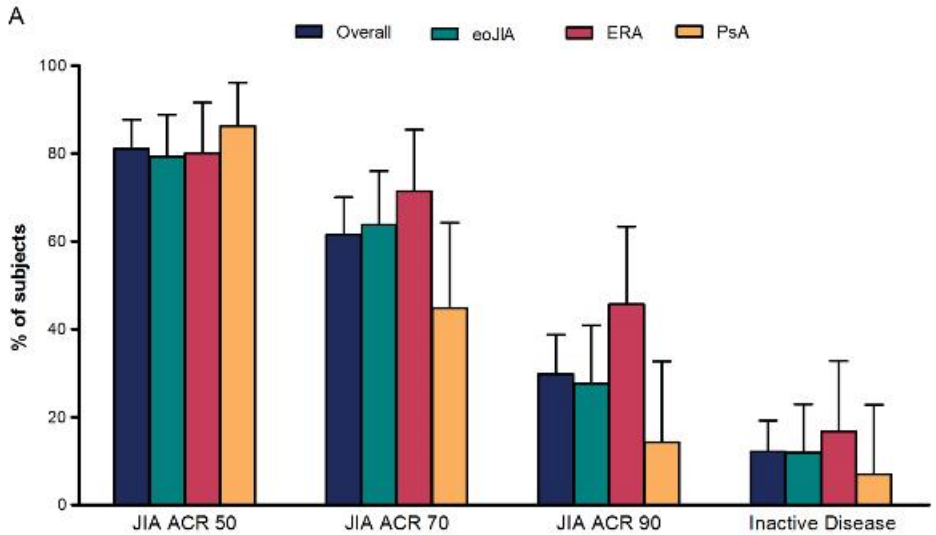
EXTENDED REPORT

Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study

Gerd Horneff,[1] Ruben Burgos-Vargas,[2] Tamas Constantin,[3] Ivan Foeldvari,[4] Jelena Vojinovic,[5] Vyacheslav G Chasnyk,[6] Joke Dehoorne,[7] Violeta Panaviene,[8] Gordana Susic,[9] Valda Stanevica,[10] Katarzyna Kobusinska,[11] Zbigniew Zuber,[12] Richard Mouy,[13] Ingrida Rumba-Rozenfelde,[14] Luciana Breda,[15] Pavla Dolezalova,[16] Chantal Job-Deslandre,[17] Nico Wulffraat,[18] Daniel Alvarez,[19] Chuanbo Zang,[19] Joseph Wajdula,[19] Deborah Woodworth,[19] Bonnie Vlahos,[19] Alberto Martini,[20,21] Nicolino Ruperto,[20] for the Paediatric Rheumatology International Trials Organisation (PRINTO)







Ann Rheum Dis. 2013 May 21.

Table 2 Changes from baseline in effectiveness measures at week 12

JIA ACR core components	Change from baseline at week 12, mean (95% CI) [%]			
	eoJIA n=58	ERA n=36	PsA n=29	Overall n=123
PGA of disease activity	−3.5 (−3.9 to −3.1) [−73.2%]	−3.9 (−4.6 to −3.3) [−70.9%]	−3.0 (−3.5 to −2.5) [−65.0%]	−3.5 (−3.8 to −3.2) [−70.6%]
Parent global assessment of child's overall well being	−2.8 (−3.5 to −2.2) [−53.1%]	−2.8 (−3.7 to −1.9) [−47.6%]	−2.4 (−3.1 to −1.6) [−47.7%]	−2.7 (−3.1 to −2.3) [−50.2%]
No. of active joints	−5.5 (−6.7 to −4.2) [−69.8%]	−4.3 (−5.4 to −3.1) [−77.7%]	−5.2 (−6.8 to −3.6) [−73.8%]	−5.1 (−5.8 to −4.3) [−73.0%]
No. of joints with LOM	−4.5 (−5.6 to −3.3) [−64.1%]	−3.4 (−4.1 to −2.6) [−67.4%]	−4.3 (−5.7 to −2.9) [−71.7%]	−4.1 (−4.8 to −3.4) [−66.9%]
CRP*, mg/l	−2.8 (−4.9 to −0.7) [−18.9%]	−13.2 (−20.5 to −5.8) [−36.8%]	−1.3 (−2.8 to −0.20) [−11.0%]	−5.4 (−7.8 to −2.9) [−22.1%]
CHAQ	−0.5 (−0.7 to −0.4) [−52.2%]	−0.5 (−0.7 to −0.3) [−57.8%]	−0.4 (−0.6 to −0.2) [−51.3%]	−0.5 (−0.6 to −0.4) [−53.6%]
Other assessments				
Parent global assessment of child's pain VAS	−3.2 (−3.8 to −2.5) [−58.9%]	−3.2 (−4.2 to −2.2) [−44.9%]	−2.6 (−3.4 to −1.8) [−46.6%]	−3.0 (−3.5 to −2.6) [−51.9%]
Morning stiffness (min)	−60.3 (−83.6 to −37.0) [−61.5%]	−65.6 (−97.6 to −33.6) [−64.1%]	−47.9 (−67.3 to −28.6) [−77.2%]	−58.9 (−73.7 to −44.1) [−66.0%]
JIA category-specific assessments				
Tender entheseal score	–	−4.4 (−6.3 to −2.4) [−57.8%]	–	–
Back pain VAS	–	−12.5 (−21.3 to −3.7) [−21.2%]	–	–
Nocturnal back pain VAS	–	−8.9 (−16.7 to −1.2) [−6.8%]	–	–
Modified Schober's test†	–	0.35‡ (−0.02 to 0.72) [9.7%]	–	–
BSA, %	–	–	−6.7 (−10.6 to −2.9) [−48.2%]	–
PGA of psoriasis§	–	–	−1.0 (−1.4 to −0.6) [−39.6%]	–

All values are the mean change from baseline (95% CI) (% change from baseline). mITT population (observed cases).
*For CRP: eoJIA n=58, ERA n=34, PsA n=28 and total n=120.
†ERA n=35.
‡change from baseline calculated after subtracting 10 from the baseline and week 12 scores.
§PsA n=28.
ACR, American College of Rheumatology; BSA, body surface area; CHAQ, Childhood Health Assessment Questionnaire; CRP, C-Reactive Protein; eoJIA, extended oligoarticular Juvenile idiopathic arthritis; ERA, enthesitis-related arthritis; LOM, limitation of motion; mITT, modified intent-to-treat; PGA, physician global assessment; VAS, visual analogue scale.

Table 3 Summary of safety findings

	No. of subjects (%)			
	eoJIA (n=60)	ERA (n=38)	PsA (n=29)	Overall (n=127)
Treatment-emergent AEs*	21 (35.0)	16 (42.1)	8 (27.6)	45 (35.4)
Treatment-emergent AEs leading to withdrawal*	0	2 (5.3)	0	2 (1.6)
Treatment-emergent non-infectious AEs in ≥5% subjects				
Headache	2 (3.3)	2 (5.3)	3 (10.3)	7 (5.5)
Abdominal pain	0	4 (10.5)	0	4 (3.1)
Diarrhoea	1 (1.7)	3 (7.9)	0	4 (3.1)
Fatigue	0	4 (10.5)	0	4 (3.1)
Pyrexia	3 (5.0)	1 (2.6)	0	4 (3.1)
Aspartate aminotransferase increased	3 (5.0)	0	0	3 (2.4)
Myalgia	0	3 (7.9)	0	3 (2.4)
Decreased appetite	0	2 (5.3)	0	2 (1.6)
Back pain	0	0	2 (6.9)	2 (1.6)
Epistaxis	0	2 (5.3)	0	2 (1.6)
Respiratory disorder	0	0	2 (6.9)	2 (1.6)
Allergic rhinitis	0	2 (5.3)	0	2 (1.6)
Wheezing	0	2 (5.3)	0	2 (1.6)
Treatment-emergent ISRs	4 (6.67)	4 (10.53)	2 (6.90)	10 (7.87)
Treatment-emergent infections	31 (51.7)	15 (39.5)	12 (41.4)	58 (45.7)
Treatment-emergent infections leading to withdrawal	1 (1.7)	0	1 (3.4)	2 (1.6)
Treatment-emergent infections ≥5% subjects				
Upper respiratory tract infection	9 (15.0)	4 (10.5)	5 (17.2)	18 (14.2)
Pharyngitis	9 (15.0)	4 (10.5)	2 (6.9)	15 (11.8)
Rhinitis	4 (6.7)	2 (5.3)	2 (6.9)	8 (6.3)
Gastroenteritis	3 (5.0)	1 (2.6)	1 (3.4)	5 (3.9)
Bronchitis	1 (1.7)	3 (7.9)	0	4 (3.1)
Sinusitis	3 (5.0)	0	0	3 (2.4)
Treatment-emergent SAEs*	0	1 (2.6)	0	1 (0.8)
Serious treatment-emergent infections	2 (3.3)	0	1 (3.4)	3 (2.4)
Infections considered preventable by vaccination in subjects not previously vaccinated	1 (1.7)	1 (2.6)	0	2 (1.6)
Medically important infections	2 (3.3)	0	1 (3.4)	3 (2.4)
Opportunistic infections	0	1 (2.6)	0	1 (0.8)

No incidences of serious treatment-emergent injection site reactions (ISRs), infections considered preventable by vaccination in subjects previously vaccinated, autoimmune disorders, demyelinating disorders, malignancies were reported and therefore not included in this table.
*Excluding infections and ISRs.
AEs, adverse events; ERA, enthesitis-related arthritis; eoJIA, extended oligoarticular juvenile idiopathic arthritis; PsA, psoriatic arthritis; SAEs, serious AEs.

New indications - etanercept

- **Polyarthritis** and **extended oligoarthritis** since **2 years of age**
- **Arthritis psoriatica** since **12 years of age**
- **ERA** since **12 years of age**

Dosage

- **0,4 mg/kg** (max 25 mg Enbrel) twice weekly

vagy

- **0,8 mg/kg** (max 50 mg) once a week

Scientific evidence – financial possibilities

Validation of the proposed ILAR classification criteria for juvenile idiopathic arthritis.

- With ILAR proposed classification criteria 88% of patients could be classified

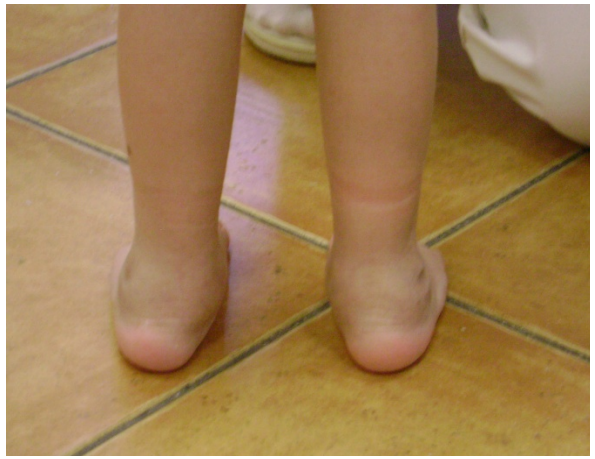
- In patients classified as "other," the psoriatic trait caused the most difficulty in classification

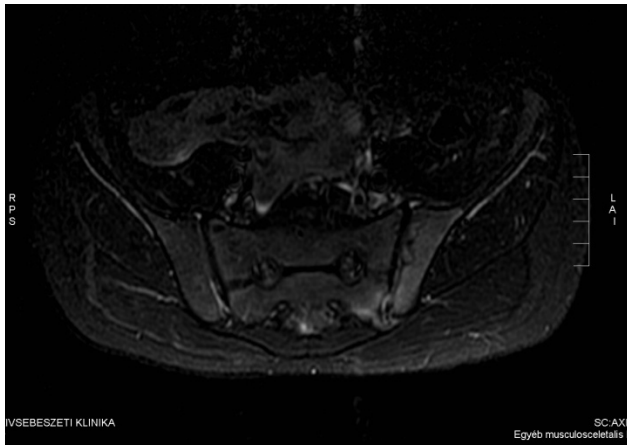
J Rheumatol. 2000 Apr;27(4):1069-72.

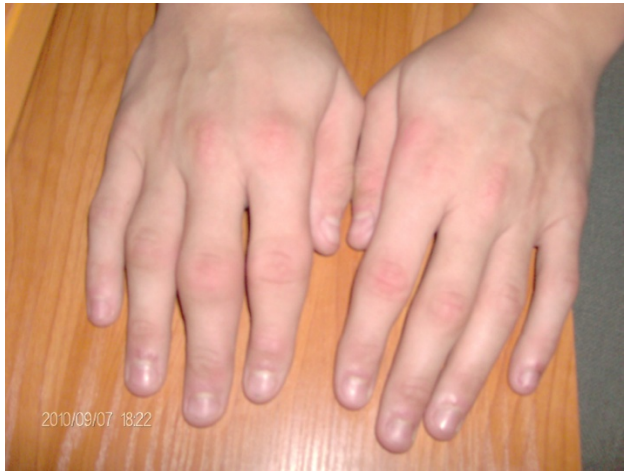
VIEWPOINT

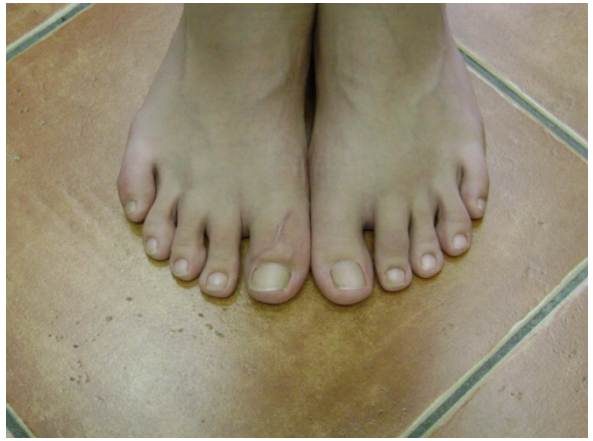
It is time to rethink juvenile idiopathic arthritis classification and nomenclature

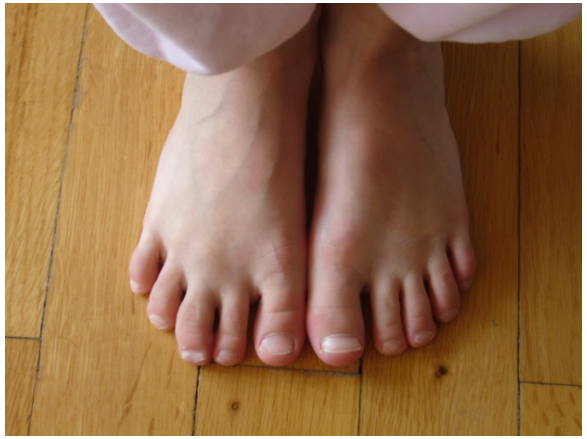
Alberto Martini

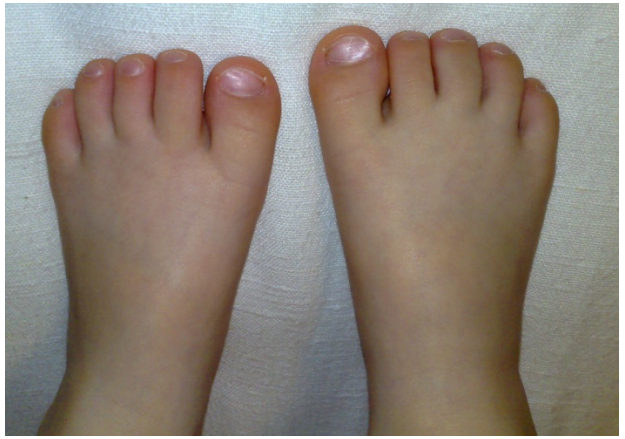




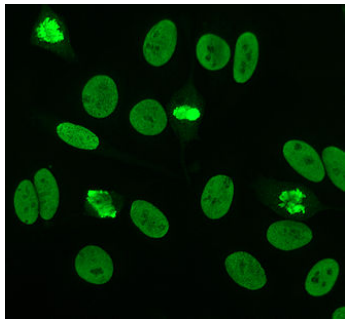






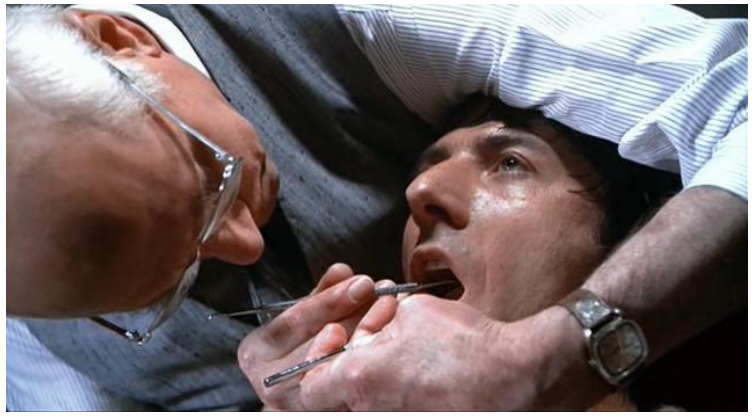


Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis



- close relationship between the presence of ANAs and
- younger age at disease presentation,
- female predominance,
- asymmetric arthritis,
- development of iridocyclitis,
- lower number of affected joints over time,
- and lack of hip involvement

Arthritis Rheum. 2011 Jan;63(1):267-75.



„Safe?”

German registry

- 604 patients
- 1149 patient year
- Etanercept monotherapy: 0.21 AEs/patient
  0.15 Aes/patient/year
- Etanercept-mtx combination: 0.34 Aes/patient
  0.16 Aes/patient/year
  - OR: 1.9 (95%, CI: 1.1 to 3.2)

G Horneff, F De Bock, I Foeldvari et al.: German JIA Registry
Ann Rheum Dis 2009;68:519–525.

Severe infection

Etanercept monoterápia	Etanercept – methotrexat kombináció
n=100	n=504
Herpes zoster	soft tissue/skin infection (3) septic arthritis sepsis Herpes zoster (2) Varicella gastroenteritis (2) UTI upper airway infection (8) pneumonia (3) other (3)

German JIA Registry
Ann Rheum Dis 2009; 68:519–525.

Severe infections

ACR Keystone Pediatric Rheumatology Symposium

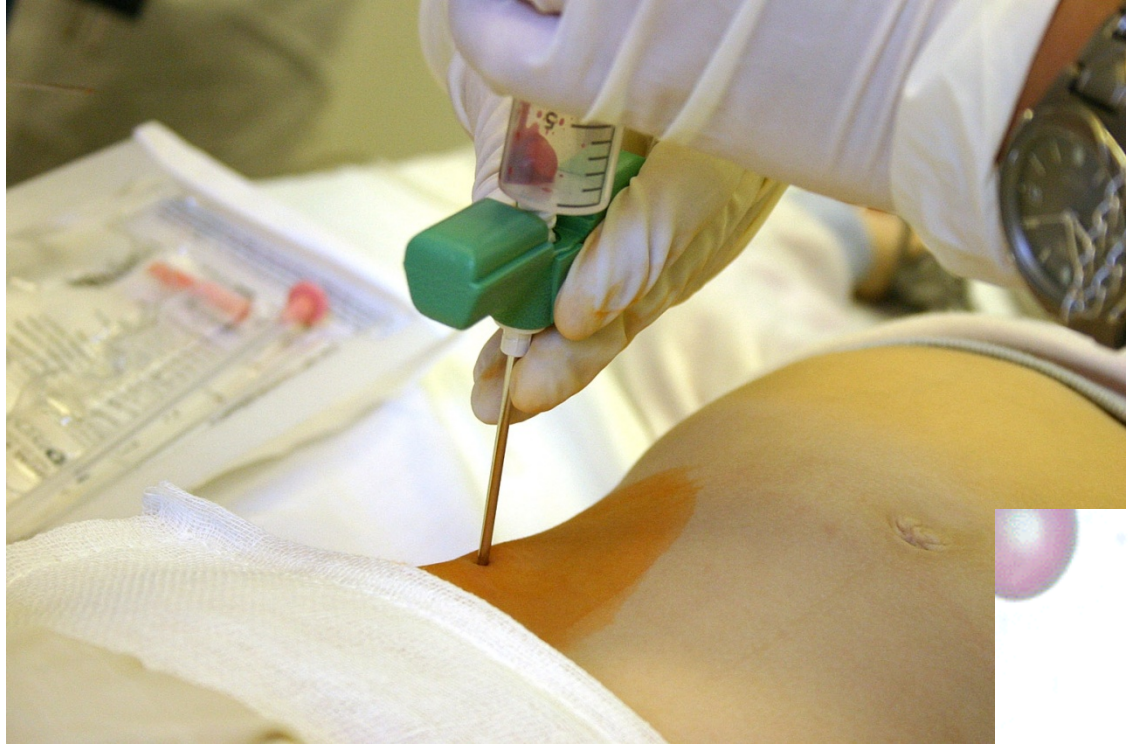
198 patients, 1208 patient-year:

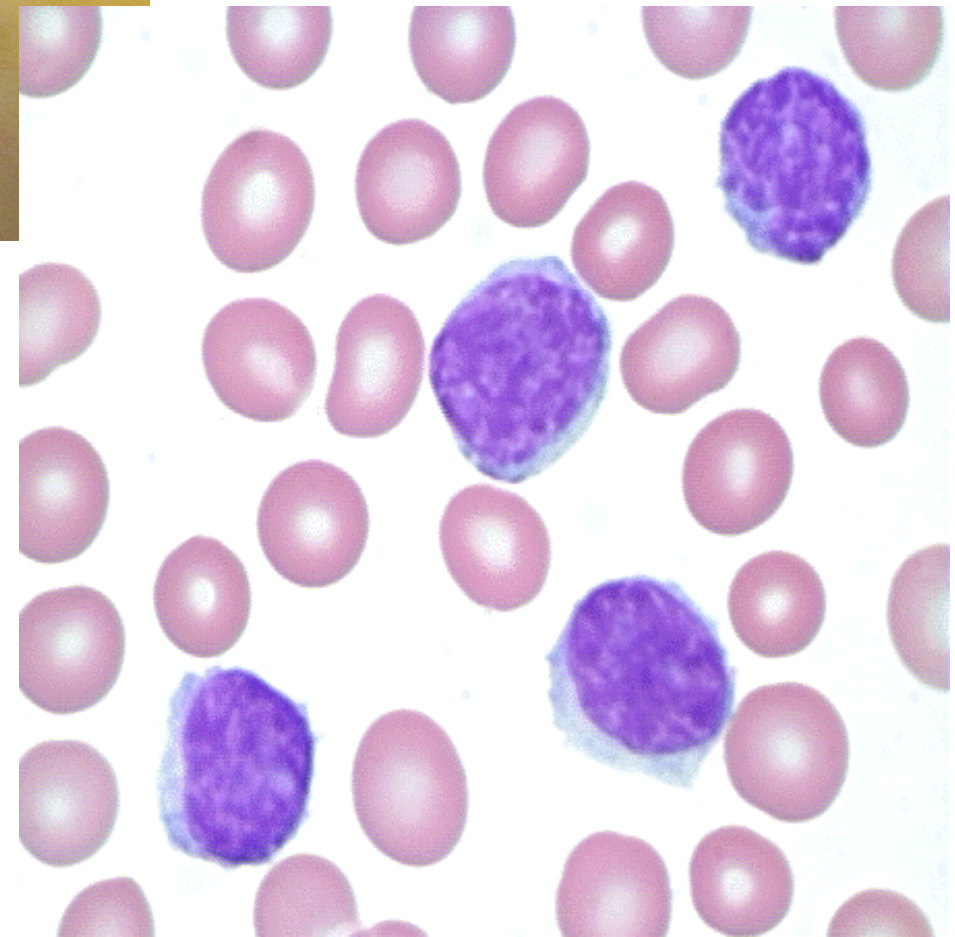
- Mtx
- Mtx- etanercept
- Etanercept

<u>SAE:</u>

SAE and new anti-drug antibodies are same on the 3 „arms”

Severe infection: 0,01 event/ patient- year





Cancer inicidence (USA)

INFLIXIMAB:

- 0,66 malignoma / 1000 patient / year

ETANERCEPT:

- 0.22 malignoma / 1000 patient / year

Background inicidence :

- 0.17 malignoma / 1000 children / year

Biologicals– practical issues

Rule out:

- Severe infection (latent tbc: relative CI)
- Malignt disorders
- Chronic virus infections (HCV, HIV)
- Cytopenias (aplasticus anaemia)
- NYHA Class III-IV cardiac failure
- Certain neurological disorders (elsősorban demyelinisatio)
- Lupus, or „lupus-like” diease (aDNS aat: relatív KI)
- Pregancy

Investigations before treatment

- Physical
- Labs: We, CRP, blood count, GPT, GGT, kreat, BUN, CK, ANA (aDNS), serology (virus: VZV, HIV, HCV)
- TBC:
  - X-ray
  - PPD/Quantiferon

Immunisation during anti-TNF treatment

- Live vaccines are contraindicated

- MMR? No active disease after accidental vaccination and good response

Rheumatology 2009

Vaccination should be considered

- Influenza (Ann Rheum Dis, 2005)
- Varicella (low dose steroid and mtx)

EULAR recommendations for vaccination in paediatric patients with rheumatic diseases
Ann Rheum Dis 2011;**70**:1704–1712

If the patient is varicella contact during treatment

- VZV serology poz: monitor
- VZV serology neg: VZIg (4 weeks)
- Florid varicella: treatment stop and acyclovir

Follow up

- Advocate healthy and active life style
- Advice against risky behaviours
- Alcohol consumption
- Tobacco use

BLOOD LIMITS

- GOT/GPT > 2X upper limit of normal
- Hb < 100 g/l
- Neu < 1.5 G/l
- Thr < 150 G/l

If your patient needs surgery

- Stop treatment and think about the half life
  - Etanercept (Enbrel): 100 h (4 days)
  - Infliximab (Remicade): 10 days
  - Adalimumab (Humira): 15-20 days
- Healing and no infection: treatent can be re-introduced