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# Diagnosis and management of Becker muscular dystrophy: the French guidelines

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Guilhem Sole, Yann Pereon and Armelle Magot had the idea for the article, all the authors performed the literature search and data analysis, Armelle Magot drafted the article. All the authors critically revised the work.

#### Keywords

Becker muscular dystrophy • Guidelines • Diagnosis • Care management • Therapeutics  
• Female carriers

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# Abstract

Becker muscular dystrophy (BMD) is one of the most frequent among neuromuscular diseases, affecting approximately 1 in 18,000 male births. It is linked to a genetic mutation on the X chromosome. In contrast to Duchenne muscular dystrophy, for which improved care and management have changed the prognosis and life expectancy of patients, few guidelines have been published for management of BMD. Many clinicians are inexperienced in managing the complications of this disease. In France, a committee of experts from a wide range of disciplines met in 2019 to establish recommendations, with the goal of improving care of patients with BMD. Here, we present the tools to provide diagnosis of BMD as quickly as possible and for differential diagnoses. Then, we describe the multidisciplinary approach essential for optimum management of BMD. We give recommendations for the initial assessment and follow-up of the neurological, respiratory, cardiac, and orthopedic consequences of males who present with BMD. Finally, we describe the optimal therapeutic management of these complications. We also provide guidance on cardiac management for female carriers.

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## Introduction

Becker muscular dystrophy (BMD) was first described in 1953 by Emile Becker as a benign variant of Duchenne muscular dystrophy (DMD) [1]. BMD is an X-linked recessive disorder that affects approximately 1:18,000 male births [2], with 50% being familial cases (38.5% for DMD). BMD is caused by *DMD* gene mutations that usually lead to a reduced size or amount of dystrophin protein and result in a more benign skeletal muscle phenotype in comparison with DMD [3, 4]. Indeed, BMD is clinically more heterogeneous, with a wide spectrum of clinical presentations ranging from asymptomatic elevation of serum creatine kinase levels and pseudo-metabolic symptoms, mild limb-girdle weakness and quadriceps myopathy [5] to initial presentation in the teenage years with loss of ambulation occurring far beyond the age of 16 years [6]. BMD patients usually remain ambulatory until the fourth or fifth decade of life but more frequently show severe cardiomyopathy. Cardiac involvement is responsible for 50% of the deaths of BMD patients and may necessitate heart transplants. Although the average age of death is 45 years, many patients have close to normal life expectancy [5]. Female carriers of BMD/DMD are usually asymptomatic, although a few of them may present with clinical symptoms ranging from mild to severe muscle weakness and/or cardiomyopathy [7–10].

Although guidelines for DMD patients have already been published [11–13], those for BMD patients are scarce. The aim of this review is to present recommendations for BMD management on the basis of an analysis of expert ratings of assessments and interventions. To gain clarity, we shall cover all forms of BMD except the most severe form (DMD). In France, diagnosis and care are generally provided in reference centers labeled in the national neuromuscular network FILNEMUS. In this review, we cover the following topics: diagnosis, rehabilitation, and cardiovascular, orthopedic/ surgical, respiratory, and nutritional management.

## Methods

As is observed typically for rare diseases, only a few largescale randomized controlled trials (RCTs) have been completed for BMD. As a result, the guidance in this article is not conventionally evidence-based. Instead, these insights are based on a critical analysis of the international literature in accordance with the “Method of Drafting of a National Diagnostic and Care Protocol for Rare Diseases” published by the French Health Authority in 2012 [14]. The content was discussed and validated by a multidisciplinary working group. Two groups were assembled and a several step process was used:

- A core leadership group composed of five specialists such as neurologists, cardiologists, geneticists, and pneumologists, performed the bibliographic research, analyzed and did the synthesis of the literature. It then drafted a first version of the guidelines with care management proposals. The bibliographic search was made from Pubmed database without restriction of language from 1970 to the present day, with main keywords being “Becker Muscular dystrophy”, “Duchenne Muscular dystrophy” and “muscular dystrophy” paired with multiple terms as “diagnosis”, “genetics”, “cognitive issues”, “imaging”, “physical therapy”, “anesthesia”, “respiratory”, “cardiac” “nutritional” “gastrointestinal”...
- A reader group composed of specialists involved in multidisciplinary care management of neuromuscular patients (rehabilitation specialists, neuropediatricians, neurologists, geneticists, cardiologists, pneumologists, and primary care practitioners) and patients and advocacy group representatives read, corrected, commented on and validated the proposals.
- The core group finalized and published the guidelines under French Health Authority.
- All participants (medical and paramedical groups) were issued from the major neuromuscular reference centers in France, within French neuromuscular network FILNEMUS.

French guidelines will be updated on an unregular basis depending on the progress in care management, diagnostic tools and treatments, basically every 5–7 years.

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### Diagnosis (Fig. 1)

The typical BMD patient is a young man presenting with a slowly progressive pelvic deficit and calf hypertrophy together with an increase in CK levels [5]. Family history can be evocative with a clear X-linked recessive inheritance. Disease onset usually appears around the age of 12 years but remains quite variable. In the beginning, only the lower-limb muscles are affected symmetrically, causing fatigability while walking. This is followed by weakness in standing up or a waddling gait. In the most severe forms, the patient may lose ambulation. The clinical distinction between DMD and BMD is based on the progression of the disease, which is reflected by the age at which the patient requires a wheelchair: before 13 years for DMD and after 16 years for BMD. Contractures could be observed during the course of the disease [5].

Cramps are a common phenomenon, occurring most often during or after physical exercise. Their mechanism remains poorly understood, but patients with less severe disease seem to

have more cramps because they show greater physical activity than those with severe BMD [15]. BMD patients, like those with DMD, develop hypokinetic cardiomyopathy characterized by progressive impairment of left ventricular systolic function and, occasionally, cavitory dilatation defining dilated cardiomyopathy (a combination of left ventricular ejection fraction (LVEF) < 45% and cavitory dilatation) [16]. Most often, left ventricular kinetics abnormalities and the presence of myocardial fibrosis predominate in the inferolateral territory before becoming more global.

Cardiac dysfunction on ultrasound (US) may be associated with clinical signs of heart failure. Untreated dysfunction and heart failure may progress to terminal heart failure, which is the main cause of death in BMD patients. Abnormalities in the heart's electrical activity are not common, unlike other neuromuscular diseases affecting the heart. Some patients develop ventricular extrasystoles or moderate conductive disorders, but the risk of sudden death, sustained ventricular tachycardia, or complete atrioventricular block remains low. The prevalence of dilated cardiomyopathies in BMD patients is estimated to be between 30 and 40% and is correlated with age: 15% before 20 years of age and 55% after 40 years of age [17, 18]. Some patients may also present only an isolated dilated cardiomyopathy without peripheral muscle involvement [19].

As in DMD, patients may show impairment of the central nervous system, mainly in childhood. Young boys do not always show muscular involvement, and more rarely, neurodevelopmental disorders are the first sign of the disease [20–24]. A prevalence of intellectual developmental disorders was found about 8%, contrasting with the value of 2% encountering in children and adolescents [25]. Among these, autism spectrum disorders, attention-deficit hyperactivity disorder, depression, anxiety disorders, and obsessive-compulsive disorder were not exceptional [26]. Indeed, BMD is associated with the prevalence of epilepsy, with a higher prevalence in BMD population than in the general population [27]. The CK plasma level guides the diagnosis toward dystrophinopathies. The important and complex expression of dystrophin in the central nervous system (gene products Dp140 or Dp71) probably partly explains the frequency and the diversity of central nervous system involvement encountered in dystrophinopathies [28].

### **Diagnostic assessment**

Even in the absence of index cases in the family, the clinical picture is often sufficiently suggestive to provide an initial indication of BMD. High CK levels are helpful, and the diagnosis can be confirmed by muscle biopsy and, more specifically, by the identification of a pathogenic variation in the *DMD* gene.

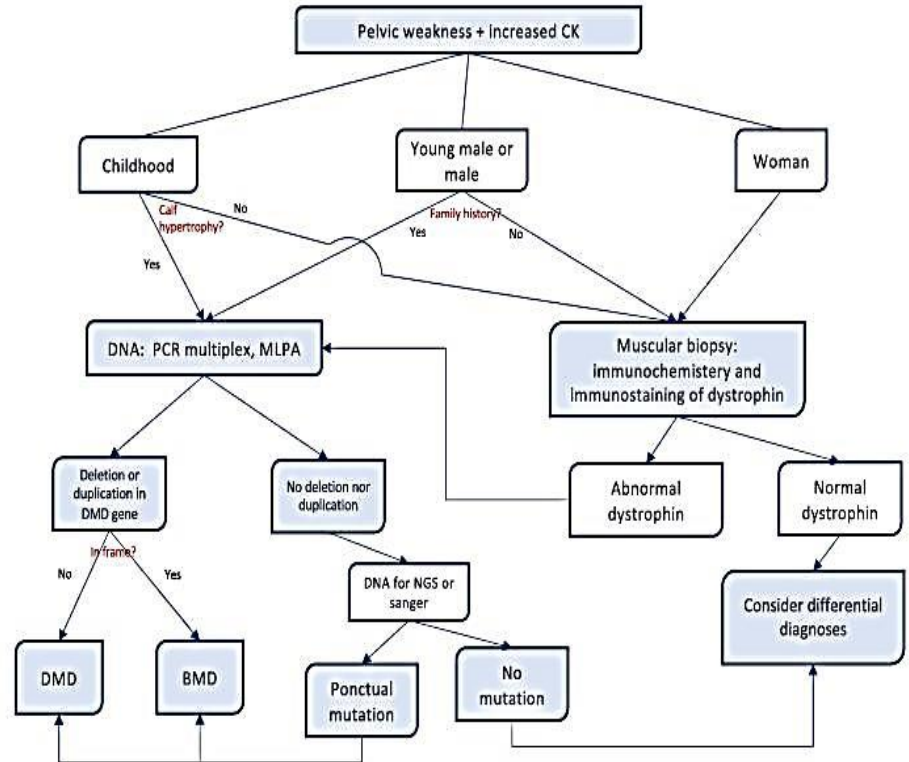
Genetic testing may come prior to muscle biopsy for the diagnostic workup—a muscle biopsy with immunohistochemistry and immunoblotting can be helpful for clarifying VUS in the dystrophin gene. Indeed, muscle biopsy remains essential in cases showing pauci-symptomatic forms or pseudo-metabolic forms with exercise intolerance. In the presence of a genetically proven index case in the family and/ or an evocative clinical picture in a man with elevated CK levels, it is reasonable to directly process genetic analysis.

Muscle biopsy is not necessary for the diagnosis in carrier women with symptoms and a familial history of dystrophinopathy. In cases involving symptomatic patients with no known family history, the assessment can be the same as that adopted to explore a limb-girdle deficit.

### **Paraclinical data Biology**

Plasma CK levels are generally higher than 1000 IU/L (even more than 10,000 IU/L in some cases) [29]. The increase in CK levels is more marked at the beginning of the disease and progressively decreases with muscle fatty involution. Some patients with benign forms may have values below 1000 IU/L. The levels of liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can be increased, which may sometimes result in misdiagnosis, especially in pseudo-metabolic forms, and may lead to liver biopsy [30].

Fig. 1 Diagnostic approach in case of suspicion of BMD



## Electrodiagnosis (EDX)

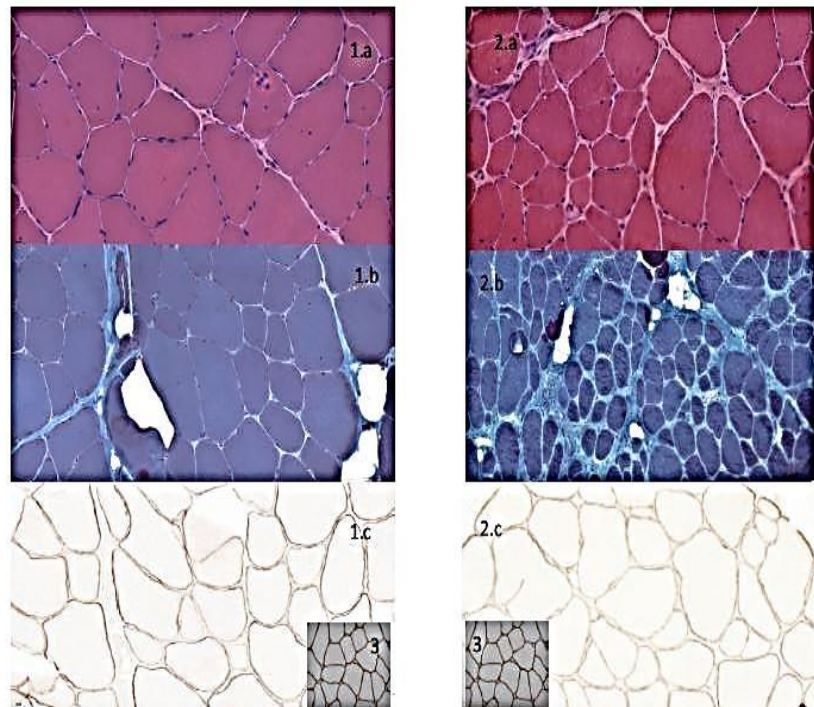
Although electromyography (EMG) and nerve-conduction studies have been a traditional part of the assessment of patients with a suspected neuromuscular disorder, the expert panels do not consider these tests to be essential for the specific assessment of BMD. EMG examination reveals nonspecific myopathic abnormalities (small size and short-duration motor unit potentials, increased recruitment). However, in the advanced stages of the disease, the number of surviving muscle fibers decreases and large areas of muscle may remain silent. The EMG pattern can be mixed or even pseudo-neuropathic [31].

## Muscle imaging

Like EMG, imaging assessments are useless for diagnosis in patients with typical clinical features and an informative family history. Nevertheless, they may be helpful for the diagnosis of atypical forms and for follow-up evaluations. In the lower limbs, the muscles affected in more than 50% of the cases are mainly the limb girdle and thigh muscles, including the gluteus maximus, gluteus medius, quadriceps femoris, adductor longus, adductor magnus, semi-tendinosus, semi-membranosus, and biceps femoris. In the upper limbs, triceps brachii and biceps brachii are preferentially involved. In most cases, the abnormalities are symmetric. Some muscles are also often spared, including the deltoideus and coraco-brachialis [32]. Magnetic resonance imaging (MRI) can define the distribution of muscle involvement and allow assessments of the degree of severity of the disease. Muscle CT scans can be performed in patients who cannot undergo MRI examinations, but they provide lower-quality information and involve substantial exposure to X-rays.

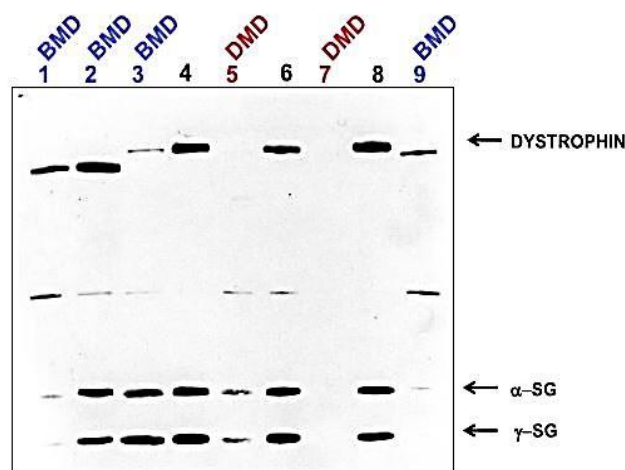


**Fig. 2** Histopathology from two patients: 1. patient with mild form of BMD, 2. patient with severe form of BMD. **a** hematoxylin and eosin. **b** Gömöri trichrome. Increased fiber size variation, fiber splitting, proliferation of endomysial and perimysial connective tissue, degenerating fibers, regenerating fibers, and necrosis and the subsequent loss of fibers, which increased internal nuclei. **c** Dystrophin Immunohistochemistry. Decreased and fragmented staining at the sarcolemma of the muscle fibers compared to control (3)



### Muscle biopsy (Figs. 2, 3)

Muscle biopsy remains very useful for the diagnosis of sporadic BMD. It is usually surgically performed in the quadriceps femoris or deltoideus muscles and must be conducted within a specialized structure, with immediate freezing of the fragments in cooled isopentane followed by freezing in liquid nitrogen and storage at  $-80^{\circ}\text{C}$  for subsequent western blot analysis, if needed. Biopsies have to be analyzed by a neuropathologist trained to evaluate neuromuscular diseases [33, 34].



**Fig. 3** Western blot analysis of muscle from a control (lane 4, 6, 8) and patients with dystrophinopathies probed with anti-dystrophin monoclonal antibody Dys2 (NCL DYS 2, Novocastra) and alpha Sarcoglycan and gamma Sarcoglycan (NCL-g-SARC et NCL-a-SARC). **BMD Patients:** 1, 2, 3, 9 with in frame deletion patient 1: truncated

dystrophin in reduced quantity, patient 2: truncated dystrophin in normal quantity, patient 3: truncated dystrophin in very small quantity, patient 9: truncated dystrophin in very low quantity. **DMD Patients:** 5, 6 with out of frame deletion Patient 5: absence of dystrophin, patient 7: absence of dystrophin



Optical microscopy examination can confirm the muscular dystrophy, demonstrating the association of necrosis, regeneration, and fibrosis. Marked variations in the fiber size, split fibers, and multinucleate and hyper-contracted bulky fibers are also markers of dystrophinopathy [35]. Fatty infiltration and both endomysial and interstitial extensive fibrosis are seen in the advanced stages of the disease. In mild clinical forms, morphologic abnormalities may be subtle: moderate variations in fiber size, scattered necrosis fibers, and rare nuclear internalizations. Inflammatory abnormalities can be observed [36].

Dystrophin immunochemistry usually shows decreased or no findings with some or all of the dedicated antibodies, but may also show normal findings. The decrease can be present in all the fibers or manifest in a fragmented manner. Diagnosis should be completed by western blotting of dystrophin [35, 37] using several antibodies targeting different parts of the protein. The bands corresponding to dystrophin show a reduced amount of protein or a reduced molecular weight. The use of several antibodies targeting different parts of the protein is necessary to increase the chances of demonstrating dystrophin expression loss.

Carrier women present dystrophin mosaic expression, with a mixture of normal- and low-intensity fibers and a non-uniform distribution of negative fibers across the samples [38, 39]. This mosaic is probably due to the formation of multi-nucleated muscle fibers from uninucleated myoblasts with variable expression of dystrophin based on differences in X-inactivation. The proportion of immunochemical abnormalities varies between 10 and 100% in carrier women depending on whether they are symptomatic or not. In this particular scenario, western blotting is only contributive when the inactivation is unbalanced and the expression of dystrophin very weak [40].

### **Genetic testing**

The genetic definition BMD vs DMD relies upon the type of mutation: out-of-frame mutations lead to truncated, nonfunctional dystrophin proteins and are associated with the DMD phenotype, whereas in-frame mutations produced a partial but functional protein found in BMD patients [41]. Genotype/phenotype correlations are always under investigation in BMD, and that due to the wide clinical spectrum of BMD among patients with different mutations, the surveillance frequency might need to be tailored for patients with specific mutations in the future [42].

Three steps are necessary because of the frequency of abnormalities in the mutational databases in the *DMD* gene [43–46].

First step: major remodeling of the *DMD* gene (deletions, 80%/duplications, 13%) is initially evaluated. *DMD* gene analysis is performed from a sample of 10 mL of whole blood on ethylene-diamine-tetraacetic acid (EDTA). Two techniques allow rapid diagnosis of most deletions and duplications: multiplex ligation-dependent probe amplification (MLPA) and semi-quantitative multiplex polymerase chain reaction (PCR) (ABI-Genescan QF-PCR) [44, 47]. MLPA is one of the most routinely used techniques. It assesses the number of copies for each of the 79 exons of the *DMD* gene. The results must always be checked by a second technique when an anomaly affecting an isolated exon is found. Semi-quantitative multiplex PCR simultaneously explores the 50 most often deleted or duplicated exons and can reveal smaller deletions or duplications from one to several bases. Isolated amplification of the exons surrounding the highlighted deletion is sometimes necessary to specify the bounds. For duplications, quantitative techniques such as real-time

PCR or digital PCR can be used to define the limits of the anomaly. *DMD* gene exon deletion or duplication can also be spotted through next-generation sequencing (NGS) after a specific copy number variation bioinformatics pipeline based on restricted gene panel, exome or genome data [48].

Second step: searching for point mutations (6%). In the absence of deletions and duplications, a point mutation should be searched for by Sanger or NGS, which identifies single-nucleotide variations, small insertions/deletions, as well as previously mentioned quantitative defects such as deletions or duplications of one or more exons.

Third step: analysis of transcripts. When no abnormality in the coding sequences (deletion, duplication, point mutation) is found, the messenger RNA (mRNA) data should be extracted from the muscle biopsy in order to search for rearrangements in the coding sequences. The mRNA is transcribed into complementary DNA (cDNA) by reverse transcription PCR (RT-PCR) and then amplified into overlapping fragments. Each fragment is explored and then sequenced by the Sanger method. This technique can highlight the point mutations affecting splicing, such as deep intronic variations that could be missed in panel or exome NGS sequencing. Their splicing effects will appear on mRNA in the form of intronic retention or the creation of a neo-exon [49].

### **Differential diagnosis**

The main differential diagnosis included limb girdle muscular dystrophy (LGMD), facio-scapulo-humeral muscular dystrophy type 1 (FSHD1), inflammatory myopathies and spinal muscular atrophy (SMA) are summarized in Table 1 [50–55].

### **Diagnosis announcement**

Diagnosis announcement is a crucial moment in patient management and is an important milestone in the doctor–patient relationship. As in all debilitating chronic diseases, the quality of the initial information can decisively influence the patient’s experience, motivation to undergo treatment, and accept the care management program. Diagnosis announcement is ideally performed by the person who is already familiar with the patient and will subsequently follow up the patient. It should be performed by a specialized physician experienced in neuromuscular diseases to ensure that the patient receives accurate information about the prognosis and therapeutic options. A dual consultation with a psychologist is strongly recommended. The psychologist will then provide support to the patient and the patient’s relatives [56].

In case of children, the information provided should be tailored to the age of the patient at the moment of the diagnosis, understand the level of information that the patient is willing to receive, that it might require the present of parents/ adult legal guardians and that the information might be provided in different steps as long as the patient growth.

### **Care management**

After diagnosis, the neuromuscular specialist will serve as the lead clinician, taking overall responsibility for care of the BMD patient and performing multiple roles and responsibilities across the individual’s lifetime. The multidisciplinary approach to caring for patients with BMD and the range of expertise required are key features of this management approach.

## **Professionals involved**

Medical: primary care physician, neurologist, cardiologist, pulmonologist, rehabilitation specialist, geneticist, and radiologist.

Paramedical and related: physiotherapist, dietitian, occupational therapist, psychomotor therapist, speech-language pathologist, chiropodist, neuropsychologist, psychologist, orthoprosthodontist, social worker, and other service providers.

## **General considerations**

BMD is a long-term condition that may benefit, depending on the country, from full health insurance coverage. BMD requires regular monitoring, ideally on a multidisciplinary basis in a reference center, throughout the life of the patient. The goal of this follow-up regimen is to assess the improvement in the patient's quality of life and prolong survival. The frequency of monitoring can be adapted to each patient's requirements but is generally biennial. The objectives of monitoring include following the course of the disease; screening for organic involvement; evaluating the psychological and socio-professional impact of the disease on school integration and family; preparing life projects; preparing, if necessary, for hospitalization in the emergency and acute care departments; delivering care and emergency care; informing about research and therapeutic trials; and educating the patient about the illness.

No curative treatment has been proven to be effective in the management of BMD. Steroids have been tested in some BMD patients but evidence for efficacy remains limited, unlike DMD patients. Steroids could be used at the discretion of the physician if side effects (weight gain, increased risk of bone fractures, cataract or behavioral changes) are not severe. The schedule and dosage should be adjusted if necessary [57].

Therapeutic management is based on symptomatic management of the pathology. Patients with the most severe presentations or those requiring special care may be reported as remarkable patients to the emergency medical service.

## **Paraclinical follow-up**

In the context of cardiological and pneumological followup, there is no reason to propose systematic complementary examinations other than those proposed above. EDX examinations have no place in the systematic monitoring of patients outside of specific situations (e.g., compression of a nerve trunk due to muscular atrophy or a positioning problem, unexplained pain of neurogenic appearance). Likewise, quantitative muscle imaging is rarely used to assess the progression of the disease [58]. There is no standardized and systematic laboratory assessment in BMD patients. In specific cases, it may be necessary to detect metabolic complications such as glucose intolerance or diabetes, dyslipidemia, or possible undernutrition (anemia, iron deficiency, or vitamin deficiency, particularly D3 deficiency). There is no interest in monitoring CKs since they are not correlated with the course of the disease.

**Table 1** Main differential diagnosis

| Condition                    | Gene   | Mode of inheritance | Pelvic girdle and lower limb muscle involvement | Shoulder girdle and upper limb muscle involvement | Other clinical features  | Immunohistochemistry findings  | Other ancillary test findings                            |
|------------------------------|--|---------------------|---|---|--|--|--|
| Becker muscular dystrophy    | <i>DMD</i>   | X-linked recessive  | Yes   | Yes, later  | Calves hypertrophy<br>Macroglossia<br>Cardiac impairment   | Dystrophic pattern<br>Decreased dystrophin immunostaining                | CK generally > 1000 IU/L                                 |
| LGMDR9 [50]                  | <i>FKRP</i>  | Recessive           | Yes   | Yes, later  | Calves hypertrophy<br>Macroglossia<br>Cardiac impairment   | Dystrophic pattern<br>Inconstant reduced $\alpha$ -Dystroglycan staining | CK 1000 to 8000 IU/L                                     |
| Bethlem collagenopathy [51]  | <i>COLVI</i>   | Dominant            | Yes   | Yes, later  | Joint contractures (Achille tendon and finger flexor), distal finger hyperlaxity<br>Keloid scare, hair keratosis | Non-specific myopathy<br>Normal dystrophin immunostaining                | CK normal to 1700 IU/L<br>Typic MRI muscular involvement |
| LGMDR 3, 4, 5, 6 [52]        | <i><math>\alpha</math>SGC, <math>\beta</math>SGC, <math>\gamma</math>SGC, <math>\delta</math>SGC</i> | Recessive           | Yes, severe                                     | Yes, severe                                       | Cardiac impairment   | Dystrophic pattern<br>Reduced or absent sarcoglycan staining             | Very High CK, often > 5000                               |
| FSHD1 [53]                   | D4Z4repeat DNA deletion  | Dominant            | No, distal weakness                             | Yes, scapular winging                             | Facial weakness<br>Asymmetrical involvement  | Varied fiber size<br>Internal nuclei<br>Inflammation (75%)               | CK Normal to < fivefold elevated                         |
| Inflammatory myopathies [54] | NA   | NA                  | Yes   | Yes   | Subacute weakness  | Inflammation   | Normal to very high CK<br>Edema at MRI                   |
| Spinal muscular atrophy [55] | <i>SMN</i>   | Recessive           | Yes   | Yes, later  | Diffuse fasciculations<br>Reduced or absent tendon reflexes  | Neurogenic pattern   | CK may be high usually < 1000 IU/L                       |

*LGMD* Limb girdle muscular dystrophy, *FSHD1* facio-scapulo-humeral muscular dystrophy type 1, *SMA* inflammatory myopathies and spinal muscular atrophy

## Neuromuscular management Initial assessment

The purpose of the initial muscle assessment is to lay the foundations for subsequent follow-up. This assessment is adapted to patient's age and functional disability. It is based on a clinical examination supplemented by tests and scales, and it requires training and experience to maintain competence.

The choice of tests to use in any particular category will be influenced by local factors; consistency within an individual clinic is important to allow comparison over time.

The clinical exam focuses on the following signs:

- Gait disorders: waddling gait, hyperlordosis.
- Weakness of the pelvic girdle muscles: inability to get up from the squatting or sitting positions (involvement of the psoas, gluteus, quadriceps)

- Weakness of the shoulder girdle muscles: inability to carry the hands above the head, impairment of the humeral muscles (biceps in particular)
- Axial weakness: scoliosis, abdominal weakness with difficulties in getting up from the lying position
- Pseudohypertrophy of the calves, tongue, or other muscles.
- Reductions in muscle extensibility and joint contractures, particularly at the ankles.

Specialized functional assessment includes standardized assessments specific to neuromuscular disorders. Different quantified tests can be offered:

- The 6-min walk test, although imperfect, is a benchmark test, especially for clinical trials. It involves measuring the patient's walking perimeter in 6 min [59].
- Timed functional tests: walking time over 10 m, time required for climbing four steps, time to get up from the lying position, sitting, holding time for the Barre and Mingazzini maneuvers [60]
- Brooke and Vignos scales [61, 62]
- Motor function measurement scale (MFM), which consists of 32 items (MFM-32) [63, 64], or 20 items for children under the age of 7 years (MFM-20) [65], which are scored from 0 (unable to perform the gesture) to 3 (normal gesture). The items close to daily life gestures are divided into three dimensions: D1 (standing position and transfers), D2 (axial and proximal motor skills), and D3 (distal motor skills) and a score is assigned to each dimension as a percentage of the rating normal. Training is mandatory to perform this scale in order to ensure reproducible results.
- Evaluation of muscle strength by manual testing (MRC score). The muscle groups tested must be tested bilaterally and remain the same during follow-up, including extensors and flexors of the neck, abductors of the shoulder, flexors and extensors of the elbow, hip, knee, and hip abductors.
- North Star Ambulatory Assessment (NSAA) was developed from the Hammersmith Scale of Motor Ability. The NSAA is a global assessment of ambulatory ability incorporating several activities and takes approximately 10 min to complete [66].
- The North Star Assessment for limb-girdle type muscular dystrophies (NSAD): Validation of the North Star Assessment for Limb-Girdle Type Muscular Dystrophies [67].
- Other tests such as manual dynamometry and quantitative manual testing can also be offered.

## **Neuromuscular monitoring**

Neuromuscular monitoring is based on clinical examination of the patient with quantified tests performed during the initial evaluation. Reproducibility is an important characteristic of these tests. In children and in the most severely affected patients, screening for the following orthopedic consequences of the disease is essential:

- Muscle and joint contractures (Achilles tendons, hip, knee, elbow flexum)
- Kyphoscoliosis
- Daily routine: assessment of the level of studies, activity, life support, accommodation (accessibility, patient lift, bathroom, and toilets), vehicle adaptation, and night-time support (medical bed, type of mattress, number of turnovers per night) is essential. In working patients, appropriate adaptation of the workstation should be verified. Finally, care should be taken to screen for pain.

## **Intervention: physical medicine and rehabilitation**

### **General considerations**

Physiotherapy plays a central role in the care of patients with neuromuscular diseases. Physiotherapy performed twice a week for a period of 30–45 min, depending on the capacity, fatigability, and availability of the patient, seems to be the most beneficial. The aim of the exercises performed during these sessions is to optimize, maintain, or improve the patient's functional capacities to avoid complications secondary to a sedentary lifestyle and deconditioning (articular, metabolic, sensorimotor, trophic and cardiorespiratory) and to avoid a loss of autonomy [68]. This physical activity must be gentle and progressive and must take into account the specificities of BMD when choosing the exercises to offer [69]. The most affected muscles (those with a muscle testing MRC rating < 4) require more precautions, specifically by limiting intense contractions and eccentric stresses and promoting aerobic metabolism. Disorders associated with BMD must be taken into account: pain (rest and stress myalgia), respiratory or cardiac involvement, and swallowing or cognitive disorders (executive problems) must be sought and monitored.

### **Management strategies**

Management strategies must fit with the patient's needs and may include the following approaches [69, 70]:

- Maintenance of segmental and spinal muscular and joint flexibility for analgesic purposes by passive mobilizations and stretching, preparation and recovery for exercise and proprioceptive stimulation: stretching, posture, etc. Note that heating is essential to prepare the muscle well.
- Maintenance of segmental and spinal force in order to improve static capacities by good muscle control (or feedforward) as effectively as possible using analytical and functional work in low resistance and endurance (< 30% max force). Working in dynamic or isometric concentric is recommended because it is less tensional.



- Static and dynamic balance work in different positions (seated and in intermediate positions corresponding to the levels of motor evolution and standing by stimulating compensations) in order to optimize peripheral inferences: proprioceptive work, changes in the support polygon, extrinsic imbalances, scenarios, etc.
- Aerobic work.
- Maintenance of functional capacities.
- Prevention and advice regarding the risk of falling.
- Promotion of adapted physical activity, self-rehabilitation, postures, self-stretching, gentle strengthening exercises, etc.
- Pain relief.

### **Orthoses**

Posture orthoses may be used in some patients. In the lower limbs, nocturnal posture orthoses can be proposed to address certain deformities (e.g., anti-flexum knee or antiequine orthosis). Orthopedic shoes are only necessary in the severest cases with major deformations that preclude the use of conventional footwear or involve discomfort or skin pain. Walking orthotics can sometimes provide functional benefit.

Use of upper limb orthoses is rare. Rest orthoses, in particular inter-phalangeal or wrist contractures, can be used in the event of nerve trunk compression.

It is exceptional to use a corset except in very severe forms of the disease, pending a possible vertebral arthrodesis [68].

### **Surgery**

Some surgeries (e.g., Achilles tendon tenotomy, gastrocnemius aponeurotomy, tendon transfers, osteotomies or foot arthrodesis) are useful, and their uses must be linked to functions such as walking and posture stability. Vertebral arthrodesis is limited to the most severe forms close to DMD [68]. In rare cases, macroglossia surgery may be required because of functional consequences (ventilation, swallowing, etc.).

### **Assistive/adaptive devices for function**

Depending on the needs and the evolution of motor impairment, the assessment may include: joint amplitude assessments, functional (evaluation of body language, strength and tiredness, grips, capture space, writing, handling of school tools, meals, leisure) and assessment of autonomy and the environment. The results of these assessments will determine the technical aids and environmental management.

### ***Technical devices for moving***

Manual wheelchair; electric scooter and/or electric wheelchair are necessary when the risks linked to walking (falls, fractures) become greater than the functional benefits.

### ***Everyday technical devices***

Specific devices facilitating meals, washing, toileting, leisure, transfers, and environmental control can be implemented.

### ***Technical devices for communication***

These include a voice-activated laptop or mini joystick in the event of low power, speech synthesis, mobile phone/hands-free desk phone, call bell.

### ***Home layout***

The home layout must take into account access from outside (inclined plane, elevator) and inside to the home, the size of the rooms, and their coating. The layout may include modifications for the bathtub and/or shower and the use of bathroom lifting seats, bathing deckchair, changing table, fitted WC, electric medical bed, height-adjustable desk, desk, page turner, transfer system (patient lift or rail ceiling), home automation, and air conditioning. Home improvement plans must be supervised by an experimental team.

### ***Vehicle layout***

It is necessary to choose a large-capacity vehicle to transport the equipment and provide a system for securing the wheelchair to the floor, a seat belt for children with a shoulder pad, and access by a ramp or electric tailgate, possibly with floor disburse.

If hypoventilation symptoms are present or an obstructive sleep apnea has been diagnosed, patients should avoid driving until treatment has been started or follow local guidelines.

### ***Arrangement of schooling or working place***

For the school, the material, human and pedagogical arrangements are decided within the framework of a personalized schooling project. In the professional world, the involvement of the rehabilitation physician is fundamental.

### **Neuropsychological management Initial assessment**

BMD patients can present autism spectrum disorders, attention– deficit hyperactivity disorder, depression, anxiety disorders, or obsessive–compulsive disorder more frequently than in general population [26, 27]. Cognitive or psychiatric assessment has to be considered at diagnosis, and especially in the event of integration or access to employment issues. Similarly, in the event of academic difficulties, assessment of cognitive disorders can be proposed. This assessment should be performed by a neuropsychologist (clinical psychologist who has specialized training and experience in the formal assessment of cognitive and psychological functions). The choice of standardized tests stays at the discretion of the

neuropsychologist but may include social functioning, emotional adjustment and behavioral regulation evaluations.

### **Neuropsychological intervention**

The neuropsychological assessment allows targeted recommendations. Neuropsychologists work with patients or families to develop strategies useful at work, home or school. For children, assessments should be performed every 2–3 years to monitor a child's developmental progress and response to interventions.

### **Psychological assessment**

BMD is a chronic, progressive disease that progressively reduces functional capacity and, in some cases, shortens the patient's life expectancy. The disease causes motor handicap with a critical impact on all dimensions of life: professional, family, social. Therefore, assessment of the patient's psychological state and quality of life, from the beginning and throughout the evolution, is recommended. The neuromuscular team should include a mental health clinician who had experience in assisting patients with chronic disease. At each neuromuscular clinic visit, mental health and quality of life should be screened. For adults, the Patient Health Questionnaire 9-item depression scale and the Generalized Anxiety Disorder 7-item scale could be used [71, 72]. Quality of life questionnaires can also be used [73].

Formal annual evaluation by the mental health clinician is advised to assess the psychological wellbeing of the individual, parents, and siblings.

Psychopharmacological interventions should be taken into account for treating moderate-to-severe psychiatric symptoms or milder symptoms that do not respond to nonpharmacological interventions. Standard prescribing practices and guidelines should be followed, with additional attention given to the individual's overall medical condition. Depending on the patient's age and disease status, it may be necessary to pay special attention to their cardiac status, potential medication interactions, and side effects when combined with existing medications (e.g., weight gain).

### **Cardiologic management Initial assessment**

The initial assessment must include at least an electrocardiogram (ECG) and an echocardiogram. The latter is the most important assessment for the diagnosis of cardiomyopathy. LVEF assessment is a key element to assess the prognosis and guide the treatment strategy [74, 75]. ECG can show inferolateral Q waves and tall right precordial R waves, which reflect the presence of myocardial fibrosis in the inferolateral segments. Conduction defects can also be observed. In cases showing abnormal cardiac systolic function (left ventricular ejection fraction below 50%) or significant conduction defects on the ECG, a 24-h Holter ECG should also be performed to search for ventricular or supraventricular arrhythmias, and the findings will serve as a reference during the follow-up [76, 77]. Cardiac MRI should also be discussed at diagnosis since it provides a more accurate estimation of cardiac function than echocardiography and can identify myocardial fibrosis, mainly in the inferolateral wall, which can be present in patients with a normal echocardiogram. Radionuclide ventriculography can sometimes be useful to monitor LVEF in patients with poor echogenicity who cannot tolerate cardiac MRI due to respiratory insufficiency or major lower-limb retractions. Natriuretic peptide assays in the blood (B-type natriuretic peptide,

brain natriuretic peptide [BNP], or N-terminal pro b-type natriuretic peptide [NT-proBNP]) can be useful for diagnostic and prognostic assessments although their performance may be reduced in patients who have lost ambulation.

For carrier women, the cardiac examinations and interpretation of results should be the same. The assessment should be made upon diagnosis, including as a part of family screening after a diagnosis of BMD in a relative [78].

### **Cardiac monitoring**

Cardiac monitoring is essential because cardiac involvement can occur later than muscular involvement in BMD patients, unlike in DMD patients. It may also appear during the follow-up when the initial assessment was normal [16–19]. The development of cardiomyopathy during follow-up should be diagnosed as early as possible, because early initiation of heart failure treatments can improve patient prognosis.

Cardiac monitoring must systematically include ECG and echocardiogram. The other examinations must be discussed with the patient on the basis of the patients' symptoms and ECG and echocardiogram findings. The frequency of these assessments depends on the initial findings. The minimum interval for a classic form of BMD with a normal echocardiogram is two years. For patients with LVEF < 50%, monitoring should be performed at least once a year. Natriuretic peptide assays can be included among other blood tests. Cardiac MRI should be considered at least every 5 years for an early diagnosis of fibrosis, which should prompt closer monitoring of the LVEF using echocardiograms.

For carrier women, a cardiologic assessment is recommended every 5 years upon diagnosis if the initial workup shows normal results [79].

### **Heart treatment**

Treatment of dilated cardiomyopathies in BMD should rely on heart failure treatments, with angiotensin-converting enzyme inhibitors (ACE inhibitors) being the first-line medication. No trial has assessed the effectiveness of prophylactic ACE inhibitor treatment in BMD patients with normal LVEF, unlike that in DMD. Thus, there is no indication to use ACE inhibitors for systematic treatment of BMD patients regardless of cardiac phenotype, such as in Duchenne MD.

Patients with LVEF < 50% and/or evidence of myocardial fibrosis on MRI should be referred to a specialized cardiologist in a tertiary center to discuss the initiation of cardioprotective treatment. On an individual basis, ACE inhibitors should be considered in this group of patients considering (1) data from the DMD population [12, 80], (2) the influence of cardiac involvement on the prognosis [81], (3) the safety and good tolerance of this treatment, and (4) the frequent underestimation of symptoms due to skeletal muscle damage.

In patients with overt heart failure or left ventricular (LV) systolic dysfunction, the therapeutic strategy should follow the recommendations for the treatment of heart failure in the general population, based on (1) ACE inhibitors (or angiotensin II antagonists), beta blockers, mineralocorticoid receptor antagonists, and other specific drugs [81–83], (2) cardiac resynchronization therapy, and (3) implantable cardiac defibrillator if LVEF < 30%.

In ambulant patients with terminal heart failure and absence of severe respiratory failure, cardiac transplantation and an LV assist device (as a bridge to transplant or destination therapy) should be considered. In patients with terminal heart failure who have lost ambulation or have significant respiratory failure, cardiac transplantation is generally not indicated, but an LV assist device as the target therapy should be discussed on an individual basis in expert centers.

There is no specificity in the management of female carriers in comparison with men in the event of impaired cardiac function.

### **Respiratory management Initial assessment**

BMD patients may experience progressive deterioration in their respiratory function related to a decrease in the strength of respiratory muscles [12, 14, 84, 85]. The rate of respiratory degradation is slow to very slow and may be underestimated for this reason. For these reasons, respiratory assessments are essential.

### **Clinical assessment**

The search for respiratory functional signs includes the following evaluations:

Assessment of damage to the inspiratory muscles (diaphragm): dyspnea (effort, speech, rest) with searches for primary decubitus orthopnea suggestive of diaphragm involvement, interrogation focused on the quality of sleep (e.g., nocturia, night awakenings, night sweats, morning asthenia, morning headache, and excessive daytime sleepiness). Patient inspection is an important part of the clinical examination, with searches for recruitment of accessory respiratory muscles, such as indrawing, respiratory pulse, and paradoxical abdominal breathing.

Assessment of damage to the expiratory muscles: effectiveness of cough with control of the abdominal contraction and searches for swallowing disorders and a medical history of recurrent respiratory infections.

### **Paraclinical evaluation**

Pulmonary function testing (PFT) includes evaluation of total pulmonary capacity (TPC), forced vital capacity (fVC) in sitting and lying positions, maximum inspiratory and expiratory pressures, sniff test, and peak cough flow. Assessments of inspiratory and expiratory muscle strength and the sniff test are the most sensitive tests for detecting alveolar hypoventilation.

The findings indicating neuromuscular respiratory damage are as follows:

- fVC < 80% when seated.
- fVC reduction of more than 20% in the supine position in favor of a diaphragmatic dysfunction.
- Inspiratory muscle strength < 80 cmH<sub>2</sub>O in males and < 60 cmH<sub>2</sub>O in females and sniff nasal inspiratory pressure (SNIP) < 60% of the theoretical values.

- Peak cough flow < 270 L/min, which indicates the need for assisted coughing techniques, or < 180 L/min, which indicates the need for mechanical-assisted coughing techniques.

Blood gas analyses are performed only if PFT shows abnormal results. Hypercapnia (  $p\text{CO}_2 > 45$  mmHg) indicates daytime alveolar hypoventilation and requires ventilation. These analyses can also be performed in patients showing respiratory symptoms unexplained by PFT according to the opinion of the pulmonologist.

Overnight explorations are performed mainly if PFT shows abnormal results. Nocturnal oximetry associated, if possible, with nocturnal transcutaneous capnography can reveal hypoventilation. These findings can also be of interest in the event of poor sleep unexplained by PFT. The necessity of polysomnography or polygraphy will be determined by the pulmonologist [86].

Lung imaging is of no interest outside of the search for associated pulmonary or thoracic complications.

### **Respiratory monitoring**

Respiratory management of BMD is comparable to that of other neuromuscular diseases, particularly that of DMD [12, 14, 86–88].

1. Respiratory management is based on regular clinical evaluations in search of diaphragmatic weakness and cough at each multidisciplinary visit. The filling of systematic questionnaires can be an important step in ensuring assessments of respiratory symptoms as for dyspnea or sleep quality. A respiratory functional exploration should be performed every 2 years, with no pulmonologist advice required at this stage if the findings are normal.
2. In cases with an abnormal FVC, the frequency of monitoring should be annual. A subsequent pulmonologist assessment, performed at least annually, will indicate the need for blood gas analysis or nightly examinations. This frequency can then be increased or decreased by the pulmonologist depending on the course of the disease.
3. In cases showing actual diaphragmatic involvement with hypoventilation, nocturnal noninvasive ventilation will be offered by the pulmonologist with a specific followup.
4. In cases showing a cough deficiency, cough aid techniques will be offered by the pulmonologist or physiotherapist. A pulmonologist follow-up is then necessary.

### **Respiratory management**

Respiratory management is the same as in any other neuromuscular disease [86–88]. Symptomatic management is based on the following steps:

- Cough aid: Respiratory physiotherapy of bronchial drainage, manual or technical assistance must be carried out, as well as inspiratory work. The use of cough aid devices (IN/EX breathers or manual aids) may allow better sputum production.



- Treatment of lower respiratory infections: It remains standard in case of normal cough. In cases involving cough troubles, respiratory infections must be treated effectively and vigorously (in particular with antibiotic therapy), and grouping should be avoided during winter epidemic periods. Antitussive and mucolytic treatments must be avoided as in any lower respiratory infection.
- Vaccinations against COVID-19, influenza, and pneumococcus are strongly recommended and carried out according to the vaccination schedule for all patients with comorbidities.
- Mechanical ventilation: Assisted ventilation (nocturnal noninvasive ventilation or invasive ventilation on tracheostomy) must be proposed as soon as diurnal and/or nocturnal alveolar hypoventilation appears (defined as  $p\text{CO}_2 > 45$  mmHg or  $T\text{cpCO}_2 > 50$  mmHg at night) [89].

At the last stage, evaluation of the long-term care project must be carried out, and the loss of ventilatory autonomy is generally irreversible [90]. A significant increase in dependence, imposed by mechanical ventilation, must be anticipated. Indeed, the loss of autonomy can make it impossible to set up mechanical ventilation. This is even more marked in cases showing the need for invasive mechanical ventilation with tracheostomy.

## **Swallowing, nutrition, gastrointestinal and urinary management**

### **Initial assessments**

Few studies have explored swallowing disorders in BMD patients [91]. Swallowing disorders are as frequent as those encountered in DMD patients with equal disabilities. Prolonged meal times (> 30 min) or meal times accompanied by fatigue, excessive spilling, drooling, pocketing, or any other clinical indicators of dysphagia make referral necessary, as do persistent coughing, choking, gagging, or wet vocal quality during eating or drinking. Aspiration is rare, but vallecular residues and a laryngeal elevation are especially notable during the pharyngeal phase in videofluoroscopic examinations and are increased with fatigue. Swallowing disorders should therefore be explored in patients showing these symptoms.

Questions about gastrointestinal reflux, gastroparesis or constipation are also relevant. Constipation can be a frequent complication of BMD, like in DMD. Risk factors include immobility, abdominal muscle weakness, and dehydration. As skeletal muscle weakness progresses, a delay in gastric emptying (gastroparesis) can occur lead to postprandial abdominal pain, nausea, vomiting, early satiety, and loss of appetite [92].

Patients with BMD may experience urinary incontinence regularly which can have a detrimental effect on various aspects of their life, including travel, social interactions, and emotional well-being [93, 94].

### **Monitoring**

Maintaining good nutritional status optimizes muscle strength and psychomotor development. Conversely, overweight worsens the motor deficit. Regular weight assessment as well as evaluations for constipation and bedsores should be performed.

Screening for swallowing disorders is important, especially in patients with respiratory impairment, by asking about difficulties in chewing, episodes of aspirations and/ or bronchial congestion, and hypersalivation and morning congestion. The type of food, the duration of the meals, and the position adopted during meals should be specified during these examinations. In case of doubt, particularly after tracheostomy, nasofibroscopy and/or radio cinema examinations can be performed.

Gastroparesis can be assessed using a scintigraphic gastric emptying scan.

Screening for urinary tract symptoms could be assess by specific questionnaires like The Barthel index of disability or the International Consultation on Incontinence Questionnaire-Urinary Incontinence Form (ICIQ-UI\_SF) [94–96].

## **Management**

### **Nutrition**

Oral feeding is the rule and artificial feeding is the exception.

#### ***Oral feeding***

The loss of walking represents a risky period of weight gain [97]. After loss of walking, the energy needs of patients with BMD are often 20–30% lower than those of the same age. Nevertheless, restrictive diets are still prohibited. In patients showing weight gain, a high-protein diet associated with caloric intake equal to the measured rest energy expenditure is most often recommended to control weight gain and should be monitored at least quarterly.

The management of swallowing disorders takes into account their etiology, factors facilitating these disorders, and their consequences. If the disorders are secondary to poor pharyngeal propulsion, the textures (mixed, adequately “slippery”) of the food and the position of the head during meals should be adapted.

In the most severe patients there is a risk of secondary undernutrition. It is then necessary to identify all the aggravating factors: involvement of the upper limbs (special cutlery, raised meal plan ...), macroglossia or involvement of chewing muscles (hygiene care oral, speech therapy, adaptation of the texture of food, surgery), digestive damage (constipation, ...), spinal deformities sources of compression, mask ventilation that causes or worsens aerogastria.

Oral nutritional supplements may be offered when increase in caloric intake becomes necessary.

#### ***Artificial feeding***

Situations necessitating artificial feeding are rare in patients with BMD. If oral feeding cannot ensure safe nutritive intake, a gastrostomy can be set up as the last resort. However, before creating a gastrostomy, the patient’s respiratory function and, in particular, the need for noninvasive ventilation should be evaluated. The gastrostomy should be placed by a team accustomed to the care of disabled patients. Consumption of food by gastrostomy will allow

rapid renutrition of the patient and ensure a marked improvement in the patient's quality of life.

### **Gastrointestinal management**

A gastroenterologist should be consulted for management of constipation, gastroesophageal reflux, and gastrointestinal motility concerns, and when gastrostomy tube placement is needed.

Constipation can be addressed through various measures, including adopting a fiber-rich diet, implementing toilet training techniques, engaging in physiotherapy, considering laxatives like polyethylene glycol, milk of magnesia, or lactulose may be necessary. Retrograde enemas might be helpful if faecal impaction occurs.

The treatment of gastroesophageal reflux involves suppressing gastric acid using histamine-2 receptor antagonists.

Treatment options of gastroparesis may include dietary modification, pharmacological therapy, and postpyloric feeding via a gastrojejunal feeding tube.

### **Urinary management**

In cases where lower urinary tract symptoms are present, it is advisable to undergo a comprehensive urological evaluation, which may include urodynamic examinations, and to receive thorough follow-up care.

### **Genetic counseling**

BMD is an X-linked recessive disease. The genetic defects in a patient can either be inherited from the carrier mother (heterozygous for the pathogenic variation) or can occur de novo [98]. In cases of de novo mutations, one of the parents may carry a germinal mosaicism (presence of populations of gametes with and without the pathogenic variation), which is associated with a risk of recurrence in the offspring. For male patients with BMD, sons inherit the Y chromosome and are therefore free from the disease, while daughters inherit the X chromosome carrying the genetic abnormality; they are therefore mandatory carriers of BMD. Heterozygous women must undergo appropriate medical monitoring and will benefit from genetic counseling regarding the risk of transmission to their own offspring: 50% risk of having a boy with BMD and 50% risk of having a carrier girl with BMD, with symptoms in 5–20% of cases (incomplete penetrance). In the event of a neomutation, the risk of recurrence is low but quite undefined (admittedly less than 10%). A prenatal or preimplantation diagnosis can be discussed depending on the severity of the disease and family experience. Any request must be presented and discussed by a multidisciplinary prenatal diagnosis committee that validates or disallows the usage of prenatal or preimplantation diagnosis. Presymptomatic diagnosis can be considered in relatives at risk even in the absence of early symptoms in life, for example, in the context of guidance for employment.

## **Anesthesia and surgery**

Although the use of halogenated anesthetics during general anesthesia should be avoided, as in all neuromuscular diseases, an extensive search of the literature did not reveal any increased risk of malignant hyperthermia-like reactions in comparison with that in the general population [99]. In one recent study, a BMD patient who was undiagnosed at the time of anesthesia showed rhabdomyolysis and cardiac arrest on hyperkalemia with succinylcholine [100]. Therefore, depolarizing muscle relaxants should be avoided, as well as botulinum toxin injections.

The other main complications have been attributed to preexisting comorbidities such as respiratory impairment or heart failure. Therefore, assessment of the benefit/risk ratio of surgery and cardiorespiratory assessment should be performed before any anesthesia [101, 102].

Patients and their family need to be trained on responding to an emergency transfer by having an “emergency kit” including the latest medical letters, the latest prescriptions, and possible care instructions for non-specialist professionals, and bringing their own ventilation device if appropriate.

## **Vaccinations**

Immunization with pneumococcal and COVID-19 vaccines and annual immunization with the influenza vaccine according to the vaccination schedule are strongly recommended, as for any disease with comorbidities [103].

The patients have no contraindications to intramuscular vaccinations, but injections should preferably be administered in a muscle that is less affected or by the subcutaneous route.

## **Bone risk prevention**

Prevention of osteopenia with calcium and vitamin D supplementation must be estimated and promptly proposed in the event of reduced mobility. There is no recommendation regarding the use of bisphosphonates. In cases with severe joint damage or increasing functional impotence, orthopedic surgery for scoliosis or the hips, etc., may be necessary.

## **Pain**

Treatment is based on massages and passive and active mobilizations; analgesics (with evaluations for constipation) according to class progression while avoiding longterm treatment; per os or IV bisphosphonates for osteoporosis; good positioning and, in particular, use of the stander when there is sciatic nerve compression in the chair; and an adapted mattress (dynamic air, static air, etc.) with multiple tests to determine an option with maximal comfort.

Analgesic pharmacological treatment (anti-inflammatory, muscle relaxants) must take into account the side effects (especially cardiac and respiratory effects) and possible drug interactions.

In case of discussion of opioid therapy, it is important to seek guidance from a healthcare professional, preferably a pain specialist, who can conduct a thorough assessment circumstances. They will take into account the severity of respiratory insufficiency, the individual's overall health status, and explore alternative pain management strategies to determine the safest and most effective treatment approach. Some opioids have a more favorable respiratory safety profile compared to others. Preference may be given to extended-release or fast-acting opioids to minimize fluctuations in blood concentration and thereby reduce the risk of respiratory depression. Initiation with the lowest effective dose of opioids is crucial, and adjustments should be made based on the individual's response. Patients taking opioids should be closely monitored with regular assessment of hypoventilation sign or appearance of nocturnal apnea. If the patient is on ventilation, the machine settings will able monitoring of nocturnal events [104].

## **Special situations**

### **Management of emergencies in BMD**

All patients with BMD must have a properly completed and up-to-date “Neuromuscular Disease Care and Emergency Card” [105]. It should specifically mention the anesthetic precautions (medicines contraindicated in case of anesthesia) and the specialist referring physician to contact. Emergency situations arise mainly in the most severely affected patients.

When the patient begins to fall, fractures can occur. The immobilization must be as short as possible and the rehabilitation program must be reinforced and adapted so as not to affect the functional prognosis.

### **Female carriers**

#### **General**

The care of a female carriers must include:

- Proposal for genetic counseling (see above)
- Information about the risk and the need to monitor cardiomyopathy (see above)

### **Special considerations for pregnancy**

As with any chronic illness, issues related to pregnancy and parenting must be discussed prior to conception. In women who are symptomatic and carriers for BMD, in addition to genetic counseling (risk of disease transmission), the predictive influence on the pregnancy depends on the functional symptoms of the disease. The pre-conceptual phase and the follow-up of the pregnancy must be organized in a multidisciplinary manner combining disease specialists (mainly myologists and pulmonologist) and a perinatal team (obstetrician and anesthesiologist). In general, the challenges of pregnancy can be schematized according to three axes:

- The influence of BMD on parenting: The risk of transmission to the offspring requires a dedicated consultation of genetic counseling. If necessary, prenatal diagnosis can be discussed in multidisciplinary prenatal diagnosis committee and organized as early as possible at 11 weeks of pregnancy through chorionic villus sampling or management in preimplantation diagnosis.
- The influence of BMD on pregnancy: Natural delivery is not contraindicated. Epidural anesthesia is probably less risky, especially in terms of respiratory symptoms, than general anesthesia.
- The influence of pregnancy on the status of BMD transmission: Myocardial damage can be aggravated by volume changes related to pregnancy and in the postpartum period [106].

Little is known about the medium- and long-term impact of pregnancy on the course of the disease. Ideally, an echocardiogram should be obtained before the start of pregnancy. Pregnancy can sometimes be accompanied by motor onset of symptoms or worsening of symptoms.

### **Data availability**

Not applicable.

### **Declarations**

### **Conflicts of interest**

The authors declare that they have no conflict of interest.

### **Ethical standard**

This study is a review of previously published data and does not involve the collection of new data from human participants or animals. Therefore, ethical approval and informed consent were not required for this study. No personally identifiable information is presented in this review. All data sources and references used in this review are appropriately cited in the reference section to ensure transparency and give proper credit to the original authors.

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