The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Juvenile idiopathic arthritis

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1 Introduction

Juvenile idiopathic Arthritis (JIA) is defined as a group of diseases, which starts before the 6th year of life and lasts at least 6 weeks, in the absence of other articular diseases (Table 1: differential diagnoses). Beside arthritis, JIA can take a non-arthritic, systemic course (Still's syndrome).

70 to 80 % of all chronic joint diseases in childhood can be defined as JIA, this represents a prevalence of 2 to 3 per 10 000 children. The disease usually starts between the 2nd and 4th or between the 8th and 12th years of life. Currently, JIA is classified into 5 entities (Table 2).

Nowadays, JIA is considered, at least in some entities, to be an auto-inflammatory rather than an autoimmune disease [1]. In fact, autoantigens are not (yet?)

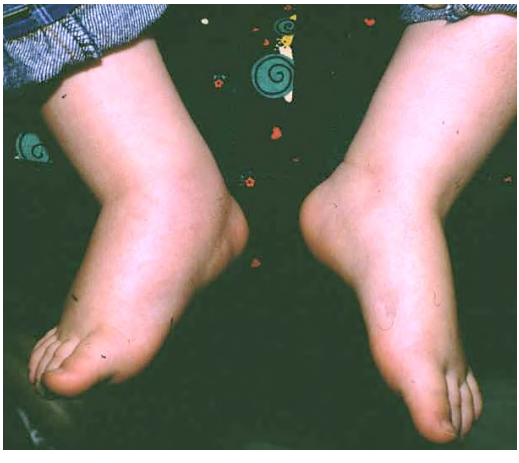

Figure 1. Clinical presentation of a swollen, arthritic ankle in a 1 year old boy with an acute JIA.

Table 1. Differential diagnoses of JIA.

Differential diagnoses
– Acute rheumatic fever
– Infections (arthritis purulenta, lyme arthritis, osteomyelitis, tuberculosis)
– Reactive arthritis (following scarlet fever [β-haemolytic group A streptococci]; urogenital infections [*Chlamydia trachomatis*, *Neisseria gonorrhoea*, *Ureaplasma urealyticum*]; enteral infections [Yersinia, Salmonella, Shigella, *Campylobacter jejuni*, *Clostridium difficile*, *Brucella abortus*]; or viral infections [Parvovirus B19, Rubella, Hepatitis B, HIV, Measles, Varicella, Mumps, EBV, Coxsackie, Adenovirus, Influenza, Parainfluenza, RS-Virus (RSV))
– Connective tissue diseases
– Immunodeficiency diseases
– Haematological diseases
– Neoplasias
– Injuries
– Foreign body
– Orthopaedic diseases
– Frostbite
– Psychogenic arthralgias

known. Autoantibodies are not considered to be of diagnostic help in this disease, but have relevance in differential diagnosis.

2 Diagnostic measurements for experts

JIA may or may not start with joint pain. Depending on the JIA entity (Table 2), different symptoms may be more obvious. Most important is the exclusion of other diseases.

The patient's history is important to determine infections which may be responsible for acute rheumatic fever, reactive arthritis, or infectious arthritis, e. g. tuberculosis. Previous injuries or accidents can indicate infections causing arthritis purulenta or osteomyelitis, but the history should also check the possibility of foreign bodies or frostbite. Frequently overlooked, systemic diseases such as immunodeficiencv diseases, haematological diseases or neoplasias can cause joint pain. Furthermore, family history gives important information about hereditary background and psycho-social situation.

Table 2. Diagnostic criteria of Juvenile idiopathic Arthritis (JIA) entities.

JIA entities	Characteristics
Systemic JIA (Still's syndrome)	– 10–15 % of JIA – Young children, both genders – Sudden onset; high, septicaemia-like fever – Maculo-papulous exanthema – Extra-articular symptoms (e.g. pancarditis, hepatosplenomegalia) – Late-onset destructive arthritis – High mortality (10 %)
Seronegative polyarthritis	– 30–40 % of JIA – Mainly female patients – Symmetric polyarthritis, small and large joints – IgM rheumatoid factor negative – Good prognosis for joints
Seropositive polyarthritis	– 5–10 % of JIA – Onset around adolescence – Symmetric polyarthritis, small and large joints – IgM rheumatoid factor positive – Poor prognosis similar to adult RA
Oligoarthritis in young children	– 25–30 % of JIA – Young children, mostly girls – 75 % ANA positivity – Asymmetric oligoarthritis of large joints – 50 % chronic iridocyclitis (10 % permanently damaging)
Oligoarthritis in older children	– 20–25 % of JIA – Older children, mostly boys – 80 % HLA-B27 association – Asymmetric oligoarthritis, common sacroiliitis – Frequently transition into ankylosing spondylitis

Abbreviations: **RA**, Rheumatoid arthritis; **ANA**, antinuclear antibodies

Examination of affected joints should be supplemented by sonography of the joints as well as the spleen and liver. Cardiac function must be investigated to exclude acute rheumatic fever by echocardiography, electrocardiography and X-ray.

Patients with signs of an antinuclear antibody (ANA)-positive disease must be seen by an ophthalmologist at regular intervals. Immunodeficiency diseases can also cause arthritis; these patients frequently have a high incidence of infections in their histories.

Orthopaedic diseases must be differentiated from "growth pains" and are mostly found in joints taking a heavy burden, by incorrect posture, heavy body weight, exercise avoidance or even incorrect shoes.

Laboratory investigation focuses on the JIA entities and the differential diagnoses to exclude. Primarily, leukocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), IgM rheumatoid factors (RF), anti-Streptolysin O titres (AST), HLA-B27 detection and autoantibody screening by indirect immunofluorescence help to make a clear diagnosis.

3 Requirements for family practitioners

JIA is a highly individual syndrome including distinct entities. The most important task for the family doctor is to not overlook a patient with suspicious symptoms and to consult a specialist as soon as possible. Please note that for most explanations for articular pain there is no need for a rheumatologist but for an oncologist, haematologist, immunologist, or an orthopaedist. To make the right decision, family doctors can examine the patient as shown above and order the first laboratory tests.

There is no confirmatory test for a diagnosis of "Juvenile idiopathic arthritis".

4 Follow up

Clinical observations

During symptomatic or immunosuppressive treatment or therapy with biological agents, signs and symptoms should gradually improve. This may take any time from weeks to months, and depends on the underlying disease entity.

Expectations

JIA can be a chronic or a self limiting disease. Usually, with adequate therapy, most patients will achieve a partial or complete remission. Spontaneous remissions also occur.

Blood tests

Clinical improvement is directly associated with an improvement in levels of inflammatory parameters (ESR, CRP). Minimal laboratory testing is required to adequately care for patients. In patients who fail to improve during treatment, additional laboratory and clinical testing can be useful to further refine the clinical diagnosis and to change the therapeutic regimen appropriately.

5 Management

The treatment must be individualised according to the JIA entity, the severity of disease, the patient's wishes and the presence of associated diseases. Altogether, the following treatment approaches can be considered [2]:

Drugs

1. *Nonsteroidal anti-inflammatory Drugs (NSAIDs)*
   These drugs reduce inflammation and relieve pain. Indomethacin, Ibuprofen, Diclofenac or Naproxen are the most common.
2. *Basic Therapeutics*
   Chronic activity in rheumatic diseases can be modulated by chloroquine or sulfasalazine.
3. *Immunosuppressive drugs*
   Autoinflammatory and autoimmune processes can be treated with drugs such as Azathioprine, Methotrexate, or cyclophosphamide
4. *Corticosteroids*
   Prednisone or intra-articularly-given triamcinolonacetonide are established anti-inflammatory compounds.
5. *Biologicals*
   Anti-TNF therapies are well established in the treatment of JIA. Furthermore, anti-IL1b therapies are a therapeutic option [3, 4].

Surgery

In selected cases, synovectomy or surgical corrections may be necessary to manage JIA.

Accompanying therapies

Physical therapy, ergotherapy and consideration of social networks must complement medical care.

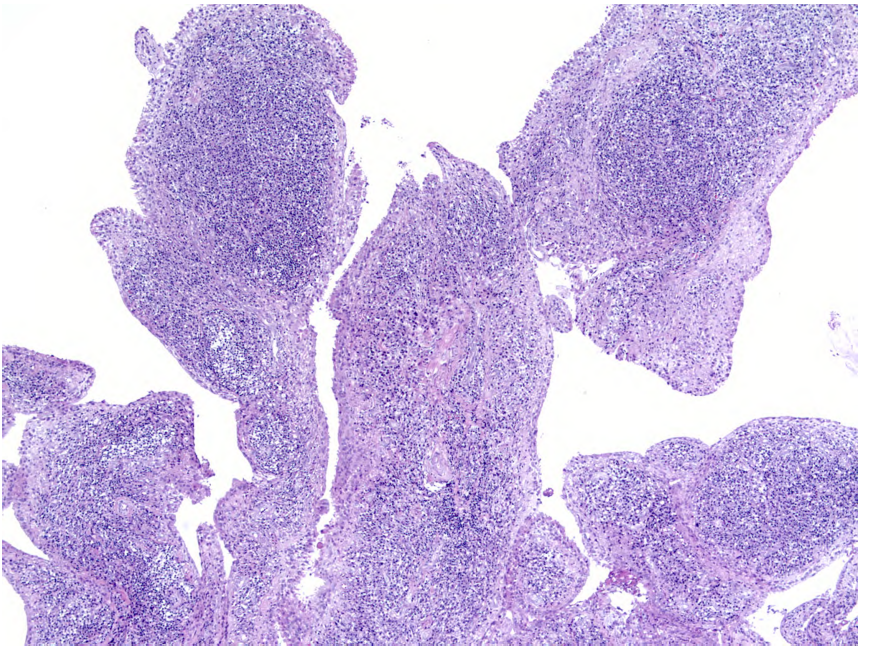

Figure 2. Histopathology of a high grade JIA synovialitis with lining cell hyperplasia, dense lymphocytic inflammatory infiltration. HE staining, original magnification 70 ×.

6 Diagnostic tests

There is no specific test for JIA. Laboratory investigation is highly dependent on the JIA entities (Table 2) and the differential diagnoses to exclude (Table 1).

7 Testing methods

Detection of CCP-antibodies is not indicated in JIA. Leukocyte count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) give a fair overview of inflammatory activity and are common in clinical labs or even in some outpatients' departments.

IgM rheumatoid factors (RF) must be detected by using isotype specific detection reagents.

Anti-Streptolysin O titres (AST), serological tests for bacterial and viral diseases and sometimes direct detection of infectious antigens should be performed as indicated by clinical findings. Tuberculosis (Tb) should be excluded by interferon-γ release assay; confirmation must be done in a specialised Tb laboratory.

Screening for antinuclear antibodies must be done by indirect immunofluorescence (HEp-2 cells). If there are any positive ANA titres, an ENA-screen should be done.

HLA-B27 positivity can be confirmed by flow cytometry or by DNA based test systems.

References

[1] Vastert SJ, Kuis W, Grom AA. Systemic JIA: new developments in the understanding of the pathophysiology and therapy. Best Pract Res Clin Rheumatol 2009; 23: 655–64.
[2] Guellac N, Niehues T. Interdisciplinary and evidence-based treatment guideline for juvenile idiopathic arthritis. Klin Pädiatr 2008; 220: 392–402.
[3] Papsdorf V, Horneff G. Complete control of disease activity and remission induced by treatment with etanercept in juvenile idiopathic arthritis. Rheumatology (Oxford) 2011; 50: 214–21.
[4] Stoll ML, Gotte AC. Biological therapies for the treatment of juvenile idiopathic arthritis: Lessons from the adult and paediatric experiences. Biologics 2008; 2: 229–52.