Treatment of Juvenile Idiopathic arthritis (JIA) in the biologics-age

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Abstract

Quality and results of treatment in rheumatic and autoinflammatory diseases of childhood and adolescent have made substancial progress within the last two decades. This has been determined through different factors:

- Medical treatment has gained effectiveness by the introduction of new drugs
- Provision of units specialized on childhood rheumatology has been substancially improved
- Multidiszipline concepts of treatment and educational programms have been established in specialized centers
- Functional treatment has been further developed introducing even sports-therapy

This paper summarizes some of the important developments in pediatric rheumatology using Juvenile idiopathic arthritis (JIA) as an exemplification.

Keywords

Juvenile Idiopathic Arthritis, pediatric and adolescent rheumatology, multidisciplinary therapy, biologics, vasculitis, collagenosis, children

The field of pediatric rheumatology includes a large number of different inflammatory diseases affecting the musculoscelettal system and/or the connective tissue. While in Juvenile idiopathic arthritis (JIA) the main symptome is inflammatory arthritis, other diseases like vasculitis (e.g. M. Behçet, Purpura Henoch-Schoenlein) and collagenoses (e.g. Systemic lupus erythematodes, Juvenile dermatomyositis) may become manifest even with multi-organ involvement. Most of the diseases within this group develop from autoimmune pathogenesis, engaging the adaptive immune system in an autoaggressive matter to attack autologous structures. Additionally there is a large number of mainly, extremly rare autoinflammatory diseases, namely the periodic fever syndromes (e.g. familiar mediteranean fever, cryopyrin associated periodic syndrome) resulting from hereditary deviations of the innate immune system [1].

Diagnosis

Prior to treatment a correct diagnosis is mandatory. As many pediatric rheumatic diseases are very rare, early symptoms will frequently be missinterpretated. Special examinations are required concerning the overall status of the patient (pediatric rheumatologist, physiotherapist), organ involvement (e.g. pdiatric cardiologist, ophthalmonologist etc.), imaging (x-ray, ultrasound, MRI), laboratory and more. This teamwork of specialist is well established in tertiary centers specialized in pediatric rheumatology.

The majority of patients (≈ 75%) with a pediatric rheumatic disorder suffers from Juvenile idioathic arthritis (JIA), a term comprising 8 subtypes according to the ILAR (international league against rheumatism) classification criteria [2]:

(i) Systemic JIA,
(ii) persistent oligoarticular JIA,

(iii) extended oligoarticular JIA,

(iv) seronegative polyarticular JIA,

(v) seropositive polyarticular JIA,

(vi) Enthesitis associated JIA,

(vii) Psoriasis-JIA,

(viii) undifferenciated JIA.

These subtypes differ not only according their presentation (number of joints, joint pattern etc.) but as well concerning extra-articular manifestations (uveitis, enthesitis, cutaneous involvement, carditis, nephritis etc.), course and prognosis. The ILAR classification mainly depends on the symptoms presenting at the onset of the disease. But it may need several month to give a definite diagnosis in JIA, as for example oligoarticular JIA will need a minimum of 6 month monitoring to decide wether the child suffers from persisting (maximum of 4 joints affected) or extended (more than 4 affected joints) oligoarticular JIA. Initially undifferentiated forms may may switch to a definit subtype within the course [3]. Moreover a number of patients may switch from one subtype to another within their course of disease [4]. Thus treatment of JIA is not based on the classification subtype but the individual disease acitivity and extra-articular manifestations (see figure 1) [5-7]. Moreover the age of the patient, co-morbidities and undesirable effects of the medication or even intolerance have to be considered.

Figure 1: Escaltation of treatment oligoarticular JIA

Drug therapies

There has been substancial progress in the treatment with antirheumatic drugs in children and adolescents within the past two decades. While non-steroidal-antirheumatic-drugs (NSAID) and steroids have been used since the early sixties, disease-modifying-drugs (DMARD) and biologics had been the precursors for the much favourable outcome in JIA today (see Tabs 1, 2).

Table 1: Drugs in childhood rheumatology

The introduction of the DMARD methotrexate (MTX) in the treatment of JIA initiated by the center in Garmisch-Partenkirchen has been the signifincant step forward in the 90-ties of the last century [8]. Today arround 60% of the patients suffering from polyarticular JIA are receiving MTX as their base drug (according data from the German research center for rheumatology (DRFZ), Berlin). Coming up with the 21st century biologic-drugs set up the next step introducing treatment opions even in severe cases of JIA, like the systemic subtype (SoJIA) [9]. It is noteworthy that more than 50% of SoJIA patients did not reach a sufficient controll of disease activity even after 10 years of treatment in the 80-ties of the 20th century .Those patients were prone for the development of severe damages like systemic amyloidosis and/or hip-arthrosis [10]. During the multicenter studies for the approval of Canakinumab (Ilaris™) [11,12] and Tocilizumab (RoACTEMRA™) [13] more than 70% of the SoJIA patients reached a pedACR70 within one year.

In Germany around 22% of all patients with are currently treated with biologics, due to their disease course. The highest rates of JIA patients on biologics are found in the systemic-onset-, the polyarticular- and the Psoriasis-JIA subgroups [14]. The broadened spectrum of effective drugs has led to new alternatives tob e used in order for a stepwise escalation of treatment whereever indicated by the individual course of disease [15]. There have been set-up recommendations [5,16] and evidence-based guidelines [6] for different subtypes and drugs.

The introduction of biologic agents into childhood rheumatology had been accompanied by several phase II and phase III studies proving efficacy and safety of these drugs in children (e.g. [11,13,17]). Moreover there have been several independent registries established to collect data on long-term safety of these drugs [18-20].

Tabelle 2: Biologic drugs currently used in pediatric rheumatology

Despite many new drugs being approved for a „labeled“ treatment in children with certain rheumatic diseases there are many patients still receiving „Off-Label“-therapies [21,22]. This is due to the fact that: (i) many diseases are too rare to establish studies including enough patients and (ii) that patients suffering from very severe courses or rare complications will need sufficient treatment immediately.

As drugs have become more effective in suppressing immune reactions, growing interest has developed concerning the prophylaxis of infectious diseases in immunocomprised patients. Special concepts and recommendation according vaccinations and medical prophylaxis have been established for pediatric patients with rheumatic diseases [23-26].

Surgical treatment with synovectomies and/or endoprothesis of joints with severe distructions are only exceptionally required nowadays. This is one oft he results from better medical treatment within the last 20 years. Nevertheless there are still some patients with an overall well controlled disease but a local inflammation inresponsive to treatment just in one joints. Arthroscopy with synovectomy might be a helpfull approach in those cases [27].

Treatment in pediatric rheumatology is a multiprofessional task

Apart from the substancial progress in drugs for pediatric rheumatic diseases there have been specialized structures and provisions developed in many countries. Starting with London in 1947 and the German Center for pediatric and adolescent rheumatology in Garmisch-Partenkirchen in 1952 (www.rheuma-kinderklinik.de, https://en.wikipedia.org/wiki/German_Center_for_Pediatric_and_Adolescent_Rheumatology) centers for pediatric rheumatology have been founded all over the world. Educational programms for trainees, special sientific working groups and national as well as international collaborations [28,29] have been set up. There is quite variability comparing the structures for pediatric rheumatology in different countries [30], but genral consense that children and youngsters suffering from rheumatic diseases should be seen by an expert specially educated in pediatric rheumatology.

Arthritis in childhood leads to significant changes not only in the affected joints, but in the range of motion of the affected extremities [31,32]. Moreover the neuro-muscular development of the children may be disturbed significantly, especially in young children

[33]. Despite sufficient drug treatment JIA-patients need specialized and continuing functional treatment helping them to regain age-based functional capacity. Treatment strategies therefore involve physiotherapists, social workers and others as well (see figure 2) [6,34-39].

Figure 2: Multidisciplinary concept developed in Garmisch-Partenkirchen:

Integration of different professionals (left side); Physiotherapy may be fun: Integrating „boldering“ (therapeutical climbing) into treatment (right side)

Physiotherapy/physical therapy

In patients with JIA re-gaining the full range of motion and function of the affected joints is the main task of treatment apart from stopping inflammation. Functional treatment with physical medicine and physiotherapy are mandatory elements of a successfull multidisciplinary treatment approach. Active arthritis needs minimal handling with only passive movements, pain releave and protection of joints from development of contractures. When inflammation is under controll and inactive disease is archieved, there will be more and more active exercises integrated into treatment. Finally having reached the state of remission patients should be adviced to return to normal physical activities including sports [35]. This approach adapted to disease activity and the controll of inflammation requires individualized training programms complided by a team of experts including physiotherapy, physical medicine, massage, ergotherapy and sports-physicians. There have been several publications demonstrating the benefit of functional treatment in JIA [32,40-42]. To date JIA-patients in remission should no longer be withdrawn from sport acitivities but rather be adviced to use the regenerative and integrating functions of sports activities.

Psychologic and social services

Chronic diseases in childhood and adolescents might not have consequences only in the present but furthermore in the future of the patients. Thus chronic disease is not

only the individual problem of the patient but sometimes the whole family. This might even raise the question of psycho-social support to the family members [43,44].

Especially in musculo-sceletal diseases as JIA, pain and physical limitations may hinder age-based development and integration. Moreover there might be consequences concerning school and professional education. But chronic disease might be a challenge as well and account for many positive aspects in the development oft he patients especially concerning self-confidence and social competence. Parents and patients frequently benefit from meeting other families having children with the same or even a similar disease. This is an important factor of self-help groups but is relevant as well in patients who are treated in specialized centers, where getting in contact to others is feasible.

Education

Education of patients and parents is mandatory in order to generate acceptance for the disease and the therapeutical means which might be necessary within the disease course. Mostly the collaboration of families and their therpeutic-team will be required for many years. Moreover patients sometimes have problems in compliance or even refuse treatment especially in their puberty. Therefore all steps of treatment have to be discussed and explained in detail to generate the appreciation of all persons involved [45,46].

Conclusion

Prognosis and results from treatment in most patients with pediatric rheumatologic diseases have substancially improved due to the development of strucured treatment approaches, specialized physicians and teams, improvement in drug therapy and multidisciplinary treatment including functional aspects. Children and adolescents suspected to suffer from rheumatic diseases should therefore be presented to a center specialized in pediatric rheumatology, in order to determine the correct diagnosis and the required treatment respectively. Early diagnosis and treatment are essential to archive remission and to enable a physiological development to the patients despite suffering from a chronic disease. Specialized centers will not provide multidisciplinary

treatment programms, but will additionally enable a successfull treatment close tot he patients residence by educating patients and families and providing helpfull advice to their family doctor.

Thus on the basis of correct diagnosis and an individualized treatment even rare or complicated pediatric rheumatic diseases should be manageable.

Legends to tables and figures

Figure 1: Stepwise escalation of treatment in oligoarticular JIA

Legend to figure 1: NSAID (nonsteroidal antirheumatic drugs), GC (Glucocortikoid), MTX (Methotrexat), MoAb (monoclonal antibody)

Table 1: Drugs in childhood rheumatology

Tabelle 2: Biologic drugs currently used in pediatric rheumatology

Legend Table 2: Poly-JIA (Polyarticular JIA), EO-JIA (Extended Oligoarticular JIA), ERA-JIA (Entesitis associated JIA), PsJIA (Psoriasis-JIA), IBD (inflammatory bowel disease, SoJIA (Systemic onset JIA), CAPS (Cryopyrin associated periodic syndrome), SLE (Systemic Lupus Erythematodes), ITP (Immunthrombocytopenia), Rf+ (Rheumatic factor positive), FMF (Familiar mediteranean fever), HIDS (Hyper-IgD Syndrome), TRAPS (TNF-alpha receptor associated periodic syndrome), IL (Interleukin), TNF (Tumor-necrosis-factor), BLyS (B-Lymphocyte Stimulator), CD (Cluster of differentiation), CTLA (Cytotoxic T-lymphocyte associated protein)

Figure 2: Multidisciplinary concept developed in Garmisch-Partenkirchen:

Integration of different professionals (left side); Physiotherapy may be fun: Integrating „boldering“ (therapeutical climbing) into treatment (right side)

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