Update in paediatric rheumatology

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Outline

- History: paediatric rheumatology 20 years ago
- The change
  - International research collaboration
  - New therapies
- Where are we now?
  - Juvenile idiopathic arthritis
  - Juvenile SLE (systemic lupus erythematoses)
  - Juvenile Dermatomyositis
  - Systemic vasculitis
  - Periodic fever syndromes
History:
Paediatric rheumatology 20 years ago

Physiotherapy
Occupational therapy
Splints, supportive measures
Surgery
Characteristic pattern of growth deformities
«Natural» course of juvenile arthritis

- Joint deformation and destructions
- Growth problems
  - Localized
  - Generalized: characteristic pattern of growth deformities
    - Short stature
    - Changed body proportions:
      - Normal head with significant retro-/micrognathia
      - Short extremities
      - Deformities of fingers/toes and hand/feet
The change: Internationale research collaboration

- Paediatric Rheumatology INternational Trials Organization – PRINTO

  Founded 1996 with 14 participating countries, now 60 countries and 550 centres
  - Randomized controlled multicenter studies
  - definition and validation of outcome criteria and development of tools (response, activity, damage, quality of life, improvement, inactive disease)
  - Patient information translated in >60 languages
  - Consensus procedures for diagnostic criteria and treatment guidelines
  - Eurofever registry for autoinflammatory diseases

- Pediatric Rheumatology Collaborative Study Group - PRCSG
The change:
New drugs - biologics

- Current EMA/FDA paediatric indication
- Approved for use in paediatric arthritis
- No longer recommended
- Approved for use in adult arthritis only, but recommended in some instances of JIA
- Approved for use in adult arthritis only

- Tofacitinib (JAK3-inhibitor)
- Ustekinumab (Anti-IL-12/IL-23)
- Certolizumab (TNF inhibitor)
- Golimumab (TNF inhibitor)
- Canakinumab (Anti-IL-1)*
- CAPS (≥2 yo, ≥7.5 kg), sJIA (≥2 yo)
- Tocilizumab (Anti-IL-6R)*
- sJIA (≥2 yo), pJIA (≥2 yo)
- Abatacept (co-stimulation blockade)*
- pJIA (≥6 yo)
- Rituximab (Anti-CD20/B cell depleting agent)
- Adalimumab (TNF inhibitor)*
- pJIA (≥2 yo)
- Anakinra (IL-1-RA)
- CAPS (≥8 months, ≥10 kg)
- Etanercept (TNF inhibitor)*
- pJIA (≥2 yo), E-pJIA (≥6 yo), psA (≥12 yo), ERA (≥12 yo)
- Leflunomide (cDMARD)*
- Infliximab (TNF inhibitor)*
- Methotrexate (cDMARD)*
- Polyarticular courses of JIA
- Sulphasalazine (cDMARD)
- pJIA, pJIA, non-axial ERA (≥6 yo)
- Ciclosporin A (cDMARD)
- Azathioprine (cDMARD)
- Penicillamine (cDMARD)
- Chloroquine or hydroxychloroquine (cDMARD)
- Gold (cDMARD)

What are biologics?

- Proteins constructed to bind to cytokines or their receptors
- Blocking or enhancing the effect of cytokines
The way of action is in the name!

Suffix

- **cept** (etanercept, rilonacept, abatacept): soluble receptor
- **ximab** (infliximab, rituximab): *chimaeric monoclonal antibody*
- **umab** (adalimumab, golimumab, canakinumab): *human monoclonal antibody*
- **ra** (anakinra): receptor antagonist
- **inib** (tofacitinib): inhibitor
What is special about biologics?

**Advantages:**
- Specific, targeted action
- Very effective
- Little (immediate) side effects

**Disadvantages:**
- Parenteral application
- Induction of anti-drug antibodies, allergic reactions (local/systemic)
- May cause immune-dysfunction => increased risk for
  - Infections
  - Cancer (?)
  - (New) autoimmune diseases
Biologics currently used for rheumatologic diseases

- **TNFα – Blocker**: etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®), golimumab (Simponi®)
- **Anti – Interleukin 1**: anakinra (Kineret®), canakinumab (Ilaris®)
- **Anti – Interleukin 6**: tocilizumab (Actremra®)
- **Anti – CD20**: rituximab (MabThera®)
- **T-cell Co-stimulation inhibitor**: abatacept (Orencia®)
- **Anti – Interleukin 23**: ustekinumab (Stelara®)
- **BLyS - inhibitor**: belimumab (Benlysta®)
Rheumatoid factor and other autoantibodies

Interleukin-4
Interleukin-6
Interleukin-10

Th0

Interferon-γ
Interleukin-12

Th2

Interferon-γ

CD4+ T cell

CD69

CD11

OPGL

Osteoclast

Fibroblast

Chondrocyte

Synovium

Production of metalloproteinases and other effector molecules

Migration of polymorphonuclear cells

Erosion of bone and cartilage
Disease activity

Number of active joints
Average per consultation

- Active
- Limited range of motion

1995 1997 1999 2001 2002 2003 2004

H. Brunner, Poster ACR 2006
Where are we today?
Juvenile idiopathic arthritis

Individualised therapy

Disease activity – risk factors
- NSAIDs
- Intraarticular steroid injections
- Conventional immunosuppression (MTX)
- Biologic drugs

Treatment goal: complete remission!

Prognosis
- Early, aggressive treatment reduces long term damage!
- New drugs: remission possible in nearly 100% of cases
- Long term studies: 80% of patients will experience disease flares in adult life
Hot topics

- Temporo-mandibular joint arthritis:
  - More common than expected, 70-80% at the time of JIA diagnosis
  - Onset asymptomatic in 80%
  - Less responsive to treatment than other joints?

- Uveitis:
  - 10-20% of all JIA-cases, usually asymptomatic onset
  - Risk factors: early onset of JIA, positive ANA, JIA subtype
  - Some TNF-blockers are less effective for uveitis than others
  - No randomized controlled studies
Systemic JIA

- Characteristic daily spiking fever, rash, hepatosplenomegaly, lymphadenopathy, serositis
- Disease course patterns:
  - Persistent polyarthritis
  - Persistent systemic inflammation
  - Flares of acute systemic inflammation.
- Does not respond well to TNF-blocade, but improves with IL-1 and IL-6-blockade
- Makrophage-Aktivation-Syndrome!!

=> Debatte: Is it an autoimmune disease or is it rather autoinflammatory?
Where are we now? Juvenile SLE (systemic lupus erythematoses)

- Inflammatory **Multisystem** disease
- Hallmark: **Auto-Antibodies**
- Complement consumption => acquired «immune deficiency»

- 20% onset < 18 years
- Prevalence 10-20/100,000 <18J (Europeans)
- Most common age at diagnosis: 11-14 years
- F > M 9 :1 (prepubertal less discrepancy)
- Higher prevalence in black, asian and south american descent

**SLE-Classification Criteria**

ACR – American College of Rheumatology

- Butterfly rash
- Orale/nasale ulcers
- Photosensitivity
- Discoide skin lesions
- Arthritis
- Pleuritis/Perikarditis
- Hematologic manifestations
- Neurologic manifestations (Krampfanfälle, Psyche)
- Kidney involvement (Glomerulonephritis)
- Autoantibodies
- Positive ANA

At least 4/11 necessary
Symptoms:
- Every patient is different!
- Non specific general malaise
- Specific organ manifestations

Blood tests:
- BSR ↑↑, (CRP), Lymphopenia
- Organ specific
- Auto antibodies (ANA, anti-DNS, …)

Treatment:
- Depends on organ involvement
- Steroids for the induction of remission
- Immunosuppression for maintenance of disease remission
- Plaquenil!

Prognosis:
- Depends on organ involvement (kidney, CNS)
- Depends on compliance with treatment
- Long term damage is organ spezific and treatment associated!
What is new?

- Improvement of outcomes through better and standardized treatment
- Treatment studies for kidney involvement: replacement of cyclophosphamide for long term treatment is safe
- New drugs:
  - Anti-CD20 (MabThera®): did not fulfill the great expectations
  - **Belimumab (Benlysta®)**: blocking BLyS (B lymphocyte stimulator), first FDA approved drug specifically for the treatment of SLE
Where are we today?
Juvenile dermatomyositis (JDM)

- **Dermatitis** (typical rash)
  - Face (heliotrope)
  - Extensor surface over joints (Gottrons papules)
  - Periungual edema (capillary angiopathy)

- **Myositis** proximal muscles (shoulder girdle, hip girdle)
  - Presentation may not be at the same time!
Epidemiology

- Prevalence 0.5-1/100,000 children
- Peak age 3-10 years
- F:M approx. 2:1

Treatment + disease course

- Early aggressive therapy (high dose steroids, MTX)
  - 60-70% good prognosis (monocyclic)
- Most important long term problem: calcinosis (40%)
What is new?

- Development of instruments for the standardized documentation of disease activity and organ damage (Myositis activity scale, Myositis damage index, …)

- Treatment study (PRINTO) comparing 3 treatment variants
  - Steroids alone
  - Steroids in combination with methotrexate
  - Steroids in combination with ciclosporine

⇒ Evidence based treatment recommendation for newly diagnosed juvenile dermatomyositis
Where are we today?
Systemic childhood vasculitis

**Symptoms suggestive for vasculitis**
- Fever, weight loss, fatigue of unknown cause
- Skin manifestations (palpable purpura, vasculitic urticaria, livedo reticularis, erythema nodosum, panniculitis, ulcers)
- Neurologic symptoms (headache, mononeuritis multiplex, focal CNS lesions, stroke)
- Arthritis/arthralgia, myositis/myalgia, serositis
- Hypertension
- Pulmonary infiltrates, pulmonary hemorrhage
- Systemic inflammation (laboratory)
- Hematuria/proteinuria

**Classification of childhood vasculitis** *(Wien 2005)*

**Large vessel vasculitis**
- Takayasu arteritis

**Medium sized vessel vasculitis**
- Kawasaki disease
- Childhood polyarteritis nodosa / Cutaneous polyarteritis

**Small vessel vasculitis**

a) Granulomatous
- Wegener’s granulomatosis
- Churg Strauss syndrome

b) Non – granulomatous
- Hennoch Schönlein purpura
- Microscopic polyangiitis
- Isolated cutaneous leucocytoclastic vasculitis

**Other vasculitides**
- Behcet’s disease
- Vasculitis secondary to infections, malignancies and drugs
- Isolated vasculitis of the CNS

S Ozen, Ann Rheum Dis / Ped Nephr 2006
Kawasaki Syndrome

Fever ≥5 days plus

- Lymphadenitis colli >1.5cm
- Conjunctivitis
- Orale manifestations
- Rash
- Extremity manifestations (4 of 5, cumulative)

=> IVIG 2g/kg + aspirine
Kawasaki – what is new?

Kobayashi-Score

- Serum-Na <133 (2 points)
- ALT>100U/l (2 points)
- Neutrophils >80% (2 points)
- Fever ≤4 days (2 points)
- CRP >100mg/l
- age <1year
- Plts<300’000/ul (1 point each)

Score ≥5 = «high risk»
⇒ add prednisolone i.v. 2mg/kg until CRP normal
⇒ significantly reduced rate of coronary aneurysm

Kobayashi et al, Lancet 2012
Hospach et al, Monatsschrift Kinderheilk 2013
Where are we today?
Periodic fever – Autoinflammatory Syndroms

- Great progress with Classification (Genetics!)
- International collaborations: Eurofever registry, Orphanet
  - Analysis of larger cohorts: information about clinical variability
  - Genotype – phenotype correlation
  - Publication of new diseases (Genetics!)
- Important disease groups
  - Cryopyrine associated periodic syndromes (CAPS)  
  - CINCA/NOMID: Chronic infantile neurologic-cutaneous-arthropathy / neonatal onset multisystem inflammatory disease (NOMID)
  - Muckle-Wells syndrome
  - Familial cold associated urticaria
  - Familial mediterranean fever (FMF)  
  - Mevalonatkinase deficiency
  - PFAPA, TRAPS, PAPA, …

IL-1 - Blockade
Colchizine, (IL-1 –Blockade)
CNS-Vasculitis

- rare!
- Diagnosis can be very difficult!
  - Unspecific symptoms
  - Unspecific laboratory changes
  - Often only minimal pathologic results
    - increased opening pressure (lumbar puncture)
    - Slightly increased cell count
    - protein↑, oligoclonal bands
  - Diagnostic imaging may give normal results!! (Dg from brain biopsy!)

Clinical signs:

- New neurologic symptoms/Ausfälle (focal or diffuse)
  - large - medium vessels: stroke (e.g. post-Varicella)
  - small vessels: diffuse neurologic or psychiatric symptoms, seizures, changes in brain function according to localisation
- Inflammation of the vessel wall (MRI – Angiography - MR Angio)

Treatment:

High dose steroids and immunosuppression => significant neurologic improvement!
Conclusion

- Enormous progress regarding knowledge of pathophysiologic mechanism of paediatric rheumatic diseases
- Enormous developments in treatment options for many diseases
- Revolution in the treatment of juvenile arthritis
- International collaboration is inevitable for this exciting process!
- There is still much to do!
Thank you for your attention!