

Growth retardation and delayed puberty in children and adolescents with juvenile idiopathic arthritis

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Abstract

Juvenile idiopathic arthritis (JIA) is the most common joint disorder in developing children. Juvenile idiopathic arthritis is difficult to diagnose and treat. In some patients, signs and symptoms can be frustratingly inconsistent, contradictory or idiosyncratic. Short stature in patients with JIA is usually due to reduced growth in the lower extremities, and only rarely due to reduced growth in the spinal column. In some studies, children with JIA were found to have infantile body proportions. Puberty is delayed in children with JIA. In children with chronic arthritic disorders, there is a strong correlation between the activity of the disease and the age of puberty. The main goals in reducing growth retardation in children with JIA are promoting timely remission and reducing the duration and dosage of corticosteroid treatment. It is important to regularly monitor physical development. Further improvements to the treatment protocol depend on continued interdisciplinary research involving paediatricians, rheumatologists and clinical anthropologists.

Key words: children, chronic disease, short stature, puberty, glucocorticosteroid therapy.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common joint disorder in developing children [1]. The incidence of JIA is between 6 and 19 per 100,000 with a prevalence of about 1 in 1000. The condition is slightly more common in females [2].

Juvenile idiopathic arthritis is difficult to diagnose and treat. In some patients, signs and symptoms can be frustratingly inconsistent, contradictory or idiosyncratic. In JIA, the clinical picture and course of inflammation vary considerably, and are different than in inflammatory conditions of the joints in adults [3]. Furthermore, the symptoms differ from patient to patient, and also change over the course of the disease. There are few reliable serological manifestations.

The classification of diseases accompanied by joint inflammation has been frequently revised. According to the criteria proposed by the International League against Rheumatism, JIA refers to inflammation of the joints in persons under 16 years old that lasts for at least 6 weeks [1]. Clinically, JIA can be divided into seven subtypes [4]:

- systemic,
- persistent oligoarticular,

- extended oligoarticular,
- polyarticular with positive rheumatoid factor (RF),
- polyarticular with negative rheumatoid factor (RF),
- psoriatic arthritis, and
- arthritis related to enthesitis.

The name juvenile idiopathic arthritis has replaced previously used names such as juvenile chronic arthritis (JCA), which had been proposed by the European League against Rheumatism, and juvenile rheumatoid arthritis (JRA), which had been proposed by the American College of Rheumatology [5, 6].

Growth disturbance

Juvenile idiopathic arthritis is characterized by chronic inflammation in various tissues of the body, and can affect joints, ligaments, muscles and internal organs. Over the long term, inflammation can cause stiffening and deformation of the affected joints, and can lead to significant growth retardation [7, 8]. Growth retardation can result in severely reduced body stature, which is defined as body height in the lowest third percentile of the population, or body height more than two standard deviations below the mean for the population.

The proportion of children with JIA that are abnormally short ranges from 10 to 40% [9, 10]. Growth retardation is significantly more severe in children with the systemic subtype of the disease and in children in whom many joints are affected [9, 11]. Growth retardation is also more severe in children with extensive joint damage than in children with early or moderate anatomical changes [7, 12].

Factors responsible for growth retardation in chronically ill children include frequent infections, primary and secondary malnutrition, long-term stress related to being chronically ill or handicapped, and side effects of therapy. It is often difficult to tell how much growth retardation can be attributed to the disease itself, and how much to the side effects of treatment [13].

Growth retardation in children with JIA is especially severe when auto-immunological activity has been elevated over a long period, which is associated with high levels of the pro-inflammatory cytokines IL-1, IL-6 and TNF- α [7, 14]. These cytokines reduce secretion of growth hormone from the pituitary gland, and also act directly on the growth plates of the long bones [15, 16].

In laboratory experiments, IL-1 and TNF- α have been found to reduce proliferation and differentiation in chondrocytes in the growth plates, to induce death in chondrocytes, and to disrupt the synthesis of type II collagen and proteoglycans [17, 18].

Inflammation also hampers blood circulation in the affected joints, which limits the supply of oxygen and nutrients to the growth plates of the long bones. At first, there is an increase in the rate

of bone formation in the vicinity of the affected joint. However, if auto-immunological activity persists for a long time, cell proliferation in the growth plates ceases before development is complete, and the length of the limbs is likely to be irreversibly affected [18]. Effective and timely treatment can preserve growth potential in children with JIA, thereby allowing bone growth to catch up [8, 10].

Short stature in patients with JIA is usually due to reduced growth in the lower extremities, and only rarely due to reduced growth in the spinal column [19, 20]. In some studies, children with JIA were found to have infantile body proportions [12, 19]. In one study, however, no abnormalities in body proportions were found [9]. The authors reported that reduced subischial leg length did not affect body proportions in children with JIA because it was proportional to the general reduction in body stature.

In experiments on the level of physical development in children with JIA, not only was the length of the lower extremities significantly reduced, but the proportions of the chest were also affected [12]. Chest width and chest capacity were both reduced.

Children with JIA are more easily exhausted by physical exertion because they are generally less physically active and experience pain related to the disease [21]. The capacity for physical exertion was particularly reduced in children with an active form of the disease and in children with many affected joints. Because children with JIA are frequently less physically active, muscle development is affected, which further contributes to the abnormal construction of the chest [21].

Another factor that reduces growth in children with JIA is long-term treatment with corticosteroids, which is usually administered to children with the systemic and polyarticular forms of the disease. Corticosteroids are usually administered when other drugs fail to bring about remission of the disease [6, 10].

Corticosteroids affect growth in many ways. High levels of corticosteroids stimulate the release of somatostatin, inhibit the release of growth hormone, insulin growth factor-1 (IGF-1) and IGF binding protein, decrease the expression of receptors for growth hormone and IGF-1, and reduce the level of IGF binding protein [22]. High levels of corticosteroids can also reduce proliferation in growth plate chondrocytes by inhibiting the expression of receptors for growth hormone and IGF-1. Furthermore, corticosteroids interfere with normal bone development by increasing the level of proteolysis in nearby muscle tissue [23].

The effect of corticosteroids on growth has been confirmed in short-term and longitudinal studies.

In studies carried out using knemometry, the rate of growth in the lower extremities was reduced in children treated with corticosteroids, as was metabolic turnover in the bone tissue [24].

In one study on children with JIA, long-term treatment with corticosteroids irreversibly reduced terminal body height, whereas treatment lasting less than one year had no effect. The effect did not depend on the dosage administered [7].

On the other hand, in a longitudinal study on pre-pubertal children with juvenile idiopathic arthritis who were treated with corticosteroids, growth rate was significantly reduced only during the first year of treatment, after which it increased. This was attributed to an improvement in the course of the disease, to the low dosages of corticosteroids used, and to the fact that the course of the disease was carefully monitored [11].

Final growth parameters are not always reduced in patients suffering from juvenile idiopathic arthritis. In some children, catch-up growth is possible when the disease is in remission or when corticosteroid treatment is interrupted. In this case, final growth parameters can approach and even reach normal levels. This is especially true for children that are younger, and thus have been suffering from the disease for a shorter time [25].

In one study on children with juvenile idiopathic arthritis, catch-up growth was reported in 70% of the subjects examined. On the other hand, growth retardation was irreversible in the other 30%, in spite of the fact that these children did not differ from the others in terms of duration of the disease activity or the dosage of corticosteroids administered. This was attributed to differences in the genetic potential for growth among the subjects [25].

Not all studies have confirmed a connection between the degree of growth retardation and the dosage of corticosteroids administered. However, it is generally believed that prednisone at a dosage of 0.25 mg/kg/day can affect growth [7, 8, 14].

Another factor responsible for growth retardation is malnourishment, which is frequently seen in children with JIA. In some cases, malnourishment can be severe enough to induce cachexia [26-28].

Malnourishment in children with JIA is caused by many factors. High levels of pro-inflammatory cytokines can reduce energy uptake and metabolism, even if the patient is on an appropriate diet. Energy intake in children with JIA is negatively correlated with IL-1 production [26]. Malnourishment is also more common in children with inflammation of the maxillo-mandibular joint, and in children in whom the digestive tract is affected to the point that nutrient assimilation is reduced. Coeliac disease, for example, is about seven times more common in children with JIA than in the general population [29]. Many of the drugs used in treating

the disease can also cause disturbances of the gastro-intestinal tract. This is particularly true for methotrexate [27].

Delayed puberty

Sexual development is also delayed in children with JIA. In children with chronic arthritic disorders, there is a strong correlation between the activity of the disease and the age of puberty [30-32]. In girls with JIA, menarche occurs almost two years later than in healthy children. In boys, puberty is delayed because testosterone production by the testicular Leydig cells is reduced [33].

On the other hand, in a study on twenty-four year old women who had suffered from JIA during childhood, menarche was found to have occurred on average at age 13, which is about the same age as in healthy individuals [34]. There was also no significant difference between the women and their healthy peers in terms of fertility, although fecundity was significantly reduced. The women had a higher incidence of gynaecological disorders, and were more likely to miscarry [34].

Treatment goals and pharmaceutical agents

The main goals in reducing growth retardation in children with JIA are promoting timely remission and reducing the duration and dosage of corticosteroid treatment. Clinical symptoms can be improved and inflammation can be controlled by administering intra-articular corticosteroids, methotrexate, immuno-suppressing drugs and biological agents [3, 6].

Long-acting corticosteroids such as triamcinolone (Hexatrione), Depo-Medrol and Diprophos can be injected directly into the affected joints in patients with chronic or recurrent inflammation [3]. No more than three or four doses should be injected into a single joint. This method is particularly useful in cases of oligoarticular arthritis because corticosteroids are administered locally, not systemically. This often reduces the risk of side effects associated with systemic treatment [35-38].

Methotrexate is a folic acid antagonist. In one study, methotrexate was administered to children under ten years old with either oligoarticular or polyarticular onset JIA [39]. The study group consisted solely of children who had not received corticosteroids during the previous year. After one year of treatment with methotrexate, the children were responding positively to treatment. The number of affected joints was reduced by half. Growth rate was significantly improved, and body height was higher in children who responded positively to treatment than in children who did not respond [39]. On the other hand, methotrexate was less effective in children with the systemic form of the disease [40].

Children receiving methotrexate may require folic acid supplements. The dosage of folic acid administered should be individually tailored to the patient's needs [41].

Etanercept and other TNF- α antagonists reduce inflammation and make it possible to use more conservative doses of corticosteroids [42, 43]. Etanercept has been found to improve the rate of growth in pre-pubertal and pubertal children [44]. Long-term studies are needed to confirm the benefits of TNF- α antagonists, and to determine the importance of negative side effects such as increased frequency of infectious disorders [45].

Infliximab is a monoclonal antibody that binds TNF- α . Preliminary reports of small-scale studies have been promising, although full-scale randomized placebo-controlled studies are needed to confirm the effectiveness and safety of the drug [46].

Adalimumab is a human monoclonal antibody that binds TNF- α , and has also been used to treat JIA. In a study on 171 patients between four and seventeen years old with oligoarticular JIA, adalimumab was administered alone or in combination with methotrexate. Adalimumab was found to be very effective and to have relatively few side effects such as headaches, respiratory tract infections, and pain and reddening at the site of injection [47].

Anakinra is an IL-6 receptor antagonist. Preliminary testing has indicated that it rapidly improves the clinical state and laboratory test results of children with systemic JIA, with noticeable positive effects after only two weeks of treatment [46, 48].

Tocilizumab is another IL-6 receptor antagonist that has proven effective in treating systemic JIA. In a study on 56 patients between two and nineteen years old, treatment with tocilizumab resulted in sustained clinical improvement and had a favourable risk-benefit profile [49].

Abatacept and atlizumab are among the biological preparations that are currently in the clinical trial phase. Abatacept is a fusion protein that blocks the activation of T lymphocytes. Atlizumab is an IL-6 receptor antagonist [46].

Growth hormone is also being evaluated for use in children with JIA who have received long-term corticosteroid treatment. In one study, regular administration of growth hormone over several years improved growth rate, although the effect on terminal body height was less than expected. There was also an increase in serum IGF-1 and IGF binding protein levels, and a reduction in the proportion of adipose tissue [10].

In another study, growth hormone was administered to pre-pubescent children. The children were then observed for four years, during which time growth rate was significantly improved. Treatment was more effective in children with

milder symptoms than in children with more active forms of the disease [50].

The major disadvantage of treatment with growth hormone is an increased risk of neoplastic disorders and scoliosis [41]. The exorbitant cost of treatment also limits its general use in minimizing growth retardation in children with JIA [8].

Conclusions

At the present time, the most effective way to reduce growth retardation in children with JIA is to control inflammation with the help of currently available drugs, while reducing the duration and dosage of treatment with corticosteroids. It is also important to regularly monitor physical development. Further improvements to the treatment protocol depend on continued interdisciplinary research involving paediatricians, rheumatologists and clinical anthropologists.

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