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Practice guidelines

French expert opinion for the management of juvenile dermatomyositis

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ABSTRACT

A guideline group consisting of a pediatric rheumatologist, internists, rheumatologists, immunologists, a physiotherapist and a patient expert elaborated guidelines related to the management of juvenile dermatomyositis on behalf of the rare autoimmune and autoinflammatory diseases network FAI^{2}R. A systematic search of the literature published between 2000 and 2015 and indexed in PubMed was undertaken. Here, we present the expert opinion for diagnosis and treatment in juvenile dermatomyositis.

The reference center for childhood inflammatory rheumatism and rare systemic diseases (RAISE), on behalf of FAI^{2}R (rare autoimmune and autoinflammatory diseases network) and Filnemus (rare neuromuscular diseases) referral centers, has drawn up a national health protocol (NHP). The objective was to detail the current optimal management of a child with juvenile dermatomyositis (JDM) for healthcare professionals.

1. Background

JDM is characterized by noninfectious inflammation of the muscles and skin, associated with vasculopathy, which is the major pathophysiological component. It is a rare disease [1–8]. The incidence has been estimated between three and four cases per million inhabitants in the United States and Great Britain. There have been no French epidemiological studies. It is, however, the most common inflammatory myopathy in children [9]. The median age of onset of childhood dermatomyositis is approximately 7 years, but disease onset occurs before the age of 4 in one-quarter of cases. It can be very severe with many complications.

2. Method

The guidelines were elaborated by a working group and outside validation by an evaluation group. The working group consisted in experts in the field of pediatric rheumatology (BBM, AB0, KB, RM), pediatric neurology (CG), internal medicine (OB, YA, EH, HM), rheumatology (AM), dermatology (EB, OC), immunology (LM, FJ), physiotherapy (VB) and an expert patient (DP). The working group

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consulted the main literature references (meta-analyses, clinical trials, and cohort studies) and the principal books on rheumatology, pediatric rheumatology, dermatology, adult and pediatric neurology, and internal medicine published in English or in French, and indexed in PubMed from 2000 to December 2015, using the key words "dermatomyositis", "juvenile dermatomyositis", and "amyopathic dermatomyositis". Only articles concerning clinical manifestations and management were selected. Expert advice was provided if data were lacking or insufficient. In 2017 a group of European experts published a standard of care for diagnosis and treatment of patients with juvenile dermatomyositis throughout Europe. We have mentioned these recommendations ("European recommendations") when they were approved by a majority of the French experts. The final document was elaborated after discussion between all the members of the working group in a 2-day workshop.

3. Recommendations

3.1. Diagnosis and initial assessment

3.1.1. Diagnosis

JDM encompasses many very heterogeneous conditions. The reason for this heterogeneity is being studied and it is becoming possible to identify homogeneous groups of patients based on antibodies (Ab) specifically associated with JDM. The only consensually defined clinical form is "amyopathic dermatomyositis", [10] characterized by purely cutaneous involvement. There are purely muscular forms called "DM sine dermatitis" of which the diagnosis is based on muscle biopsy and the presence of specific Abs.

Diagnostic criteria for dermatomyositis, established by Bohan and Peter in 1975, include five items: characteristic skin rash, proximal muscle weakness, raised muscle enzymes, myopathic changes on electromyogram (EMG), and typical muscle biopsy (Box 1) [11,12]. These are currently being revised through the International Myositis Classification Criteria Project. Current practice reveals the necessity of broadening diagnostic criteria by incorporating new techniques, such as MRI, and the significance of skin disease in JDM.

Box 1. Bohan and Peter's criteria [11]

The diagnosis of dermatomyositis (DM) is considered definite, probable, and possible when skin rash is associated with three, two, or one muscular criteria, respectively*.

1. Symmetric proximal muscle weakness determined by physical examination.
2. Elevation of serum skeletal muscle enzymes, including creatine kinase, aldolase, serum glutamate oxaloacetate and pyruvate transaminases, lactate dehydrogenase.
3. The electromyographic triad of short, small, polyphasic motor unit potentials; fibrillations, positive sharp waves, and insertional irritability; and bizarre, high-frequency repetitive discharges.
4. Muscle biopsy: abnormalities of degeneration, regeneration, necrosis, phagocytosis, and an interstitial mononuclear infiltrate.
5. Typical skin rash of DM, including a heliotrope rash and Gottron's sign/papules.

* Exclusion criteria: central or peripheral neurologic diseases, muscular dystrophies, granulomatous and infectious myositis, metabolic and endocrine myopathies, and myasthenia gravis.

3.1.2. Clinical assessment

Clinical examination is essential to guide the diagnosis and identify signs of muscular (severity of the deficit and swallowing disorders) and extramuscular (respiratory or digestive) involvement. The skin (especially the hands, face, elbows, knees, and back) and the oral mucosa must be examined carefully: the dermatological manifestations, which are the key elements of the diagnosis, can be subtle. Height and weight growth and pubertal stage must be systematically evaluated.

The patient's medical history must be collected so as to:

- establish a genealogical tree that can detail the personal and/or family history of inflammatory myositis, autoimmune diseases, and hereditary myopathies;
- determine whether a drug was ingested in the weeks before the first signs;
- determine how muscular involvement emerged (involvement is subacute for a few weeks or months, in contrast to genetic myopathy, in which the muscular involvement develops much more slowly and is insidious);
- seek all functional signs to guide the diagnosis and identify signs of severity;
- evaluate growth and the stages of psychomotor development.

Muscle involvement generally progresses within a few weeks, with varying severity. Muscular involvement is bilateral, proximal, and symmetrical: it predominates in the scapular and pelvic girdles but can also affect the axial muscles, especially in children. Pain, due to pressure sensitivity of the muscle mass, is possible, but is not generally as intense as that observed for acute myositis. Muscle involvement should be assessed using the standardized CMAS (Childhood Myositis Assessment Scale), which evaluates muscular endurance, and the MMT (Manual Muscle Testing), which evaluates muscular strength. The assessment should include a search for signs of severity:

- the effect on swallowing: search for signs suggestive of dysphagia (cough during feeding, water glass test: time to drink 100 mL of water), modification of the voice (nasal), examine contraction of the palate;
- respiratory failure;
- cardiac involvement;
- digestive impairment (abdominal pain, pseudo-occlusion, or digestive hemorrhage).

Cutaneous signs are characteristic of JDM. They can be of varying intensity, sometimes very discreet, and should be carefully sought when there is evidence of a muscular deficit. Characteristic skin lesions are:

- facial involvement: erythematous or even purplish coloration of the upper eyelids, frequent erythema of the cheekbones, sometimes of the forehead and temples, with a purplish red heliotropic aspect;
- involvement of the hands: Gottron papules;
- macular lesions, violin-shaped and/or confluent symmetrical squamous erythematosus on the tops of the extensions of the metacarpophalangeal and/or interphalangeal joints;
- peri-nail telangiectasias, sometimes visible to the naked eye, and gingival telangiectasias.

There are many other nonspecific cutaneous signs: cutaneous and/or mucosal ulcerations, digital necrosis, Raynaud's phenomenon, edematous forms of poikiloderma, lipodystrophy, erythroderma, follicular hyperkeratosis, panniculitis, alopecia, vasculitis, mechanic's hands, photosensitivity, and lichenoid or even necrotic erythema. Calcinosis is rare in the initial phase. In some forms,

Table 1
Presentation of juvenile dermatomyositis (JDM) depending on autoantibody specificity.

Antibody name	Antigenic target	Severity of motor deficit	Particularities of cutaneous lesions	Associations that could affect the vital prognosis
Anti-Mi-2	Nucleosome remodeling-deacetylase	++	None	None
Anti-TIF1γ	Transcriptional intermediary factor 1 γ	++	None	Cancer in adults
Anti-MDA5	Melanoma differentiation-associated gene 5	±	Ulcers, palmar papules, fissuring hyperkeratosis of the fingers, digital necrosis	Interstitial pneumopathy, sometimes rapidly progressive in adults and in some children
Anti-SAE	Small ubiquitin-like modifier-activating enzyme	+	None	None
Anti-NXP2	Nuclear matrix protein 2	++	Calcinosis Severe vasculopathic lesions	Cancer in adults

cutaneous involvement is absent or atypical. Consequently, muscle biopsy is necessary to confirm the diagnosis in these forms.

Other signs are:

- involvement of the joints in 25–50 % of cases;
- cardiac involvement: subclinical cardiac manifestations are present in half of the cases, although clinical failure is rare [13,14];
- lung involvement and/or impairment of the respiratory muscles: it is very important to test respiratory involvement, because it is a major cause of mortality. Impairment may be due to diaphragmatic and/or intercostal involvement (restrictive ventilatory disorder), inflammation of the parenchymatous tissue, or inhalation pneumonitis due to difficulty swallowing. There may be subclinical abnormalities in respiratory functional test results [15–17];
- early or late digestive impairment, sometimes very severe [18].

This is due to involvement of the musculature and vasculitis. In its vasculopathic form, it is characterized by ulcerations, perforations, and hemorrhages that can be life-threatening. In some cases, damage to the digestive mucosa can lead to digestive malabsorption, reducing the absorption of orally administered drugs.

Fever is usually absent or moderate. An alteration of the general condition with slimming or asthenia may be a complication of swallowing problems or a sign of the loss of muscle mass.

The clinical presentations according to the various specific associated autoantibodies are shown in Table 1.

3.1.3. Paraclinical explorations

The paraclinical examinations that are necessary to establish the diagnosis are:

- determination of muscle enzyme levels: the elevation of at least one muscular enzyme among CK, ASAT, LDH, or aldolase is observed in about 90 % of patients. In practice, it is recommended to test only CK (expert opinion). The absence of the elevation of a muscle enzyme does not eliminate the diagnosis.

Paraclinical examinations which may be useful to establish the diagnosis are:

- muscle biopsy: it is not systematically performed for typical cases but is indispensable for atypical cases. It can help confirm the diagnosis (for example, for cases of no or atypical cutaneous involvement). The biopsy must be performed and analyzed at an expert referral center. The site to biopsy is principally guided by clinical examination or MRI. In practice, the sample should be taken near and/or include affected muscle; the deltoid muscle is usually studied (very frequently involved, easy to perform and to study). Expert groups have issued recommendations on the techniques required for reliable analysis. Four types of lesion can be observed [19]:
  - inflammatory involvement: mainly perimysial and perivascular inflammation composed of B and T lymphocytes, $CD4^+$ cells, of which some are thought to secrete interferon (IFN), and macrophages,
  - vascular involvement: capillary loss associated with an early capillary deposition of the complement C5b-9 membranolytic attack complex (MAC), thickening of the endothelium of arterioles,
  - muscular involvement: necrosis/regeneration, perifascicular atrophy, micro-infarction, myofibrillar loss, re-expression of HLA class I molecules with perifascicular reinforcement,
  - endo- and perimysial fibrosis. A score to quantify these lesions has been validated in children [20];
- cutaneous biopsy: it must be easily performed if the diagnosis remains unclear. In most cases it shows an aspect close to that of lupus with usually discrete interface dermatitis with basal vacuolation, rare apoptotic keratinocytes, and a lymphocytic infiltration of the superficial dermis;
- MRI of the muscle: it can be useful to confirm muscle involvement in atypical cases. It is also a diagnostic criterion according to the ENMC. The T2 STIR (short tau inversion recovery) sequences can detect muscular edema, which is an indirect and nonspecific indication of inflammation. The sensitivity of MRI for the diagnosis of myositis varies from 70 to 100 %, depending on the study. Nonetheless, a normal MRI does not exclude muscular involvement. The utility of MRI to guide the biopsy to improve its accuracy is debatable [21,22];
- capillaroscopy is not necessary for the diagnosis, but the presence of significant anomalies may indicate JDM [23,24];
- electromyogram is not useful for typical cases [12,25].

The paraclinical examinations necessary to classify the JDM are:

- the search for autoantibodies:
  - myositis-specific antibodies (MSA) not observed in other autoimmune diseases: anti-Mi2, anti-SAE, anti-TIF1-gamma, anti-NXP2, or anti-MDA5,
  - myositis-associated autoantibodies (MAA) that can be present in other autoimmune diseases: nonspecific anti-nucleus, anti-U1RNP, anti-RO52, anti-RO60, anti-SSB, anti-Ku, or anti-PM/Scl. This examination must be performed by an expert laboratory.

Myositis-specific autoantibodies not only differentiate unique phenotypes of patients with distinct demographic and clinical features, but they are also associated with long-term outcomes,

including mortality, disease course, calcinosis, and lipodystrophy (Table 1) [26–36]. In addition, muscle biopsy findings in combination with myositis-specific autoantibodies aid prediction of outcomes in juvenile dermatomyositis [33,35]. These features emphasize the heterogeneity of JDM.

The paraclinical examinations that are necessary to investigate complications and/or specific disorders are:

- complete blood cell count (CBC), AST, ALT, gamma-GT, creatinine, albuminuria in cases with edema (capillary leakage), glycemia, triglyceridemia, fasting cholesterol, and bone densitometry;
- respiratory function tests with a study of CO diffusion (DLCO) to search for pulmonary involvement; a pulmonary scan should always be performed if a low-dose technique is available, and in all cases if there is a clinical or radiological anomaly or one identified by respiratory function test. In other cases, a chest x-ray should be performed;
- electrocardiographic examination.

4. Differential diagnosis

The differential diagnosis arises mainly in the absence of typical cutaneous involvement. The examinations to be performed are based on the duration of the muscular disorder, the age at onset, the medical history, and the presence of fever/inflammatory syndrome and other associated signs. A muscle biopsy by an expert pathology laboratory should be performed in the event of isolated prolonged muscular involvement. Genetic and/or metabolic studies may be considered, with the help of an expert center, for muscular dystrophy or myopathies resulting from a constitutional metabolic disease. In cases of acute febrile muscular impairment, blood culture, viral serology, and parasitic serology, based on clinical and paraclinical features, should be performed. In cases of acute muscular atrophy associated with atypical skin manifestations and noncutaneous and muscular involvement and/or severe inflammatory syndrome, the patient should be tested for the presence of autoantibodies indicative of other causes (anti-DNA, anti-Sm, anti-Scl70).

In all cases, muscle biopsy should be performed if there is diagnostic doubt.

5. Therapeutic management

The treatment of JDM is essentially based on systemic corticosteroid therapy, associated with an immunosuppressant to limit cortisone use. Rehabilitation is essential.

All patients suspected of inflammatory myopathies should be referred to a specialized center (European recommendations [37]).

The following signs of severity require urgent care (European recommendations):

- severe impairment leading to bed confinement;
- CMAS score < 15 or MMT8 score < 30;
- severe interstitial parenchymatous pulmonary disease;
- digestive vasculitis (determined by imaging or the presence of melena/rectorrhagia);
- hospitalization in an intensive care unit;
- swallowing disorders leading to dysphagia or requiring aspiration or a nasogastric tube;
- severe cutaneous ulcerations;
- myocarditis;
- age < 1 year.

5.1. Medical treatments

5.1.1. The first-line treatment

The first-line treatment recommended at the diagnosis of JDM involves high-dose corticosteroids (oral or intravenous) and methotrexate (European recommendations [37]). This recommendation was supported by a randomized trial that concluded that combined treatment with prednisone and either ciclosporin or methotrexate was more effective than prednisone alone. The safety profile and steroid-sparing effect favored the combination of prednisone plus methotrexate [38].

5.1.2. In cases of resistance to treatment

In cases of resistance to treatment in a newly diagnosed patient, therapeutic intensification should be considered within 12 weeks, after consultation with a specialized center (European recommendations) [35]. In case of intolerance to methotrexate, other treatment should be prescribed (European recommendations). The decision to introduce second-line treatment should be discussed with centers with expertise. The French Working Group recommends that mycophenolate be considered as a second-line approach [39]. Intravenous immunoglobulins (IVIG) can be proposed as an adjuvant treatment in cases of corticosteroid dependence or corticosteroid resistance, particularly for persistent skin disorders (European recommendations).

5.1.3. Various third-line

Various third-line treatments can be proposed in cases of intolerance or ineffectiveness of previous treatments. The evidence of their efficacy is mostly only from small uncontrolled series: cyclosporine A, azathioprine, cyclophosphamide, and tacrolimus [1,40–42]. In a double-blind, placebo-phase trial in adult and pediatric myositis patients, patients were randomized to receive either rituximab early or rituximab late. Although there were no significant differences in the two treatment arms for the primary and secondary end points, 83 % of adult and juvenile myositis patients with refractory disease met the definition of improvement. JDM subset and lower disease damage strongly predict clinical improvement in patients with refractory myositis [43,44]. The French Working Group recommends early consideration of plasma exchange or immunoadsorption, possibly in combination with rituximab, for some severe acute forms, including vasculopathic forms (expert opinion).

No data are available to determine optimal duration of treatment. European recommendations are to propose discontinuation of the immunosuppressants after a remission period of at least 1 year without corticosteroids.

5.1.4. For the rare cases of severe respiratory impairment

For the rare cases of severe respiratory impairment, the recommendations presented pertain to adults, but can be extrapolated to children, in whom this manifestation is rare. Such cases are mostly associated with anti-MDA5 antibodies and are characterized by rapidly progressive pneumonia, with a PaO_2 of less than 60 mmHg in patients admitted to intensive care; the mortality rate is extremely high. For these patients, bolus corticosteroid therapy combined with cyclophosphamide or cyclosporine therapy can be used. Some authors also suggest joint treatments from the outset and considering plasma exchange.

5.1.5. Treatment of cutaneous involvement (outside of basic treatment)

Cutaneous involvement is often amenable to topical treatment; it may develop differently from that of muscular involvement.

Preventive treatment is based on photoprotection: the efficacy has not been demonstrated in JDM, but it is nonetheless recommended by all experts because of the photo-induced or photo-aggravated character of the heliotropic rash of JDM. It involves wearing protective clothing associated with the use of topical products with a solar protection index of 50, renewed regularly if exposed to the sun. Local treatments can be considered: dermocorticoids or 0.03/0.1 % topical tacrolimus, often proposed as an alternative in the event of failure or side effects of dermocorticoids (expert opinion). Some systemic treatments may also be effective: hydroxychloroquine as monotherapy, or associated with, or relaying, anti-inflammatory topicals. IVIG may be a useful adjuvant treatment for JDM refractory to conventional therapy, especially if the skin involvement is extensive (European recommendations). There is no indication to intensify immunosuppressive systemic treatment in the event of complete muscular response and partial skin response (expert opinion). There is also no indication for immunosuppressive systemic therapy in cases of amyopathic JDM (expert opinion), because no randomized study has shown that early treatment prevents the secondary onset of muscle damage or the occurrence of calcinosis.

5.1.6. Treatment of calcinosis.

If calcinosis emerges or is present, intensification of immunosuppressive therapy should be considered (European recommendations). Improvement has been reported for some patients on bisphosphonates (pamidronate/alendronate), infliximab, abatacept, diltiazem, probenecid, IVIG, or local application of sodium thiosulfate. However, no recommendation for specific treatment can be currently proposed. In the extended disabling forms, surgical excision can be considered. Calcinosis often evolves towards spontaneous regression within a few years.

5.2. Physiotherapy

Physiotherapy is an essential component of care. The recommendations for physiotherapists for the management of JDM are available on the SOFREMIP website: sofremip.sfpediatrie.com/.

5.3. Analgesic treatment

Analgesic treatment is required in case of musculoskeletal pain. Recommended intake of calcium and vitamin D are required in all children who receive prolonged corticosteroid treatment.

5.4. Other elements of care

In case of pain related to arthritis, an analgesic treatment must be associated with the specific treatment.

The standard vaccination schedule for children should be followed, in accordance with vaccine guidelines. Vaccination against influenza and pneumococcal disease is recommended for all patients requiring immunosuppressive therapy or biotherapy. It is recommended that patients receiving immunosuppressive therapy or biotherapy not be simultaneously vaccinated with live vaccines. Calcium and vitamin D supplements are often given to improve overall bone density.

6. Follow-up

Complications related to JDM or treatment may occur during the course of the disease and require specialized management [45–47]. The complications may be muscular and articular, cutaneous (stretch marks, skin atrophy, pigmentation disorders), metabolic (lipodystrophy, insulin resistance) [48], ophthalmological (cataract, related to prolonged corticosteroid therapy), and cardiovascular (pericarditis, myocarditis, arterial hypertension), and there may be obesity associated with corticosteroid therapy, osteoporosis, and stunted growth. The follow-up should monitor the activity and severity of the disease and the efficacy and tolerance of the treatments, according to different scores [49–57]. The details of follow-up depend on the severity of JDM and must be carried out in association with an expert center.

Disclosure of interest

The authors declare that they have no competing interest.

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