Duchenne Parent Project

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DIAGNOSIS AND MANAGEMENT OF BECKER MUSCULAR DYSTROPHY

Guide for families

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Introduction

Becker muscular dystrophy

Currently there is no cure for Becker muscular dystrophy (BMD); however, there are, and it should be emphasized, numerous therapies that can improve, even significantly, the clinical condition of patients and their quality of life. It should also be kept in mind that scientific research has made substantial progress in the last decades, and it is in order to be ready to use the new therapies in the best possible way that it assumes fundamental importance to receive a timely diagnosis and to try to preserve muscle strength and function.

Historically, BMD has often been treated as a "less severe form" of Duchenne muscular dystrophy (DMD), using the same clinical approach. Over time, the need to consider BMD as a disease on its own has arisen for several reasons. First, because of the desire of the patients themselves and their families, who are well aware of the differences and second, because the growing number of new therapies now allows more specific, targeted, and different approaches in DMD and BMD.

Based on these needs, this guide was created to provide BMD patients and their families with a flexible but not less accurate tool to receive information on various aspects of the disease: physiotherapeutic, psychological, cardiological and pneumological, to mention a few.

The clinical recommendations set forth in these guidelines are up-to-date and are the result of collaborative work between specialists in neuromuscular diseases and Parent Project aps.

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BMD **DIAGNOSIS**

BMD DIAGNOSIS

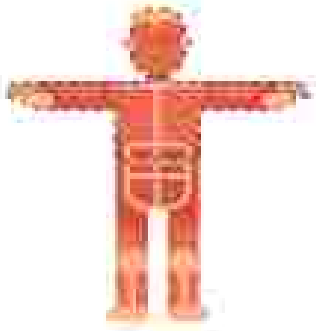
The path leading to the diagnosis of a neuromuscular disease is always difficult and intricate: both for patients and their family members and for physicians and health care providers. The chronic and often disabling nature of neuromuscular diseases challenges the diagnostic process in reaching a precise diagnosis of a specific neuromuscular disease. This great complexity is driven by both the great (and ever-increasing) number of muscle diseases described, and by the wide variability in the clinical expression of each of these diseases among patients carrying the same genetic mutation and even within the same family.

It is therefore not surprising that this diagnostic pathway is often very long with numerous consequences on patients' lives: anxiety, uncertainty, sometimes invasive procedures, investment of time and expenses in travel and visits. Reaching an accurate neuromuscular diagnosis concludes this "diagnostic odyssey," but, on the same time, it raises many new questions: the progression of the disease, the clinical management over time, the possible complications, genetic counseling, and approaches to care and therapy.

All these considerations apply to neuromuscular diseases in general, and to BMD among these. In this chapter, we will review the diagnostic process starting from which symptoms or signs raise the clinical suspicion of BMD to the medical expert in neuromuscular diseases (neurologist, pediatric neurologist, child neuropsychiatrist, or other), which examinations are needed to confirm this suspicion, and which consequences the results of the diagnostic pathway will have on various aspects of patients' daily lives, with special emphasis on the crucial moment of the diagnosis communication.

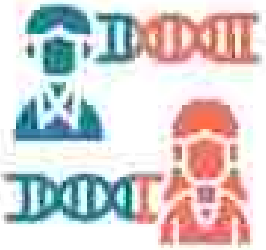
Suspicion of BMD

The first clinical suspicion of BMD may arise mainly from the following clinical observations:



Muscle weakness in the pelvic and femoral muscles.

An occasional finding of elevated creatine kinase (CK) in the blood.

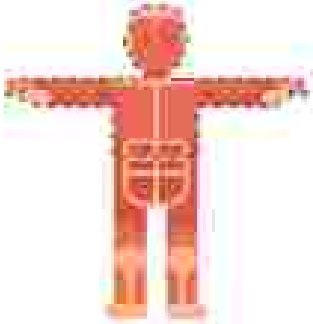


A positive family history of BMD (or yet uncharacterized neuromuscular disease).

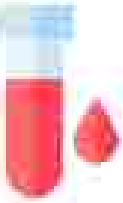
Before going into detail of these various warning situation and their implications, it is good to remember the extreme phenotypic (i.e., clinical manifestations) variability of BMD. Indeed, the diagnostic definition of BMD can include people of any age and with very different functional status. Possible pictures range from people who are perfectly normal or presenting only muscle pain or cramping after exertion, to others who present marked muscle weakness or even with loss of ambulation and, in the most severe cases, with important motor deficit in the upper limbs. Thus, it is possible that children or adults come to medical attention because muscle weakness, or to be diagnosed when symptoms has not appeared yet because of the patient's young age. Symptoms may even never develop, as BMD may be extremely mild.

Muscle weakness

Muscle weakness is the cardinal symptom/sign of all muscle diseases. In muscular dystrophies, muscle weakness is due to degeneration of contractile muscle fibers and their progressive replacement with non-contractile fibrous (scar) tissue. The most affected muscles in BMD are those of the pelvic and femoral compartments, as well as the axial muscles of the spine, especially at the lumbar level. The resulting muscle weakness makes difficult and tiring actions such as running, going up the stairs, and getting up from the floor or a chair. Usually BMD, which, unlike DMD, has a later onset and a milder progression, allows to acquire in the early years of life the ability to walk and run or climbing stairs or raising from the floor in a normal manner, while motor difficulties begin to appear in youth or adulthood.



Occasional finding of elevated creatine phosphokinase CK



CK (also called creatin-phospho-kinase, CPK) is a muscle enzyme whose elevated blood levels are a very sensitive indication of muscle damage. In patients with BMD, CK is often very high. If the maximum normal values indicated by testing laboratories are around 200- 300 units per liter (U/L), in most cases of BMD the CK value reaches thousand units. Patients with DMD, in whom muscle damage is more severe, usually present when first diagnosed (around 2-5 years of age) values as high as 10,000–20,000 U/L, which then tend to decrease over time, although CK remains variable among various measurements and increase with muscle overexertion. In non-ambulatory DMD patients, CK values decrease to a few hundred to a thousand, and finally returns to normal values in patients with severe muscle weakness indicating severe muscle atrophy and loss of function. In BMD, the observed CK values are generally lower, although they can reach the same levels as in DMD especially in children and after exercise. They are also generally more constant throughout life, and their tendency to decrease in the advanced stages of the disease is less prominent since BMD patients rarely reach the level of extreme muscle atrophy that is seen in advanced DMD. However, it should be emphasized that CK values in children and young people with BMD are poorly predictive of a more or less benign course of the disease. Finally, although normal CK values in ambulatory BMD subjects are extremely rare, they are not impossible to observe, especially when at rest or in asymptomatic forms.

Since BMD is often characterized by a long pre-symptomatic phase, it is quite frequent that elevated CK is the first finding that raises a suspicion of a neuromuscular disease.

In preschool children (up to 5 years of age) in whom CK values are constantly elevated (10,000 U/L or more), suspicion of DMD must be taken into consideration. There are guidelines suggesting to prescribe first the test to detect deletions and duplications of the gene for dystrophin (DMD), after the diagnostic suspect raised by a physician with expertise in

neuromuscular disease. In children older than 5 years of age or older boys or boys with CK values that are not so high (1500-10,000 U/L), BMD has to be suspected, but the diagnostic process, compared with DMD, is less defined and more tailored to each patient based on the suggestions made by the neuromuscular disease expert physician. DMD gene testing might be the first test to be requested if the clinical features are indicative, e.g., calf hypertrophy, thigh hypotrophy, gait characteristics... However, in some cases, a muscle biopsy might be more indicated (see the section on differential diagnosis).
The finding of elevated CK is often encountered occasionally in the course of tests performed for various reasons: routine tests, hospitalizations for infection, trauma, or other incidental events, preoperative examinations for surgery, etc... It is important to note that when muscle damage is significant and CK exceeds approximately 1000 U/L, aspartate and alanine transferase enzymes (AST and ALT), which derive from both muscle tissue and liver tissue, are also often significantly elevated. In these cases, it is important to recognize the muscular origin of the rise in AST and ALT, when simultaneous with the rise in CK, to avoid to the patient unnecessary, sometimes even invasive, liver tests.

Family History

It is increasingly rare for women who have siblings, uncles or cousins in the maternal line affected with BMD to go into pregnancy without first consulting the geneticist or at least the treating physician. However, in the event that in the family an individual, with a degree of parenthood compatible with maternal transmission, shows muscle weakness or elevated CK, and carries a known DMD gene mutation it is correct to direct molecular investigations to check the presence of a specific mutation known in the family member. In the case of asymptomatic male subjects who discover that they are at genetic risk due to diagnosis in a family member, a pre-symptomatic diagnosis should be pursued only with the consensus of the subject, waiting until early adulthood in the case of minors. A cardiological screening with echocardiogram, to rule out an under recognized cardiomyopathy, is however indicated.

Other BMD atypical presentations

Rarely, the first clinical symptom or sign leading to the suspicion of BMD may be different from those we analyzed before. For example, the patient may arrive to medical attention for muscle pain (myalgia) and/or muscle cramps, especially after exercise. In dystrophinopathies and in other muscle diseases, but also in healthy people the exercise that more than others causes muscle pain (and raised CK) is the so-called "eccentric exercise," that is, exercise in which the muscle contracts when lengthened. A classic example is running downhill or descending many floors of stairs: in this type of activity, the quadriceps femoris contracts in elongation to control knee flexion during descending. If the muscle damage after exercise is particularly intense, CK raises in the blood to several or even hundreds of thousands of unit for liter an event referred to as "rhabdomyolysis" (literally "striated muscle breakdown"). In this case myoglobin, released in large quantities from the muscle, can pass into the urine, giving it a dark, coke-like color (myoglobinuria), with the risk of severe kidney damage. This event can occur in all patients with dystrophinopathy after major exercise, or due to high fever, dehydration, exposure to extreme temperatures, or a combination of these factors. In cases where rhabdomyolysis or myoglobinuria is the onset symptom of BMD, it is referred to as a "pseudometabolic presentation", as these events are more

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common in muscle diseases other than BMD, so-called "metabolic" diseases, i.e., diseases in which the muscle misuses energy substrates, such as sugars and fats.

Hypertrophy of certain muscle groups, primarily the calves, is often prominent in BMD, and could in some cases be the first sign of a muscle problem, however because of the wide variability in muscle size even within the normal population, it is difficult that the observation of a few hypertrophied muscle groups prompts the patient to consult the physician.

Cardiac involvement in BMD is often "disproportionate" to the severity of muscle weakness. There are families in which dystrophinopathy may manifest primarily or exclusively at the cardiac level as dilated cardiomyopathy ("X-linked cardiomyopathy"). In these patients, the finding of dilatation or pump deficit of the cardiac ventricles, or an episode of heart failure, with symptoms such as edema (swelling from fluid retention) in the lower extremities and dyspnea (shortness of breath) on exertion, may be the first sign of the disease. In these cases, careful patients neuromuscular examination may point out to clinical signs compatible with BMD, or may be completely normal. Diagnosis may be difficult if there is no known family history for dystrophinopathy, as the cardiomyopathy may be confused with viral myocarditis or other dilated cardiomyopathies (familial and not). CK, which is usually elevated, although less than in "typical" BMD, provides an important diagnostic indication, directing to muscle biopsy or genetic testing.

Finally, BMD, like all dystrophinopathies, may be accompanied by central nervous system (CNS) involvement, leading to problems such as delayed language acquisition, learning difficulties, or neuropsychiatric disorders. These will be covered in a dedicated section of this booklet, but we also want to mention here the CNS involvement, which, although more rarely than muscle and heart involvement, may be the first sign of the disease. In the cases with neuropsychiatric manifestations and in the absence of muscle weakness, diagnosis may be difficult and the CK levels may help.

BMD "DIFFERENTIAL DIAGNOSIS"

In clinical medicine, the concept of "differential diagnosis" denotes the set of various diagnostic hypotheses that the physician should consider when faced with a patient presenting with a certain disorder, or abnormality found in diagnostic investigations. Thus, somehow like what happens in an investigation looking for a culprit, the physician tries to gather information (from the clinical examination, from the patient's history, from targeted investigations) to rule out or confirm each of these hypotheses.

The "differential diagnosis" of BMD is not particularly rich, since the presenting picture of BMD is relatively typical and shared by only a few extremely rare muscle diseases (e.g., sarcoglycanopathies). In contrast, muscle diseases that may present with a BMD-like phenotype are more numerous and, while still rare diseases, they have all together a similar or higher incidence than BMD. These diseases include limb girdle muscular dystrophies (LGMD), involving the pelvic and/or scapular muscles, spinal muscular atrophy (SMA) type 3 or 4, and metabolic myopathies. Table 1 summarizes similarities and differences of these diseases with respect to BMD, and what investigations are useful to distinguish them.

TABLE 1: BMD Differential Diagnosis

Disease	Common features	Uncommon features	Tests useful for differential diagnosis
Duchenne Muscular dystrophy (DMD)	X-linked transmission, proximal muscle weakness, calf or other muscles hypertrophy, ankle contracture, possible dilated cardiomyopathy, elevated CK	Onset of muscle weakness by age 5 years, loss of ambulation by age 12 or 16 years (without or with glucocorticoid treatment, respectively), absent dystrophin	Muscle biopsy, genetics
Limb-girdle muscular dystrophy due to calpain-3 deficiency (LGMD-R1)	Proximal muscle weakness, winging of scapula, ankle contracture, elevated CK	Recessive inheritance, rare calf hypertrophy, greater shoulder girdle weakness, no cardiomyopathy, normal dystrophin, calpain-3 deficiency (not constant)	Muscle MRI, echocardiogram, muscle biopsy with muscle protein study, genetics
Limb-girdle muscular dystrophy due to dysferlin mutations (LGMD-R2)	Proximal muscle weakness, CK (very) high	Recessive inheritance, early distal muscle weakness, atrophy rather than hypertrophy of calves, not cardiomyopathy, normal dystrophin, dysferlin deficiency	Muscle MRI, echocardiogram, muscle biopsy with muscle protein study, genetics
Limb-girdle muscular dystrophy due to one forms of sarcoglycanopathy (LGMD-R3/R4/R5/R6)	Proximal muscle weakness, elevated CK, hypertrophy of calf and other muscles, possible cardiomyopathy	Difficult to differentiate on the basis of clinical manifestation alone, recessive inheritance, normal dystrophin, deficiency of one or more sarcoglycans (which may be secondarily reduced in dystrophinopathies)	Muscle biopsy with muscle protein study, genetics
Limb-girdle muscular dystrophy due to alpha-dystroglycan glycosylation defects (LGMD-R9/R13/R20)	Proximal muscle weakness, elevated CK, hypertrophy of calf and other muscles, possible cardiomyopathy	Difficult to differentiate on the basis of clinical manifestations alone, recessive inheritance, normal dystrophin, alpha-dystroglycan glycosylation deficiency (inconstant)	Muscle biopsy with muscle protein study, genetics

TABLE 1: RMD Differential Diagnosis

Disease	Common features	Uncommon features	Tests useful for differential diagnosis
Spinal muscular atrophy type 2 or 3 (SMA2, SMA3)	Proximal muscle weakness, (mildly) elevated CK, calf hypertrophy, and relative thigh atrophy	Recessive inheritance, neurogenic tremor, increased hypotonia, not cardiomyopathy, neurogenic EMG, normal dystrophin	Electromyography, muscle biopsy, genetics
Late-onset Pompe disease (alpha-glucosidase deficiency, GAA)	Proximal muscle weakness, elevated CK, acidosis, myalgias	Recessive inheritance, slight if any hypertrophic cardiomyopathy (if present) more restrictive than dilated, reduced GAA enzyme activity, vacuolar myopathy, normal dystrophin	Muscle MRI, muscle biopsy, genetics, GAA enzyme activity on blood spot
Fatty acid metabolism disorders (carnitine-palmityl transferase deficiency, other lipid myopathies)	Episodes of rhabdomyolysis/ myoglobinuria, sometimes proximal muscle weakness	Recessive inheritance, usually no fixed muscle weakness, multiple episodes of rhabdomyolysis without muscle weakness, normal or slightly elevated CK levels between episodes, altered acylcarnitine profile, lipid accumulation at biopsy, normal dystrophin	Muscle MRI, muscle biopsy, genetics, circulating fatty acid profile (acylcarnitine)
Emery-Dreifuss Muscular Dystrophy (EMD)	X-linked inheritance, proximal muscle weakness, dilated cardiomyopathy	Early joint contractures, muscle atrophy rather than hypertrophy, normal dystrophin	Muscle MRI, muscle biopsy, genetics

It should be noticed that at the top of Table 1, summarizing the differential diagnosis of BMD, we find the main form of dystrophinopathy, namely DMD. The distinction between DMD and BMD is not always simple and there is in fact a widely recognized clinical entity, "Intermediate muscular dystrophy, "IMD", that is a muscular dystrophy presenting an intermediate severity between DMD and BMD. The exact boundaries between DMD, IMD, and BMD are not absolute and ambiguity exists. These boundaries can be approached on at least three different levels: clinical, biochemical (i.e. detection and quantification of the dystrophin protein), and genetic. By definition, DMD includes patients who clinically lose ambulation by the age of 13 (or 16, if treated with glucocorticosteroids), biochemically they do not have detectable dystrophin in the

muscle and genetically carry mutations in the DMD gene that are incompatible with normal production of the protein. On the contrary, patients with BMD never lose ambulation before the age of 16, have some residual amount of dystrophin in the muscle, even if quantitatively and qualitatively abnormal, and carry mutations that allow the production of an altered and partially functioning dystrophin protein. However, some cases challenge these distinctions, mainly because of a discordance between clinical, biochemical, and genetic features. For example, patients with typical DMD mutations and absent dystrophin can walk without support beyond the age of 16. Furthermore, since very low (trace) dystrophin levels can be detected only by extremely sensitive methods and not by others, inaccuracies in diagnostic definition may occur. These differential aspects between BMD and DMD should be considered very carefully especially when making a prediction about the possible course of the disease in pediatric patients.

Confirmation or exclusion of BMD diagnosis

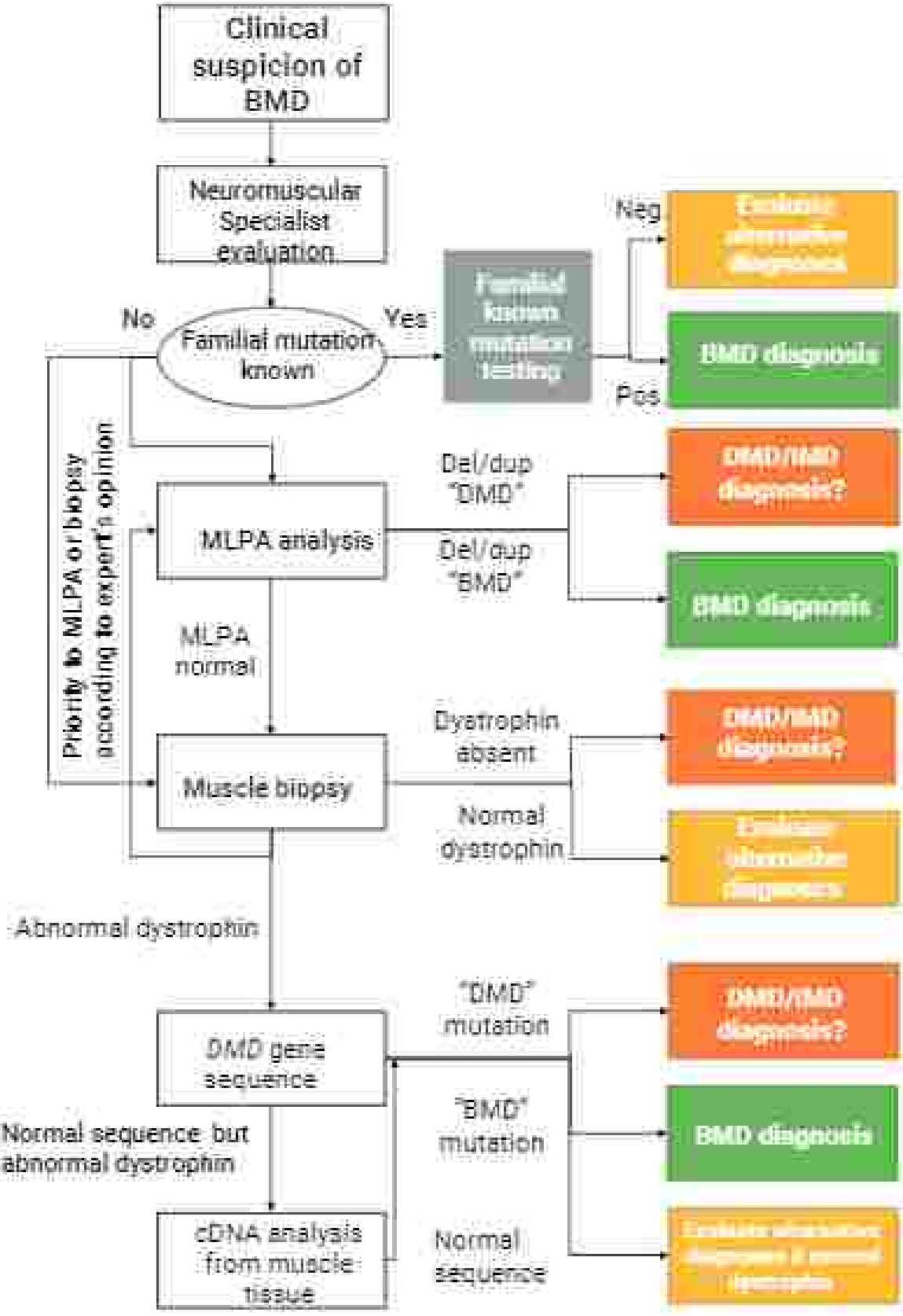
When a clinical suspicion of BMD (see previous paragraphs) is made, the physician must plan and prioritize the necessary examinations to confirm or to exclude the diagnosis. The first tests are CK measurement and electromyography, which can also be requested, and initially interpreted, by a non-specialist physician. CK is elevated in almost all cases, and electromyography shows primitive muscle damage or rule out muscle damage resulting from a neurogenic process (i.e., peripheral nerves or motor neurons in the spinal cord).

At this point, the patient should be referred to the neuromuscular specialist, who, as mentioned above, can decide whether to directly request a genetic analysis of the gene for dystrophin, usually an MLPA ("multiple ligation-dependent probe amplification") assay, to identify deletions and duplications of pieces of the gene, which are the cause of about 80 percent of BMD cases, or schedule a muscle biopsy. If the MLPA shows a deletion in the gene for dystrophin compatible with the production of an abnormal dystrophin in reduced amount, the diagnosis of BMD is confirmed. However, it should be kept in mind that in pediatric patients until at least 5 years old, it is difficult to clinically differentiate a DMD from BMD. Therefore, as mentioned above, there may be exceptions to the rules regarding typical DMD mutations and typical BMD mutations, and rarely a severe phenotype may develop despite the mutation being a typical BMD mutation. In such cases, muscle biopsy may help, as the presence of dystrophin, particularly if discrete or abundant amounts (above 10%–30% on Western Blot) makes the prediction of a BMD phenotype much more reliable.

Muscle biopsy is also suggested in cases where the MLPA is negative (no deletions or duplications are detected), since the study on muscle tissue of dystrophin itself or other muscle proteins (sarcoglycans, calpain, dysferlin) helps to direct further genetic analysis toward the most appropriate gene. The increasing availability and accessibility of next-generation technology ("Next Generation Sequencing," NGS) applied to panels of genes involved in muscular dystrophies could provide an alternative to the muscle biopsy. However it should always be kept in mind, that NGS often identify variants of uncertain significance, which in turn require correlation with clinical, biochemical, and biopsy data in order to be correctly interpreted.

THE BMD DIAGNOSTIC PROCESS IS ILLUSTRATED IN THE FLOWCHART IN FIGURE 1

FIGURE 1. FLOWCHART OF THE BMD DIAGNOSTIC PROCESS



BMD carriers Diagnosis

The symptomatic presentation in a female BMD carrier is very rare. CK may sometimes be high, but in most cases it is normal. However, as described in the genetic diagnosis chapter, all women at genetic risk should be tested by MLPA or sequencing to establish a carrier status.

BMD diagnosis communication

The communication of a neuromuscular disease diagnosis is a very challenging moment because of the profound psychological impact it can have on the patient and his family members and/or caregivers. A good communication of the diagnosis is the basis for building a therapeutic alliance between the physician and the patient. Therefore, it is advisable that it be accompanied by a multidisciplinary patient care taking.

The communication of BMD diagnosis, as in general of all other neuromuscular diseases, is a particularly difficult and challenging task faced by the physician. All these diseases are characterized by being progressive and leading to a disability that worsens over time. The high variability in severity of the BMD phenotype in dictates a tailored approach to the communication even more than in DMD. For example, it is evident that the way of communicating the diagnosis will be different depending on whether the patient is a young adult with a progressive muscle weakness and a "typical" BMD, or a 60-year-old man with hyperCKemia and normal muscle strength and function, or a still asymptomatic three-year-old child.

Therefore, it is important for the clinician to attempt to identify with accuracy the severity of the BMD and to distinguish the severe phenotype, including the IMD phenotype, the "typical," mild, or even asymptomatic presentation (see below), and to transfer this information to the patient or parents, specifying the possible doubts and emphasizing the elements of hope. As with DMD, adherence to a basic set of rules for communicating the diagnosis is essential, such as: holding the interview in person, with adequate time available and in a quiet and reserved space; verify the patient's/caregiver's knowledge and expectations at the beginning of the interview; giving space to emotional reactions and allowing time to express them. In the case of children, it is recommended to hold the initial interview with parents only, while the inclusion of adolescents in the communication should be evaluated on a case-by-case basis. It is beyond the scope of this paper to provide a comprehensive "handbook" for a good diagnosis communication, but it is clear that this always needs the professional skills of the physician (specialized expertise and experience) but also more individual aspects such as sensitivity, humanity, empathy and willingness to listen.

From diagnosis to prognosis and to clinical management

As mentioned several times in other sections of this booklet, within the definition of BMD are included very different clinical pictures. Let us briefly recall the main ones.

Severe BMD, IMD type, with loss of ambulation in adolescence or young adulthood;

Typical BMD with loss of ambulation in adulthood;

"Mild" dystrophinopathies with loss of ambulation in late life or without loss of ambulation, but with muscle weakness on clinical examination;

Asymptomatic dystrophinopathies (normal muscle strength and function) with high CK, with or without cramps/myalgia/myoglobinuria.

To further complicate the clinical picture, recall that each of these forms may or may not be accompanied by cognitive/linguistic/psychiatric disorders and dilated cardiomyopathy. Since various studies have suggested robust genotype/phenotype correlations (i.e., correlations between specific mutations in the gene for dystrophin and specific clinical pictures), although not without exceptions, it is advisable that the experienced neuromuscular clinician accompanies the diagnosis with the formulation of a prognosis based on these correlations. It is clear that the older the patient is at the time of diagnosis, the more the prognosis should be based on the patient's actual functional status, rather than on the molecular data. From approximately 25-30 years of age onward, clinical examination of muscle strength holds more prognostic value than any biochemical and genetic tests. Much more complex is the prognostic assessment in pediatric or even preschool patients, in whom even if asymptomatic this does not exclude that the phenotype may be expressed in later years. The evaluation of subtler phenotypic features, such as atrophy, hypertrophy, and contractures is of particular relevance, whereas rhabdomyolyses or the presence of myalgias in pediatric age does not necessarily rule out a mild form of BMD.

The molecular bases of these correlations are complex, involving several mechanisms: in the case of mutations in the first exons (approximately the first 10) of the gene for dystrophin, the "re-initiation" of protein translation by the ribosome (the machinery that produces the protein from the "information" derived from the genetic code, messenger RNA) could be downstream of the mutation. In few cases of IMD, especially in patients carrying the deletion of exon 45, "alternative splicing," i.e., the inclusion or exclusion of exons contiguous to the deletion in the messenger mRNA, can restore the correct reading of the gene in the context of a typical BMD mutation. Particularly crucial in differentiating between "typical" or mild forms of BMD are the stability and mechanical properties of the protein derived from the messenger RNA carrying the deletion. For example, the dystrophin protein missing the regions encoded by exons 48-47, is less stable and functional than the protein missing the regions encoded by exons 45-51, even if the amount of genetic information lost in the latter case is greater.
A critical and cautious use of these correlations will help the clinician to manage the clinical follow-up in the most correct way, reassuring the patient and/or parents where indicated, and minimizing anxiety about future development of the disease; but also providing objective suggestions, suitable to plan the implementation of measures to cope with the disability, when indicated, and to create full awareness about choices regarding reproductive health. These issues are introduced in the next chapters of this document, devoted to genetic and family counseling and neuromuscular management of BMD.

"DMD" AND "BMD" MUTATIONS

In the text we have referred to the so-called "out of frame" mutations, literally "out of the [reading] frame," as "DMD mutations" for simplicity. These are the mutations in which the reading frame of the genetic code is altered, and therefore the entire information contained in the gene is unreadable and is lost. As a result, dystrophin is absent. On the other hand, in the case of mutations that we have for simplicity called "BMD" mutations ("in frame" mutations) the reading frame is maintained, and although there is an error in the genetic code, it is readable, and a certain amount of a more or less functioning dystrophin is produced. In most cases, "out of frame" mutations are deletions in which the number of nucleotides ("letters" of the genetic code) lost is not equal to or is a multiple of 3, whereas if the number of nucleotides lost is equal to 3 or a multiple of 3, the mutation is "in frame." This is because the "words" of the genetic code ("codons") always consist of 3 "letters" (nucleotides).

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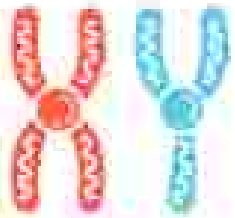
GENETIC DIAGNOSIS

3. GENETIC DIAGNOSIS AND GENETIC COUNSELING



Becker muscular dystrophy (BMD) is caused by mutations in the dystrophin gene, located on the X chromosome. The sex chromosomes are the X and Y chromosomes. The female has 2 X chromosomes (hence XX) and the male has one X chromosome and one Y chromosome (hence XY), as a consequence BMD occurs only in males because they have only one defective copy (hemizygous) of the dystrophin gene while females (XX), due to the presence of the normal copy of the dystrophin gene located on the second X chromosome, are termed "**carriers**," and are almost always asymptomatic (only in very rare cases symptomatic). Mutations in the dystrophin gene result in both a reduction in the amount of dystrophin in muscle and in modifications of the protein itself, thus both quantitative and qualitative changes in the protein. In contrast to Duchenne muscular dystrophy (DMD), in which dystrophin is absent, in BMD dystrophin is present but it is reduced in quantity and it is abnormal and therefore its "functions" are altered.

BMD GENETIC DIAGNOSIS

The suspicion of BMD in a patient, based on the clinical picture or family history, must always be confirmed by a genetic test, that is, a test that studies DNA. This test is generally performed on peripheral blood from which DNA is extracted. **Genetic testing** is always necessary, even if the diagnosis of BMD has already been made clinically and/or confirmed by the study of dystrophin in muscle biopsy.
Genetic confirmation of the diagnosis is achieved with the detection of a mutation, that is, an alteration in the DNA of the gene for dystrophin, which causes the dystrophin protein itself to malfunction.
Genetic diagnosis is important for several reasons: for the patient, as it allows a genetic confirmation of the clinical diagnosis; for the family in order to adopt proactive measures (awareness of the risk of recurrence of the disease in the family, carrier diagnosis, or establish the presence of "de novo" mutations that are therefore not familial) and to make informed decisions regarding reproductive choices in future pregnancy (including prenatal diagnosis or preimplantation diagnosis); and finally because a genetic diagnosis is necessary to access clinical trials and personalized therapies already approved by EMA and AIFA. For all these reasons, a medical geneticist consultation is necessary for the patient and family, to plan and to perform the genetic test, to interpret it, and then to communicate the result, managing appropriately the impact of the diagnosis on the person and his or her family context.
The type of mutations that can be identified in the gene for dystrophin in BMD patients is broad, just as it is in DMD patients.
The most frequent mutations in BMD patients (approximately 87-89% of cases) are **deletions** (i.e., "absence of a part of the gene") and **duplications** (i.e., "repeating of a part of the gene"). In about 11-13% of BMD patients, **small mutations** are identified, that is, mutations that alter one or a few nucleotides (or "letters") of the DNA. These small mutations include "**nonsense mutations**," i.e., mutations in which the change in one nucleotide ("letter" of the DNA) leads to the formation of a stop signal that is interpreted as "stop dystrophin production" even though the dystrophin is not yet "finished" (nonsense mutation). Rarely (less than 1%) **atypical mutations**, which act by complex mechanisms, can also cause BMD. Therefore, in view of this wide variability of mutations that can be observed in BMD patients, genetic diagnosis is a process consisting of several steps and the use of different types of genetic tests-a process called "**multistep**" ("multi-step").
Considering that deletions and duplications are the most frequent mutations in the dystrophin gene, the first stage of the diagnostic process involves the use of a method that can identify rapidly deletions and duplications: this method is called "**MLPA**" (from the English Multiple Ligation-dependent Probe Amplification), and is the most commonly used assay (**I Level of analysis**). The CGH (Comparative Genomic Hybridization) technique also identifies deletions and duplications, in an even more precise way than MLPA, but being expensive, it is normally used as a second choice or in special cases.
If no deletions/duplications are identified and a strong clinical suspicion of dystrophinopathy remains, it

is appropriate to investigate whether the patient has a small mutation. This type of mutation is identified by sequencing ("reading letter by letter") all regions of the gene ("exons") that code for the protein, through "**Next Generation Sequencing**" techniques (II Level analysis).
Finally, in a small percentage of patients, employing MLPA and sequencing techniques may fail to reach diagnosis. This is, as anticipated, a very small percentage of BMD patients (less than 5%) carrying rare and atypical mutations and their detection requires the use of more complex laboratory methods (**array- CGH and/or RNA analysis: III level analysis**).
Through this "multistep" approach, about 99% of mutations in the dystrophin gene can be identified.

Once the BMD causing mutation has been identified, it is, in some cases, possible to attempt the correlation between the type of mutation identified and the clinical picture observed in the patient: the so-called "**genotype-phenotype correlations.**"
The clinical difference between DMD (more severe) and BMD (milder) is largely explained at the molecular level. In DMD patients the mutations in the gene for dystrophin prevent the production of dystrophin in the muscle (dystrophin absent) while mutations in BMD patients allow the production of a generally shorter, but partially functioning protein (see Explanatory Box in Chapter 2).
However, genotype-phenotype correlation is not always feasible because of the well-known exceptions to the rule of the "frame." In cases where correlation is possible, it is relevant for prognosis and clinical management of the disease.
Another type of genotype-phenotype correlation is related to the location of deletions (more frequently). There are some deletions in BMD patients that are often associated with the presence of **early cardiomyopathy** and, in these cases, the identification of these mutations allows cardiological prevention early in the childhood/youth ages. Other mutations are associated with a very mild disease and, in some rare cases, even with complete absence of symptoms, and the patient maintains the ability to ambulate throughout life.
Knowledge of disease prognosis, when possible, is of course relevant to patients' life planning.

BMD GENETIC COUNSELING

Genetic diagnosis in a child/adult affected by BMD provides detailed information about the disease causing mutation.

If BMD has previously occurred in the family, the risk of recurrence of the disease can be assessed. Through genetic counseling and targeted genetic testing can be determined whether other family members are affected by BMD or whether there are carrier females in the family. Once the mutation in the dystrophin gene that causes BMD in the child/adult is identified, a targeted genetic investigation is offered first to the patient's mother. This diagnostic procedure is usually rapid, because it focuses on finding a precise and already known mutation in the dystrophin gene. The same genetic analysis can then be extended to other female members of the maternal branch of the family (sisters, daughters, aunts, cousins): for all of them it is appropriate to offer genetic testing to establish a possible carrier status.

If the disease-causing mutation in the family is not known and the BMD patient is no longer available for genetic testing, a complete analysis of the gene for dystrophin must be performed in at-risk family members (mothers, sisters) in order to identify the BMD gene mutation following the multistep process already outlined: MLPA first, followed by sequencing. This multistep diagnosis is offered to the closest patient's consanguineous family member (mother, sister) and then, once the mutation has been identified, extending the investigation to all females at risk of being carriers in the family, as established by recent guidelines.

In Italy, genetic investigation to establish the carrier status is appropriate for all females of legal age at risk, whether they have even mild signs or symptoms of the disease (such as an elevated CK confirmed by at least 3 different testing determinations, or symptoms such as muscle weakness and fatigue) or completely asymptomatic with normal CK. In asymptomatic under-aged females, genetic testing is not routinely offered (international guidelines of the World Health Organization, WHO, and guidelines for dystrophinopathies). In contrast, in the case of females exhibiting signs or symptoms of BMD (including increased CK), genetic testing is appropriate and should always be preceded by genetic counseling and acquisition of informed consent from both parents or legal guardians.

Carrier diagnosis in at-risk female adults should be made as early as possible for timely prevention and procreation planning. All genetic testing to identify a carrier status must always be preceded by genetic counseling ("pre-test genetic counseling").

Patient with BMD

BMD patients will always have healthy male children (because they pass on the Y chromosome to males) and always obligate carrier female daughters (because they pass on to all female daughters their single X chromosome with the gene for dystrophin mutated) as described next.

BMD Female carrier

In the event that genetic testing identifies the mutation in at risk female, the latter will be called a "carrier." Carrier females, with very rare exceptions, are asymptomatic; however they have a 50% risk of transmitting the mutation to their child at each pregnancy: male offspring who inherit the mutation will be affected by BMD while female daughters who inherit the mutation will be asymptomatic carriers.

The result of the genetic test should be given during a "post-test genetic counseling": such counseling will allow people to discuss the results and consequences of the test, to know the likelihood of transmit the mutation to their children, and to plan reproductive choices.

Rarely, female carriers may develop clinical symptoms mainly affecting skeletal muscle and the heart. Symptoms are usually mild, and only exceptionally severe. However, because all female carriers are at risk of developing heart disease, mostly in later life, the diagnosis of carrier is relevant for clinical follow-up and cardiologic prevention.

Non DMD carrier Female

In about 20% of BMD the disease is caused by a "de novo" mutation, that is, a mutation that is not inherited from a carrier mother but occurred in the egg cell in the very early stages of the embryo development of the BMD individual. In this case, the mutation is present only in the BMD patient. However, the presence of a de novo mutation, i.e., absent in the patient's mother at the constitutional level, does not rule out a possible recurrence of disease due to "germline mosaicism," i.e., the presence of multiple mutated egg cells in the maternal ovaries. Although the precise frequency of this occurrence is unknown, it is estimated, based on the few published works, to be 7 percent.

The guidelines, therefore, recommend prenatal diagnosis "in all mothers of BMD patients," even if they resulted not being carriers, for the possible presence of germinal mosaicism.

In cases where an at-risk female has a negative genetic test and is not the mother of a BMD patient, prenatal diagnosis is not appropriate because her risk of BMD recurrence is equal to that of the general population.

Reproductive choices, prenatal diagnosis, preimplantation diagnosis

As anticipated, the diagnosis of carrier in at-risk female of legal age should be carried out as early as possible: knowing the carrier status before planning a pregnancy will allow to access all available prenatal interventions and to plan in a timely manner the pregnancy, increasing the success of the test, which is linked to precise prenatal timing.

In case the female's genotype could not be obtained prior to a pregnancy, the modern diagnostic techniques- particularly the Next Generation Sequencing- will allow identification of carrier status even in an ongoing pregnancy.

Once pregnancy is ongoing, it is possible to assess whether the genetic mutation is present in the embryo/fetus through various prenatal investigations.

It is important to emphasize that, in accordance with national and international guidelines, molecular diagnosis of DMD/BMD is carried out only in male fetuses (with rare exceptions, for psychiatric/psychological reasons): this is because, as already anticipated, females are asymptomatic, and the rare occurrence of symptomatic females is not predictable, nor related to the mutation per se or its transmission.

Recommended prenatal diagnostic techniques differ on the basis of gestational period, the type of technique used, and the information they provide.

To date the female carrier, in order to understand whether the unborn child has inherited the mutation that causes the disease, can choose between invasive prenatal investigations (offered within the National Health Service, SSN) and non-invasive (currently in Italy accessible only through private Centers or in some Regions such as Tuscany and Emilia Romagna, in ongoing pilot projects).

Invasive prenatal diagnostic techniques

Invasive prenatal diagnostic techniques include **chorionic villus sampling**, **amniocentesis** and **funiculocentesis or percutaneous Umbilical Cord Blood Sampling (PUBS)**.

Chorionic villus sampling is an invasive technique because it involves the collection of chorionic villus, which constitute the embryonic part of the placenta. It is the technique of choice (to date, within the scope of diagnosis offered by the NHS) for the molecular diagnosis of Mendelian genes-diseases (and thus also for the diagnosis of DMD/BMD) because it is a technique that can be perform early in the pregnancy course: preferably between the 10th and 12th week, and allows to obtain quite abundant biological material. Report of a prenatal diagnosis on chorionic villus sampling requires about 10 to 15 days. Alternatively, amniocentesis, an examination that can be performed in the second trimester of the pregnancy- preferably between weeks XV and XVII-which consists of amniotic fluid sampling.

In this case molecular diagnosis is more complex and takes longer (up to 3-4 weeks).

Finally, **funiculocentesis** or **cordocentesis** is the invasive prenatal diagnostic technique that can be per-

formed later in the pregnancy course, between the 18th and 20th week. This technique involves the collection of blood from the umbilical cord; however, since it is performed in a late phase of pregnancy, it does not ensure to obtain a molecular diagnosis in the legal time frame for a possible termination.
All these techniques allow to analyze the fetus DNA and, therefore, to perform an accurate diagnosis of the disease through the identification of the causative mutation in early or later stages of the pregnancy. If the prenatal diagnosis identifies a mutation in the dystrophin gene in the fetus, the couple will decide whether to continue or to terminate the pregnancy, according to the timeframe provided by the Italian law. For this reason, it is of great importance to carry out genetic counseling as soon as possible to have access to an early prenatal diagnostic technique (possibly chorionic villus sampling).

Non-invasive prenatal diagnostic techniques

The techniques described above are invasive and thus are associated with a risk (ranging from 0.2% to 2%) of miscarriage. For this reason, in recent years, non-invasive prenatal diagnostic techniques such as "**Non-invasive prenatal testing- NIPT**", are becoming more popular, but at the moment are not offered within the NHS. In Tuscany and Emilia Romagna regions pilot projects of NIPT are ongoing. Unlike chorionic villus sampling and amniocentesis, this test is non-invasive since it consists of the analysis of fetal DNA present in maternal blood. It has been shown that, starting from the first trimester of pregnancy, free DNA of fetal origin is present in maternal blood and can be collected in a simple and non-invasive way and used for the study of some fetal pathologies. This technique, which can be performed as early as the 9th week of pregnancy, allows to determine **the sex of the unborn child** and the screening for the most frequent diseases related to chromosomal abnormalities (such as Down syndrome or chromosome 21 trisomy) reliably, accurately, and non-invasively. Diagnosis of the causative mutation in the dystrophin gene is currently not feasible via NIPT, and it needs further technical validation in order to be used in the diagnostic setting.
However, the knowledge of the sex of the unborn child, through NIPT, allows to target molecular investigations with invasive methods (chorionic villus sampling or amniocentesis) only to pregnancies of male fetuses, avoiding invasive procedures in the case of female fetuses.

Preimplantation genetic diagnosis

A procedure that is complementary to prenatal diagnosis techniques - and recently made available under the NHS for women carrying a genetic disease - is the **Preimplantation Genetic Diagnosis ("PGD")**.

PGD represents a new methodology, complementary to prenatal diagnostic techniques, to identify the presence of genetic diseases or chromosomal alterations in embryos generated in vitro in couples at high reproductive risk.

GENETIC DIAGNOSIS

PGD combines the use of medically assisted procreation (PMA) techniques with the latest research in genetics.
PMA refers to all procedures involving the processing of male gametes (spermatozoa), female gametes (oocytes) or embryos aimed at achieving a pregnancy.
PMA can use of different techniques ranging from the less invasive Level I to the more complex Level II and III procedures according to the specific case.
For DMD/BMD preimplantation diagnosis Level II techniques are suggested, i.e. IVF embryo transfer (in which fertilization takes place outside the female body and the resulting embryos are transferred into the uterus) and ICSI (in which a single sperm is injected directly into the oocyte).
Couples requesting access to preimplantation diagnosis techniques will begin the PMA procedure, which will allow recovery of oocytes to be fertilized with paternal sperm. Once fertilization is achieved, one or two cells (blastomeres) will be harvested from embryos at the earliest stages of development (3 days old). The DNA extracted from these cells will be analyzed depending on the type of genetic or chromosomal disease to be diagnosed. Only embryos not affected by the genetic disease will be transferred into the uterus.
PGD (now suggested and technically feasible also for other genetic diseases besides DMD/BMD) avoids the need for therapeutic abortion.
In order to get more information regarding the centers (public and private) that perform PMA and other techniques, it is possible to consult the website of the Istituto Superiore di Sanità (www.iss.it/rpma).

PRACTICAL ASPECTS AND PRESCRIPTION OF A GENETIC TESTS THROUGH THE NATIONAL HEALTH SYSTEM

BMD is a rare disease as defined by the Ministerial Decree No. 279/2001 and subsequent DPCM Jan. 12, 2017 (G.U. No. 65, 03/18/2017). The designation of Rare Disease entails patients and their families to several relevant health benefits, both during the diagnostic process and when the diagnosis is established. The latter is particularly relevant considering that BMD is a chronic disease requiring multiple health interventions to manage and care for the patient and his family.
The exemption code R99 (Services required in the diagnostic process of a rare disease (ex art. 5 paragraph 2 of Ministerial Decree 18.05.2001 No. 279) should be used for all prescriptions devoted to confirm or rule out the diagnosis and to access the genetic counseling and the genetic testing in the diagnostic process.
The same R99 code should be used for genetic testing on the patient's family members (women are possible carriers). The R99 code can only be used by a specialist doctor in the public setting. Once the diagnosis has been established, the BMD patient needs to be certified as a rare patient. To achieve this, the patient should enroll into the National Rare Disease Registry, the disease will be associated to a specific ORPHA code and the patient will access for free to all health care services related to his condition and to the services provided by the European Reference Networks (ERNs, https // ern-euro-nmd.eu). It is therefore essential that the patient be certified at the time of diagnosis in the Regional Registries, which then refer to the National Registry managed by the Istituto Superiore di Sanità (ISS). Suitable centers and physicians have been identified in all Italian Regions for certification. The patients must request their certification to the designated physician and obtain their code and their certificate, which must then be used for any future health needs.
Health prescriptions (on an SSN prescription) to access genetic counseling can be done by the general practitioner or by a specialist (such as neurologist or pediatrician), while requests (again on an SSN prescription) for genetic testing can only be made by the specialist (any specialisation).
In order for the patient to be eligible for a free service the exemption code should be used in any prescription.
The R99 exemption code can also be used for carrier testing or for any prenatal diagnostics.

Psychological aspects in genetic and family counseling

Psychological aspects in genetic counseling

If a women is a BMD carrier and the couple plans another pregnancy sharing the experiences that may arise during this phase could be of great help. The couple can take advantage of pre-conception counseling with the help of a psychologist.

Psychological support during genetic counseling

The period of genetic testing is a waiting time in which the hope of receiving good news alternates with the fear of being a carrier. Often the individual facing the diagnostic pathway, may manifest unusual emotional reactions compared to her usual functioning, generating experiences of anxiety and inadequacy in managing the waiting time. In order to manage the emotional state experienced, it may be important and of great help to have the support of a professional psychologist with whom to share thoughts and experiences, identify strategies to manage this time of suspension, and recognize the meaning and value of the emotions experienced.

Main experiences of carrier women and psychological support

When the mother discovers that she is a carrier of the condition, she may experience disorientation, feelings of guilt, helplessness, anger, and confrontation. Together with her partner, she faces disillusionment with respect to her life plan.

It is difficult to define what is the most appropriate way to deal with the situation; it is certainly important to pay proper attention to psychological manifestations that may disturb personal and family balance.

Anxiety, insomnia, tachycardia, excessive worry over their child's future and their own health

Mood alterations: inability to cope, sense of injustice and helplessness over what happened, feelings of guilt

Difficulty concentrating, repetitive thoughts, irritability, withdrawal

At this delicate stage, it is advisable to take advantage of psychological support, in order to assess the possible initiation of individual, couple or family therapy, which will allow to process the experiences and identify the resources needed to cope with the emotional burden of the diagnosis and the needed family reorganization.

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NEUROMUSCULAR MANAGEMENT

NEUROMUSCULAR MANAGEMENT

The main goal of a BMD patient neuromuscular management is to preserve strength and motor function.

When ASSESSMENTS AND and

A BMD patient should have regular clinical evaluations with a specialist who knows the natural history of the disease and has the expertise to follow its progress. The specialist must therefore be able to implement preventive therapies and early intervention on the various complications associated with this disease.
The BMD clinical signs and symptoms are highly variable in term of age of onset and progression, and therefore clinical follow-ups may also have a different timing depending on the patient's age and clinical manifestations. In the early stages of the disease, first and second decades, boys often present with an isolated increase in CK or exercise intolerance (onset of pain during physical activity). Annual clinical checkups for motor assessment are recommended at this stage. When the first signs of muscle weakness or initial joint retractions will appear (typical is the tendency to walk on the toes, an expression of initial Achilles tendon strain) it will be important that clinical evaluation be semiannual.

The clinical tests to be performed should be aimed at evaluating:

Muscle strength can be measured either manually (utilizing the conventional MRC scale of muscle strength, which is based on the execution of movements by the patient against the resistance exerted by the operator) or through equipment (dynamometers, fixed or mobile) that allow more sensitive and quantitative measurement of the strength of different muscle groups. Based on the entity of the muscle weakness found and according to the velocity of progression, the rehabilitation project will aim to the active, active assisted or passive mobilization of various muscle groups.

Joint movements. When assessing a BMD patient, it is important to monitor the occurrence or progression of joint stiffness or muscle-tendon contractures. When joint contracture or rigidity are encountered, it will be important to set up rehabilitative interventions such as stretching exercises or the use of positioning orthoses to counteract extremity deformities.

Timed motor functions. The use of timed tests (testing the time to get up from the floor, to walk, to climb and go down several stairs) is very useful. These provide important information on how the pathology is progressing in the patient and how he or she is responding to treatments.

Motor function rating scales. Motor function rating scales allow scoring individual patient abilities (e.g., jumping, standing on one leg, getting up from the floor, etc.). These abilities require the use of different muscles (as opposed to the MRC or dynamometer which measures the strength of a single muscle at a time). There are many clinical scales, and some of them are used and validated internationally. They are simple to be delivered but it is important that the physiotherapist would be instructed on how to perform the tests. The use of these scales makes it possible to monitor the patient's clinical changes over time, and to understand the effect of a rehabilitation treatment, a drug or the progression of the disease.

Muscle magnetic resonance imaging: imaging is a radiological method that, without exposure to X-rays, allows to study the muscle health. New radiological techniques allow in a single setting, both qualitative and quantitative measurements of the entire skeletal musculature. This examination can be performed without sedation and can also be performed in pediatric age from the age of 6-10 years. This examination, integrated with clinical evaluation, provides a lot of information and can detect even small changes in muscle tissue.

Questionnaires on quality of life and personal autonomies in daily life:
These questionnaires explore the patient's difficulties in activities of daily living and allow the attending physicians to suggest aids to improve autonomy.

Pharmacological treatments for skeletal muscles

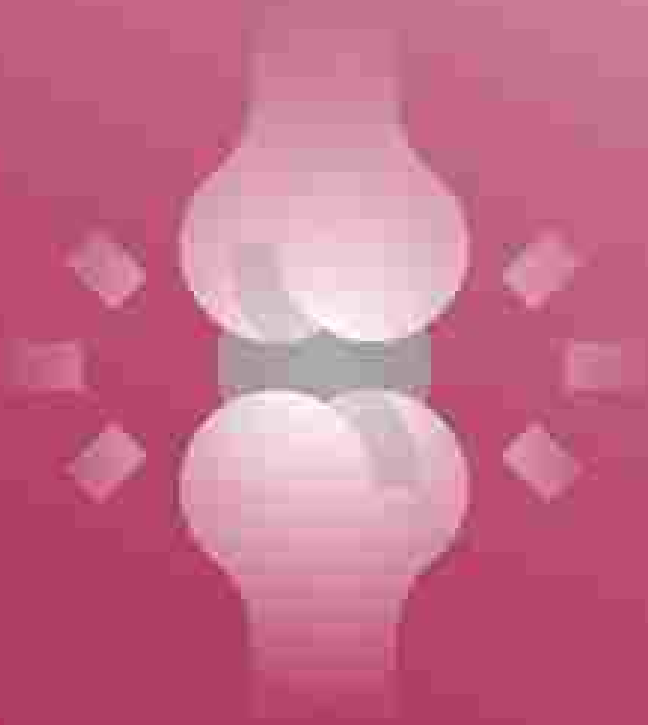
To date no pharmacological treatments with proven clinical efficacy and codified guidelines are available for BMD.
In DMD, the therapeutic effect of glucocorticoids or "steroids" (GC) is recognized. The chronic GC use has been shown to increase muscle strength, delay loss of ambulation, reduce the risk of scoliosis, and preserve respiratory function.
GC slow muscle degeneration through a direct anti-inflammatory effect on muscle and by mitigating muscle-damaging events that are triggered by dystrophin defect and inflammation.
In BMD, no controlled clinical trials have ever been conducted to demonstrate a possible positive effect of GC. These studies are hampered by the great clinical (asymptomatic patients and patients with severe muscle weakness) and biochemical variability in BMD (different mutations with different dystrophin levels in the muscle), which does not allow an easy identification of a homogeneous group of patients.
However, since the biological mechanisms underlying muscle degeneration in BMD patients are similar, albeit milder, than those observed in DMD, it is possible that GC might have a protective role in BMD as well. Indeed, there are several reports in the scientific literature regarding BMD patients treated successfully with GC.
It is therefore important to consider GC as a therapeutic option even in BMD patients, carefully considering the age of onset of symptoms, and the clinical progression of the disease. The referring neurologist/children neuropsychiatrist should reserve this therapy only for patients with progressive and severe muscle weakness. The specialist should therefore consider the GC option as "individualized therapy." If a GC therapy has been decided, it is necessary to carefully monitor the positive effects and the possible side effects over time.
In the BMD patient diagnosed in developmental age and on chronic GC therapy, it is important to control pubertal development in order to identify any hormone deficiencies and provide replacement therapy if necessary.

In these patients, a condition called hypogonadism that involves a reduction in the production of hormones involved not only in sexual maturation, but also in statural growth should be considered. GC may also be responsible of various metabolic complications. GC intake can reduce serum (blood) testosterone levels, thus contributing to both growth retardation and bone fragility.

Treatment with testosterone, which is one of the reduced hormones in hypogonadism, can result in clinical benefits on the musculoskeletal system, with increased muscle mass and strength and positive effects on bone health. This hormone can be taken through injections or patches, and the dosage is calculated taking into account the initial serum levels of the patient.

Among the various effects, positive and negative, induced by GC, there is a serious complication related to an abrupt discontinuation of GC intake: the so-called "adrenal crisis." Physiologically, cortisol is a hormone produced by the adrenal gland that is useful in coping with stressful situations; when GC are chronically administered, as in the case of patients with muscular dystrophy, endogenous production is reduced.

In case of abrupt discontinuation of GC intake or in case of increased need of the body (following a fracture or surgery for example), an adrenal crisis may occur. This is a true medical emergency recognizable by the onset of dehydration and a confusional state, headache, sudden lowering of blood pressure, tachycardia, sweating, and sometimes vomiting. In this case it is mandatory to access immediately the emergency room.



BONE HEALTH

5

Bone has a main mechanical function, supporting and sustaining posture and movement, mediated by the insertion of muscle tendons on the bone itself. Given this function, the structure of the bone has to change according to the needs of the individual, to better accomplish to the different demands that arise in daily life. For example, a lean individual with little muscle mass will have thinner and generally less strong bone, while a muscular athlete will usually have firmer bone. Such biological behavior of bone is regulated first and foremost by the genes we inherit, but also by the nutrition and exercise we perform. Bone is capable of regulating its size and structure, including its composition, throughout the entire individual's life from birth until death, through the production of substances secreted from distant organs (endocrine hormones) or from the bone itself (cytokines) that are produced according to the needs to which the bone itself must respond.

Muscle activity is one of the main regulating factors of this "bone metabolism," and it acts from the earliest stages of skeletal growth, allowing bone to become progressively stronger as growth progresses, until it reaches a "peak bone mass", which constitutes the stock of bone that will accompany the individual throughout life and that will decrease during old age. Having a high peak bone mass means having more bone reserve when old age will force us to spend it.

Muscle diseases always negatively affect bone health, and those occurring in prepubertal ages, such as BMD, make it difficult to achieve a good level of peak bone mass and hinder the maintenance of good bone health. In an individual with BMD, the bone may be more fragile than that of a healthy peer, and thus fracture even from minor trauma.

It is worth mentioning that: in patients taking glucocorticoids (GC), these may promote bone fragility through a reduction in mineral content of bone, leading to early bone weakness compared with subjects of the same age, with an increased risk of fracture due to minimal trauma, particularly at the level of the vertebrae and long bones, such as the femur or tibia. Fracture is a very negative event in the clinical history of the disease because it can be followed by further limitation of the ability to walk and perform activities of daily living.

To protect the bone health, the first recommendation is to encourage movement, within the patient's limits and possibilities, and to perform it in the open air. Physical exercises and targeted physiotherapy allow the muscles to move and allow the bone to be stimulated. Outdoor activity is helpful for skin production of vitamin D. In addition, a healthy, balanced diet containing the right vitamin and calcium intake is foremost important. Vitamin D and calcium deficiency need to be supplemented in the form of vials or tablets to be taken according to a doctor's prescription. Calcium and vitamin D supplementation is mandatory in cases of chronic GC use.

To better quantify the deficit of vitamin D, it is useful to perform an annual blood draw to assay 25-hydroxy vitamin D [25(OH)D] levels (which is the reference metabolite for assessing vitamin D levels in the blood and, therefore, possible hypovitaminosis) and to determine the nutritional intake of calcium through questionnaires easily available on the Internet or through apps, which allow to calculate, accurately and in a few minutes, the daily intake compared to the recommended amount based on the patient's age (*https://www.osteoporosis.foundation/educational-hub/topic/calcium-calculator*).

Finally, it is important for BMD patients to regularly take a specific examination that quantifies bone density (so-called bone densitometry or MOC). This method allows the measurement of mineral mass and bone density with scans of the spine at the level of the lumbar vertebrae and the whole body. The MOC should be performed at least every 24 months.

The technique uses X-rays but at a very low dosage compared to common radiography. If a person experiences a persistent back pain, it may be useful to prescribe a lateral projection X-ray examination of the spine to evaluate if there are ruptures in the structure (fractures) of the vertebrae.
Monitoring bone density and bone structure in patients at risk of fractures is necessary to prevent the occurrence of new fractures and to start therapy with specific bone health drugs such as bisphosphonates, which increase bone strength through their bone resorption inhibition, which can be excessive as a result of muscle activity deficit and chronic cortisone use.

Orthopedic management

Orthopedic management in a BMD patient has the main goal of maintaining walking ability and prolonging it as much as possible and, in the advanced stages, of optimizing wheelchair posture.
During the walking phase, it is advisable for the patient to preserve as much as possible an overall good joint mobility and symmetry in foot placement in order to avoid the development of contractures/retractions, which in the long run can lead to joint deformities, that are difficult to correct with physical therapy. In this regard, it is recommended: the use of overnight leg-foot orthoses during this phase, especially when the ankle joint starts to lose its range of motion. These orthoses stabilize the foot in a neutral position and are custom-made to accommodate the characteristics of the individual wearing them. It is preferable to use them at night, so the individual is more tolerant of wearing them and allows the orthoses to perform their function of preventing joint deformities through prolonged stretching of the at-risk joint and muscle structures.

To delay the loss of ambulation, leg-ankle-foot orthoses can be used; these are worn while walking to provide support, enabling the patient to remain upright for longer and delaying the need for a wheelchair.

In this phase, "functional" surgical interventions can be useful. These are minor operations that allow the lengthening of a shortened tendon (most commonly a retracted Achilles tendon causing a condition called equinus foot, where the foot tends to rest on the ground with only the toes). More rarely, and in particular cases, other shortened tendons can be lengthened, such as the posterior thigh tendons (which cause a flexed knee) or the lateral thigh tendons (resulting in forced hip abduction). Tendons can also be transferred to a different joint surface to take over the function of a tendon that is no longer effective (such as the transfer of the posterior tibialis tendon). These interventions are considered on a case-by-case basis, carefully evaluating the likelihood of success and the guarantee of functional recovery.

In the non ambulatory phase, the patient will need to adapt to using a wheelchair, which must have all the technical features to prevent postural deterioration and to maintain the highest possible level of interaction with the surrounding world as long as possible. It is important for an expert team to assess potential posture systems and cushions to keep the patient from assuming abnormal positions, promote proper relief of any areas under increased pressure on the support surface, and correctly align arm and foot support in term of height and length. In this phase, day-time static orthoses can also be used, provided they are well tolerated by the patient, both for the lower limbs, to prevent foot structure changes, and for the upper limbs to maintain a good manual grip and allow the patient to interact with the environment. A helpful support tool is the use of standing boards: these aids allow safe maintenance of an upright position and can also be used at home.

In this phase, the introduction of transfer boards and slides is important to facilitate transfer at home from the wheelchair to various support surfaces.
Maintaining ambulation and correct posture is crucial to prevent a serious complication: scoliosis.

Scoliosis is a deformity of the spine (which tends to curve sideways) that occurs in these patients due to a weakness in the muscles that keep the back straight and aligned. Over time, and with worsening spinal deformity, scoliosis can also lead to respiratory complications.

It is important to monitor the alignment of the spine proactively through standing X-rays, performed annually for scoliotic curves <20° and at least every six months for curves >20° (the degrees of a curve are measured on an anteroposterior projection X-ray of the spine by an experienced physician).

To date, the use of a brace in the early stages to promote proper spinal alignment is not generally recommended; however, in some cases, after a thorough assessment of the flexibility of the scoliosis by an experienced physician, a brace may be used to prevent the curve from worsening. If the patient is in a wheelchair, the introduction of a custom postural support system can be helpful to ensure correct and symmetrical support in a seated position.

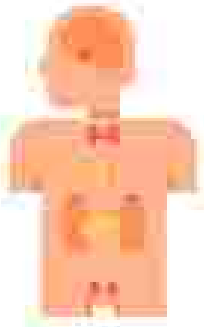
In cases of severe scoliosis, surgical intervention may be recommended to align the spine as much as possible using rods and screws, to prevent further deformity.

In the case of long bone fractures, which are common in these individuals, orthopedic intervention will be based on patient's needs and possibilities. For example, for thigh or leg fractures, if the patient is ambulatory, internal fixators are preferred to enable rapid rehabilitation. In non-ambulatory patients, immobilization with casts or braces is preferred to facilitate bone healing in patients who would not be able to bear weight on the fractured limb.

Managing a patient with BMD who has suffered a fracture requires consultation with family members and consideration of the patient's own needs.

A serious complication of fracture is fat embolism, where a fragment of fatty tissue from the fracture site enters the bloodstream and can lodge in the lungs causing respiratory crisis. This is a medical emergency, so when a patient with BMD falls and/or fractures, it is always advisable to take him to the Emergency Room for appropriate management of the condition, including the prevention of this complication.

Endocrinological management



In patients with BMD diagnosed during developmental age, it is important to monitor growth parameters (height and weight) and pubertal development to identify any hormonal deficiencies and provide appropriate replacement therapy if needed. Metabolic alterations can also result from malnutrition, especially in advanced stages when respiratory complications require increased caloric intake. In addition, there may be a predisposition to diabetes and obesity facilitate by reduced movement and potential confinement to a wheelchair. Obesity should be addressed through a balanced diet, taking into account the residual level of physical activity, reducing calorie intake in case of weight gain and loss of ambulation, and ensuring the right intake of micronutrients, particularly calcium and vitamin D.

MANAGEMENT OF NEUROMOTOR REHABILITATION

NEUROMOTOR REHABILITATION MANAGEMENT

The optimization of multidisciplinary clinical management, including the muscle care, cardiac and respiratory function, nutritional and gastrointestinal aspects, physical therapy, and psychological support, has led over the past 30 years to an increased life expectancy in both DMD and BMD, an improved overall cardiorespiratory well-being, reduced hospitalizations, and thus to a significant improvement in quality of life.

For effective neuromotor rehabilitation, patients with BMD require a multidisciplinary team to guide them through rehabilitative and habilitative treatments, and educate them on proper physical exercise based on their muscle and cardiac clinical condition. The team should include a neurologist/child neuropsychiatrist, cardiologist, pulmonologist, physiatrist, physical therapist, assistive device specialist, occupational therapist, speech therapist, and orthopedic specialist. These professionals will intervene based on the clinical picture presented by the patient.

Timing for the assessment and goals

Multidisciplinary evaluation should be performed every 10-12 months or more frequently if the patient has lost the ability to walk or has cardiomyopathy.

The goals of rehabilitation in BMD are:

Preserving autonomy	Delay the evolution of symptoms	Preventing complications

The rehabilitative intervention therefore can be:

Preventive	Curative	Compensatory

Interventions

Exercise

Exercise is defined as planned and structured physical activity practiced regularly with the goal of improving or maintaining good physical fitness. It is well documented that exercise has beneficial effects on muscle, increasing strength and endurance. However, it should be noted that uncontrolled exercise can have counterproductive effects on dystrophic muscle.
On the other hand, it has been shown that low-intensity and aerobic muscle exercise improves the physical well-being of patients with BMD and muscle strength in specific areas, without inducing muscle damage (no changes in CK levels or muscle morphology in biopsies) and/or cardiac damage. The benefits persist over time and are associated with an overall improvement in health and psychological well-being.

FIGURE 3: CHANGES IN SKELETAL MUSCLE DUE TO "DISUSE"

It is also known that disuse atrophy (lack of exercise), related to the absence of mechanical muscle loading, causes a reduction in muscle mass and consequently in the number of muscle fibers.
In BMD (as in other muscular dystrophies), muscle weakness can lead to sedentary lifestyle. The sedentary lifestyle induces a reduction in muscle mass and changes in metabolism, potentially leading to weight gain, which further reduces motor activity and strength the muscle can generate, exacerbating muscle weakness.

- The response to exercise is specific, related to two factors: type of exercise (intensity, duration, and frequency) and the patient's clinical condition.
- Aerobic exercise is well tolerated, safe, improves patient well-being and endurance and its effect is lasting. Recommended aerobic activities are swimming and generally water activities.
- Exercises conducted with the aid of robotic devices and exoskeletons (external movable structures) can be useful in patients with severe motor impairment.
- All activities should be monitored by a physical therapist experienced in neuromuscular diseases.

Mobility and stretching

Maintaining good join motion and symmetry across different joints contributes to preserving good functionality and prevents the development of contractures. For preventing muscle-tendon retraction it is essential to:

- Perform daily muscle stretching, including self-management, following exercise education by an experienced physical therapist;
- Use orthoses, braces, and other aids (specially for non-ambulatory patients): such as leg-foot braces for nightly ankle stretching, and manual or motorized static devices (to maintain an upright posture, if retractions do not compromise posture tolerance severely).

Prevention of falls and fractures

Minimizing the risk of falls is crucial both at home and in the workplace for ambulatory and non-ambulatory patients alike. **Therefore, it is recommended to:**

- remove carpets, wires and uneven surfaces at home;
- evaluate the slipperiness of support surfaces;
- place non-slip mats in the shower and bathtub; place grab bars;
- install grab bars and handrails where there are stairs and steps.

For the wheelchair bound patient, it is critical to:

- educate patient and family members on the safe use of wheelchairs;
- raise awareness of the risk of wheelchair falls both at home and outdoor;
- instruct family members on positioning changes, use of lifts and ramps.

Wheelchairs and other aids

It is advisable to consider various aids in advance to ensure safety in movement (lifts), independence (e.g., bathroom handles, raised toilet seats for ambulatory patients) electronic wheelchair for patients with significant muscle weakness), and participation in rewarding activities (manual or electronic wheelchair or motorized scooters).
It is useful to adapt the bed and mattress, particularly for patients with compromised motor function, to prevent pressure injuries and facilitate independent position changes during the night (adjustable beds).
It is recommended the use of manual and electrical standing systems to maintain an upright position (orthostasis) in individuals with moderate-severe muscle weakness (hypostenia) in the lower limbs combined with contracture, ensuring adequate posture and good tolerance.
Simple devices are available to facilitate meal autonomy, such as elevated lip trays, curved utensils, and adapted straws. In recent years, advanced technologies have been made available such as robotic/bluetooth environmental control systems, voice recognition systems for PC, phones, intercoms, and door opening/closing within the home.

Pain management

Identifying the cause of pain is essential for appropriate intervention. Many pains can be attributed to incorrect posture: for example, lumbar sciatica may occur in ambulatory patients with significant lumbar hyperlordosis. Attempting to control spine pain by avoiding upright posture or walking may increase the risk of sedentary behavior. Spine pain may also result from incorrect wheelchair posture or severe osteoporosis (common in long-term wheelchair users without rehabilitation treatment). In these cases, symptomatic treatment may include non-steroidal anti-inflammatory drugs (NSAIDs), or in rare cases, steroids, as directed by a physician. The use of opioid analgesics should be approached with extreme caution.
Correction of posture and the use of appropriate orthoses are essential parts of pain management.
Myalgia and cramps are common in BMD: they can be treated with massage therapy, muscle stretching and mineral supplements.

General guidelines based on clinical situation

Patient with good mobility autonomy, good muscle strength in all areas, no heart disease, and no high risk of cardiomyopathy

- Low-intensity, daily aerobic exercise
- Prevention of tendon retractions and maintenance of adequate joint range of motion with stretching and manipulation

Patient with good or slightly reduced autonomy and cardiomyopathy

- Limited physical exercise with adequate supports
- Water activities only if assistance for entering/exiting the pool
- Prevention of retractions with targeted stretching and use of lightweight leg-foot braces overnight
- Attention to the home and work environment to prevent falls
- Monitoring of bone and general metabolic conditions
- Body weight monitoring

Patient with reduced mobility autonomy , reduced muscle strength levels especially in the proximal districts of the lower limb, absence of heart disease

- Limited physical exercise with appropriate supports
- Water activities only if there are facilitations for entering/exiting the pool.
- Prevention of retractions with targeted stretching and use of lightweight leg-foot braces overnight.
- Use of standing systems.
- Attention to the home and work environmental to prevent falls
- Monitoring of bone and general metabolic conditions.
- Body weight monitoring.

Non-ambulatory patient

- Limited physical exercise with appropriate supports
- Water activities only if there are facilitations for entering/exiting the pool.
- Prevention of retractions with targeted stretching and use of lightweight leg-foot braces overnight.
- Attention to home and work environmental to prevent falls
- Facilitation of independence (wheelchairs, home automation systems, meal facilitation etc.).
- Monitoring of bone and general metabolic conditions.
- Body weight monitoring.

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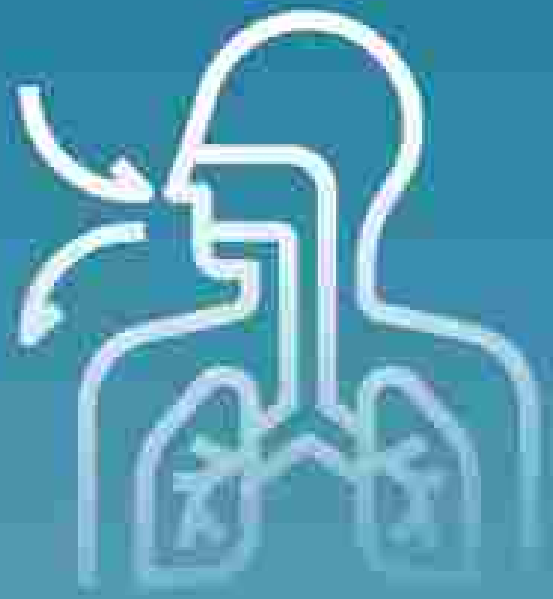


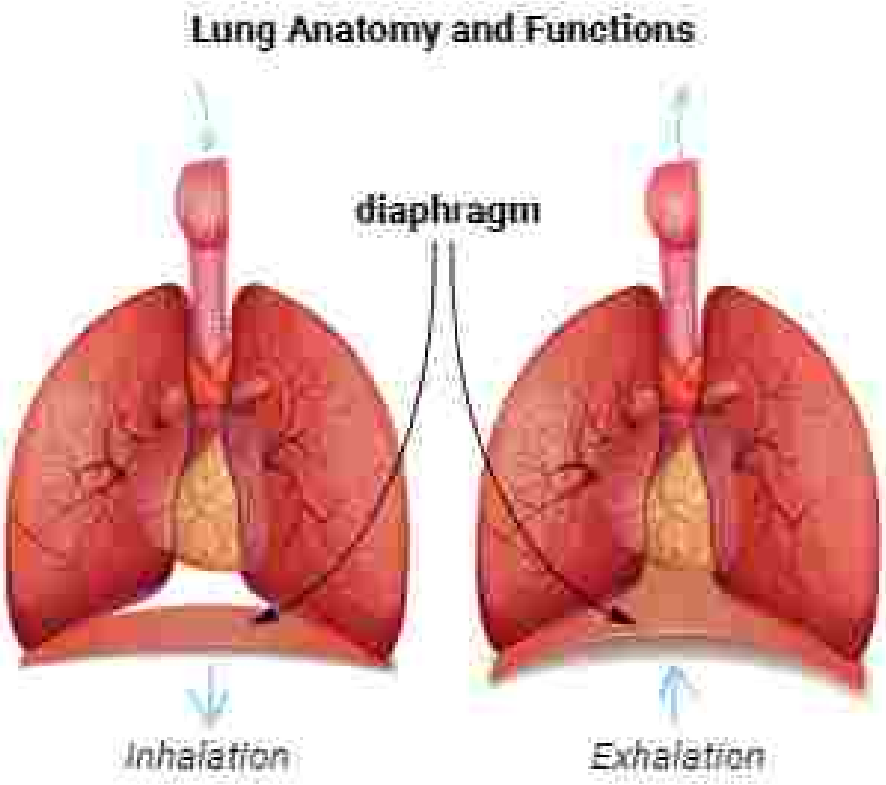
RESPIRATORY MANAGEMENT

RESPIRATORY MANAGEMENT

THE ONSET OF RESPIRATORY INSUFFICIENCY

Neuromuscular diseases, including BMD, can significantly impact respiratory function due to the involvement of the so-called "**ventilatory pump**", which includes the respiratory muscles responsible for transporting atmospheric air to the lungs for gas exchange (alveolar ventilation).

In BMD, the involvement of the **diaphragm muscle** (an key part of the "ventilatory pump") can cause a reduction in lung ventilation, potentially leading to the onset of true Respiratory Insufficiency (RI), characterized by reduced oxygenation and retention of carbon dioxide (CO2). The progression toward RI in BMD generally follows two patterns: more frequently, it is chronic and late-onset, driven by so-called progressive global hypoventilation (Chronic Respiratory Insufficiency, CRI). However, it is not uncommon to encounter acute-onset RI (Acute Respiratory Insufficiency, ARI), which can occur even during periods of relative respiratory well-being ("clear sky" RI). This is typically triggered by a respiratory tract infection, leading to bronchial secretion congestion due to ineffective cough mechanism.



Progressive CRI in BMD is fundamentally due to inspiratory muscle weakness, leading to a reduced ability to generate normal levels of pressure and airflow during inspiration. Initially, this inspiratory muscles weakness affects lung volumes, causing a restrictive ventilatory deficit that can be assessed through spirometry. Eventually, it leads to overt RI, with CO2 retention. The severity of CO2 retention is closely related to the degree of respiratory muscle weakness.

Changes in sleep respiration play an important role in the onset of CR. In healthy individuals, sleep-induced variations in gas exchange are modest, but they become more pronounced in patients with respiratory muscle weakness, particularly when the diaphragm is significantly involved. BMD patients may experience nocturnal-only RI while maintaining satisfactory daytime ventilation. Over time, nocturnal hypoventilation predisposes them to stable, even daytime, CO_2 retention. The coexistence of obstructive sleep apnea syndrome (OSA), characterized by airway obstruction at the neck level due to the weakness of the pharyngeal and laryngeal muscles, can exacerbate respiratory exchange problems in BMD. This is especially likely when symptoms like snoring and excess weight are present.

The integrity of the cough mechanism is crucial in the onset of ARI. During a respiratory infection, a compromised cough mechanism leads to accumulation of bronchial secretions which impair gas exchanges and reduces lung oxygenation capacity resulting in hypoxemia and decreased oxygen availability to tissues. Other potential causes of ARI in BMD include the development of congestive heart failure with resultant pulmonary edema.

Assessment of Respiratory function

In BMD, respiratory impairment affects only about 50 percent of patients, and the severity is variable. The frequency of clinical and functional respiratory assessment depends on the rate of disease progression in the individual patient. For slow progression, semi-annual or annual evaluations may be reasonable.

Clinical data

The progression of ventilatory deficit and the development of respiratory insufficiency (RI) are often insidious in BMD patients. Non-specific symptoms such as fatigue, sleepiness, and difficulty concentrating can be early indicators of RI. Dyspnea, or the sensation of difficult or labored breathing, is often absent; sometimes orthopnea (difficulty sleeping in a supine position) is present, necessitating a semi-sitting position during sleep. Symptoms like nighttime awakenings, nightmares, daytime sleepiness, and morning headache can reflect sleep-related respiratory alterations, with abnormal CO_2 retention.

Instrumental data

Measurement of Respiratory muscle

Respiratory muscles strength can be evaluated by measuring Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP) at the mouth using a simple device (pressure transducer) during maximal respiratory efforts. CO_2 retention generally occurs when the MIP value is less than 40 percent of the predicted value; however, the reduction in MIP and MEP does not precisely predict the severity of RI.

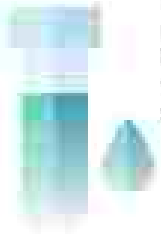
Measurement of Lung volumes

Lung volumes are assessed using spirometry. The reference parameters is the measurement of Forced Vital Capacity (FVC, the total volume of air that can be forcibly exhaled after maximal inhalation). Since inspiratory muscles strength decreases significantly (by at least 50%) before a significant drop in FVC occurs, spirometry is not useful for the early diagnosis of respiratory muscle deficit. Instead, more sensitive parameters, such as MIP and MEP measurements, can reveal this deficit. In BMD there is a progressive reduction in FVC, preceded by a significant decrease in MIP and MEP.

Assessment of cough efficacy

Cough effectiveness can be simply evaluated by measuring the Peak Cough Expiratory Flow (PCEF), also known peak cough flow. PCEF represents the maximum expiratory flow generated during a cough and provides direct information on the ability to clear the airway. A minimum value between 160 and 270 L/min allows effective coughing; below this level, cough assistance techniques are indicated. Measuring PCEF during synchronous thoracic and abdominal compression helps determine how much these maneuvers increase cough effectiveness.

Blood gas analyses



Measuring the partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) in arterial blood is the most important parameter for assessing gas exchange efficacy and it is essential for diagnosing RI. An abnormal increase in $PaCO_2$ (> 45 mm Hg) indicates alveolar hypoventilation, which is the final effect of progressive loss of ventilatory capacity.

Nocturnal cardio-respiratory monitoring

This investigation is recommended in all cases where sleep-related hypoventilation is suspected based on clinical data. It aims to diagnose latent ventilatory insufficiency that is still not apparent during wakefulness but manifests at night. The study involves simultaneous recording and monitoring during sleep of several parameters: oronasal airflow, separate thoracic and abdominal movements, ECG, SaO_2.

TREATMENT OF RESPIRATORY COMPLICATIONS

Long-term ventilatory support

To delay and counteract chronic respirator insufficiency (CRI) secondary to progressive hypoventilation, BMD patients can be initiated on Non-Invasive Ventilation (NIV). A mechanical ventilator assists the patient's ventilation by delivering air volumes through a nasal or oronasal mask, or a mouthpiece, without the need for a tracheostomy. This treatment is applied long-term at home, generally during nighttime hours.

The indication for NIV in stable patient are defined by the following conditions:

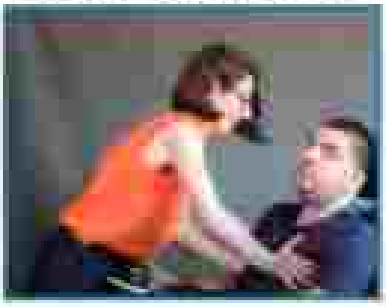
- **Daytime hypercapnia ($PaCO_2$ > 50 mm Hg);**
- **Nocturnal hypercapnia ($PaCO_2$ > 45 mm Hg) associated with symptoms attributable to by ventilation (tiredness, dyspnea, morning headache);**
- **FVC < 50% predicted, in rapidly progressive diseases.**

NIV leads to several favorable effects: a) MIP and FVC stabilize or improve temporarily; gas exchanges during wakefulness tends to normalize quickly; b) the risk of respiratory complications and the need for hospitalization decrease; c) symptoms induced by CO_2 retention are reduced, improving the perception of health status and social integration; and d) life expectancy increases.

Cough assistance

Manual and/or mechanical cough assistance maneuvers can enhance the effectiveness of coughing. Manual cough assistance, primarily based on thoracic and abdominal compression maneuvers, requires patient cooperation, good coordination between the patient and the caregiver, and significant physical effort from the caregiver due to the need for frequent sessions.





Clinical studies document the greater effectiveness of combining pulmonary hyperinflation (achieved by compressing an Ambu bag that pushes air into the lungs) with manual cough assistance, compared to manual assistance alone. Additionally, lung hyperinflation is known to help improve lung expansion capacity, reducing the risk of respiratory complications.

When manual assistance is inadequate, an effective alternative is mechanical assistance. This can be implemented using devices that provide deep insufflations (forced air intake into the lungs) followed immediately by equally deep exsufflations (expiratory flow induced by the machine strong enough to push secretions toward the airways, thus facilitating their expulsion or suction). The insufflation and exsufflation pressures and the delivery times are independently adjustable. Insufflation and exsufflation pressures ranging between +40 and -40 cm H_2O are generally effective and tolerated by most patients; additional benefit may come from the application of synchronous abdominal pressure during exsufflation.

Mechanical insufflation-exhalation can be delivered through an oronasal mask, mouthpiece or tracheostomy cannula. Phase cycling (transition from inspiration to expiratory) can be initiated manually or automatically; in the former case, coordination between the patient, caregiver, and device is facilitated.

A special mention is warranted for the administration of oxygen therapy to correct hypoxemia associated with bronchial secretion buildup due to ineffective coughing: this procedure can be dangerous and lead to misinterpretation of the patient's clinical progression. Oxygen therapy corrects blood oxygen level without addressing the cause of hypoxemia, namely secretions retention. This can result in unnoticed, "masked" progression towards more severe complications (atelectasis, lung collapse, pneumonia).

The use of mucolytics can increase the volume and fluidity of mucus: in cases of ineffective cough the administration of these drugs can lead to choking crisis. Therefore, they should be used as part of a program that also includes bronchial clearance techniques. Specifically, aerosol administration, characterized by an immediate, short and better controllable effect, should be preferred, while oral administration, due to its prolonged and delayed effect, should generally be avoided.

CARDIAC MANAGEMENT

CARDIAC MANAGEMENT

Cardiac impairment is the main cause of morbidity and mortality in many neuromuscular diseases. The wide heterogeneity among various neuromuscular diseases and the limited understanding of the specific mechanisms leading to cardiac pathology make diagnosis and treatment a complex challenge.

BMD patients have a 50% chance of developing cardiac involvement regardless of muscle impairment. The role of dystrophin in cardiac muscle, as in skeletal muscle, is to protect the muscle from the contraction-induced damage. Reduced or abnormal dystrophin leads to exercise-induced cardiac cell death with release of heart-specific proteins (troponins) into the bloodstream.

Patient with BMD, especially those with mild forms do, not have the functional motor limitation present in DMD patients, and are able to perform significant muscle exertions. This can cause cardiac overload, which might be detrimental.

In cardiac muscle, as in skeletal muscle, cardiac cells can undergo cell death. The resulting fibro-adipose replacement generates scar tissue that begins in the outer heart layer (epicardium) and progresses to the inner layer (endocardium). Myocardial fibrosis leads to thinning of the heart wall, loss of contractility and progression to dilated cardiomyopathy.

Occasionally, although much more rarely, hypertrophic cardiomyopathy has been observed.

Female carriers are at risk of developing cardiac involvement, with a prevalence of 15% under age 18 and 43% over 18 years.

CARDIAC FUNCTION EVALUATION

The goal of proper cardiological management is to detect and treat cardiac damage early. This involves a baseline evaluation to be performed annually starting from the BMD diagnosis and every 3 to 5 years in female carriers, with increased frequency depending on the clinical picture.
A baseline cardiac evaluation should include blood tests (including CK and troponin), a baseline electrocardiogram (ECG), 24-hour Holter ECG, and a transthoracic echocardiogram. Blood tests can detect cardiac damage through an increase in troponins, which should be monitored over time, and by measuring other proteins (natriuretic peptides) that increase in the case of ventricular pressure overload and thus cardiomyopathy.
A baseline ECG can show signs of cardiomyopathy in the subclinical phase, as a Holter ECG, which can detect arrhythmias even before the clear onset of cardiomyopathy. The transthoracic echocardiogram is an exam that evaluates the size and anatomical characteristics of the heart and is essential for assessing its function. During an echocardiogram, multiple parameters are evaluated: the size of the heart chambers, shape, thicknesses of the heart walls, valvular structure, morphological characteristics, ejection fraction (amount of blood the heart pumps from the left ventricle with each beat), strain (myocardial contractility index), and diastolic function (alteration in the ventricle's relaxation capacity and thus its ability to be filled with blood).
Cardiac MRI is a third-level exam that more accurately assesses the previously mentioned parameters and has significant diagnostic sensitivity for characterizing myocardial tissue through fibrosis identification. The exam involves the use of a contrast agent to identify areas of fibrosis, and through advanced techniques, allows an evaluation of early cardiac muscle involvement.

Drug therapy for the heart:

Ace Inhibitors (ACEIs, enalapril, captopril, ramipril, perindopril, etc.) acids are antihypertensive drugs that have been shown to delay the progression of left ventricular dysfunction in DMD even in patients with normal cardiac function, and provide benefits in terms of extending survival. Unfortunately, for DMD the only shared indication for initiating ACE therapy is the presence of a reduced ejection fraction, while there are no guidelines suggesting when to start therapy in the asymptomatic patient. In DMD after age 6, the use of perindopril is recommended to prevent progression to the clinical form.

Beta-blockersdrugs that reduce heart rate; bisoprolol, carvedilol, nartopridol, etc.). These are used to reduce heart rate, which is often elevated in DMD, lower blood pressure and improve left ventricular function. Unfortunately, their use is limited by the frequent presence of hypotension in DMD patients. This class of drugs has been shown to improve ventricular function when it is at least moderately impaired and unresponsive to other therapies.

Sartans - antihypertensive drugs; losartan, valsartan, irbesartan, candesartan, etc.). There are no specific studies on the use of sartans in DMD.

Diuretics (drugs that increase urine production) Diuretics should be used in cases of hepatic and/or pulmonary congestion. Among the most widely used diuretic drugs; spironolactone, canrenone, eplerenone, etc.). These drugs should be added, according to guidelines, to ACEIs and beta-blockers in case of therapeutic failure and persistence of symptoms. Recent studies suggest a possible role of eplerenone in addition to aceis in reducing the decline of ventricular function in DMD. The exact mechanism is not known, but it is believed to be secondary to an anti-inflammatory effect of eplerenone.

Ivabradine: this is a drug that slows the heart rate without causing hypotension, unlike beta- blockers, and can improve heart function, although clinical studies are needed to prove it.

Sacubitril/Valsartan: this combination of two antihypertensive drugs may play a significant role in reducing the risk of heart failure in patients with moderate ventricular dysfunction and elevated levels of certain proteins, used as markers of heart failure (NT pro-BNP). Currently, there is no data for the use of this drug in DMD.

Antiarrhythmic Drugs: In the presence of arrhythmias, antiarrhythmic drugs that do not affect heart tissue used in common clinical practice should be used.

NON-PHARMACOLOGICAL THERAPY:

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS ICD: the ICD is a small electronic device that constantly records all heartbeats and intervenes when it detects a serious arrhythmia. ICD implantation should be considered in case of high arrhythmic risk and severe reduction of ejection fraction (ejection fraction <35% and presence of ventricular tachycardia) to prevent sudden cardiac death.

VENTRICULAR ASSIST DEVICE VAD: this is a mechanical pump that is implanted in the chest to help the heart pump enough blood. In refractory heart failure, when the heart cannot pump an adequate amount of blood, the VAD is considered a possible therapeutic strategy, always considering potential complications during anesthesia, possible difficulties in weaning from invasive ventilation, and complications related to immunosuppression. It can be used as a bridge solution while for cardiac transplantation.

HEART TRANSPLANTATION: heart transplantation is a therapeutic option for SMD when medical therapy can no longer maintain adequate cardiac function.

Therefore, in all SMD patients, it is important to perform periodic cardiac function checks over time to monitor the progress of cardiomyopathy and the response to therapy.

Table 2. Cardiac Management in BMD Patients

Level I screening: • cardiological examination + ECG
Level II screening •Echocardiograph, 24-hour Holter-ECG, cardiac biomarkers (troponin, NT pro-BNP), cardiopulmonary test*
Prevention of cardiomyopathy evolution of - ACEI - eplerenone
Treatment of heart failure and arrhythmias -Beta-blockers -diuretics -other antiarrhythmic drugs -digoxine
Advanced therapies of heart failure and arrhythmias -sacubitril/valsartan -ICD -VAD -Cardiac transplantation

*Cardiopulmonary testing allows integrated analysis of cardiovascular, respiratory, and metabolic responses to exercise.

ANESTHESIA AND SEDATION DURING SURGERY

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ANESTHESIA AND SEDATION DURING SURGERY

If a patient with BMD needs to undergo surgery under anesthesia or sedation, the following issues should be considered, as summarized in **Table 3**.

✓ Patients with BMD frequently have dilated cardiomyopathy, which may pose a risk of heart failure during anesthesia and the postoperative period. Therefore, a cardiologist should be consulted before the patient undergoes anesthesia or sedation. An echocardiogram should also be performed, unless it has been done recently (within six months before the surgery, depending on the severity of the cardiomyopathy). Knowing the degree of cardiac impairment is important because this information guides the anesthesiologist not only in the type of anesthesia to use, but also in the type of hemodynamic monitoring to implement during and after surgery.

✓ Patients with BMD may also be at risk of postoperative respiratory complications. Therefore, a pulmonologist should be consulted before performing any surgical procedure under general anesthesia or sedation. Preoperatively, spirometry will be conducted to measure the forced vital capacity (FVC), and the effectiveness of the cough will be assessed by measuring the peak cough flow (Peak Expiratory Cough Flow o Peak Cough Expiratory Flow - PCEF). These tests should not be repeated if they have been done recently (within six months before surgery). If the FVC is less than 50% of the predicted value, training in the use of Non-Invasive Ventilation (NIV) should be conducted before the surgery. In these cases, NIV may be applied immediately postoperatively to reduce the risk of respiratory complications. If the peak cough flow is less than 270 l/minute, training in cough-assistance techniques will also be performed before surgery. These techniques may be necessary at the end of general anesthesia to facilitate expectoration of bronchial secretions.

✓ If general anesthesia is required for a patient with BMD, only intravenous anesthetics should be administered for both induction and maintenance of anesthesia. The most commonly used drug for induction and maintenance in BMD patients is propofol (a short-acting anesthetic). Inhaled halogenated anesthetics (such as sevoflurane and desflurane) should be strictly avoided. **The use of halogenated anesthetics in these patients poses a high risk of rhabdomyolysis, a life- threatening complication characterized by massive muscle fibers damage, leading to the release of muscle proteins and ions (myoglobin and potassium) into the bloodstream. Myoglobin is dangerous for the kidneys as it can cause renal failure, and potassium is dangerous for the heart as it can cause life-threatening arrhythmias.**

✓ If it is necessary to completely block muscle activity, during general anesthesia, either for the type of surgical procedure (such as laparoscopy (endoscopic examination of the abdominal cavity performed by small incisions of the abdominal walls), or laparotomy (opening the abdomen)) or for tracheal intubation, succinylcholine (a muscle relaxant) should never be used. Succinylcholine can also cause rhabdomyolysis. In these cases, non-depolarizing curars (another class of muscle relaxant), such as rocuronium, should be used. It is also important for the anesthesiologist to note that the effect of non-depolarizing curars in patients with dystrophinopathies start more slowly and lasts longer than in healthy patients. Therefore, at the end of anesthesia, the action of the curare should

✓ In BMD patients opioids, such as morphine, should also be used with caution both during anesthesia and in the postoperative period. These drugs can dangerously slow both the rate and depth of breathing.

ANESTHESIA AND SEDATION DURING SURGERY

✓ If the patient regularly takes glucocorticoids (GC), additional stress doses steroids (hydrocortisone) should be administered intravenously during surgery and in the postoperative period. Guidelines for intravenous doses of hydrocortisone to cover surgical stress can be found in the PJ Nicholoff Steroid Protocol at the following link: www.parentprojectmd.org/PJ.

Therefore, if a patient with DMD requires a scheduled surgery that necessitates anesthesia or sedation, the procedure should be performed in a hospital where the staff involved in the operation and postoperative care are well-acquainted with the specific issues of the condition and capable of managing them.

Table 3 Management of BMD patients undergoing anesthesia or sedation

1 Cardiological evaluation: prior to the procedure the patient must undergo a cardiological evaluation with a recent echocardiogram and ECG (no more than six months old). In cases of severe cardiac impairment, more intensive monitoring is essential.

2 Pulmonological evaluation: it is useful for the patient to have a recent (not more than six months old) measurement of forced vital capacity (FVC) and peak cough flow. If the FVC is less than 50% of the predicted value, the patient should be trained to use NIV before the procedure. If the peak cough flow is less than 270 l/minute, the patient should be trained to use cough assistance techniques prior to the procedure. NIV and/or cough assistance techniques may be necessary after general anesthesia.

3 General anesthesia: only intravenously anesthetics (e.g., propofol) should be used for both induction and maintenance of anesthesia, strictly avoiding the use of halogenated inhalational anesthetics (e.g. Sevoflurane and desflurane).

4 Muscle relaxation: if complete muscle relaxation is necessary, succinylcholine should never be used. Non-depolarizing curare, such as rocuronium, may be used. At the end of anesthesia, the effect must be completely antagonize using reversal agents like sugammadex.

5 Opioids: use opioids with caution both intraoperatively and post-operatively.

6 Glucocorticoids: if the patient regularly takes glucocorticoids, consider administring additional intravenous doses of hydrocortisone.

7 Experienced team: for scheduled surgeries requiring anesthesia or sedation, the procedure should be performed by team experienced in managing the specific challenges of the condition.

Key: ECG = electrocardiogram; FVC = forced vital capacity; NIV = non-invasive ventilation.

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EMERGENCY MANAGEMEMENT and EMERGENCY CARD

EMERGENCY MANAGEMENT AND EMERGENCY CARD

Becker muscular dystrophy (BMD) presents risk of cardiac and respiratory complications, which can lead to life-threatening situations. The management of emergency in patients with BMD is summarized in Table 4.

Typical cardiac issues in BMD patients included dilated cardiomyopathy with impaired heart contractility, arrhythmias, and intra-cardiac conduction abnormalities. These can lead to the following complications: acute heart failure, hypotension, or acute respiratory failure (ARF) from cardiogenic pulmonary edema, malignant arrhythmias (both bradycardic and tachycardic). When any of these complications are suspected, it is crucial to conduct a thorough cardiological evaluation, including an electrocardiogram (ECG), chest X-ray, echocardiogram, and assess blood levels of certain proteins that may be elevated (e.g. natriuretic peptide) as well as blood oxygenation levels using pulse oximeter or blood gas analysis. In the event of acute heart failure, it is necessary to urgently assess heart function to initiate the most appropriate therapy (inotropes, diuretics, vasodilators, etc.) in accordance with current guidelines. For arrhythmias, it is essential to identify the type of arrhythmia on the ECG to administer the most appropriate pharmacological therapy or consider the use of a pace maker (PM) or defibrillator (ICD) (see Chapter 8).
If all therapies fail, cardiac transplantation may be considered. Mechanical ventricular assist devices can be used while awaiting for transplantation (see Chapter 8), especially as life-saving strategies until a heart transplant is possible. In the presence of acute pulmonary edema (excess fluid in the lungs), it is important to combine noninvasive ventilation (NIV) with oxygen therapy.

BMD patients may develop respiratory muscle alteration, leading to reduced breathing capacity, significant cough deficiency with decreased ability to expel bronchial secretions, and a higher predisposition to obstructive sleep apnea. Therefore, especially in the case of respiratory infections or following anesthesia, acute respiratory failure (ARF), characterized by oxygenation deficit and carbon dioxide buildup may develop. In the case of ARF, it is essential to combine NIV with mechanical cough assistance, using a cough machine or manual cough assistance techniques. As soon as possible, a chest X-ray and

EMERGENCY MANAGEMENT AND EMERGENCY CARD

an evaluation of blood oxygenation and carbon dioxide levels through arterial blood by gas analysis should be performed. If a respiratory infection is suspected and the pulse oximetry is < 95% in room air, broad-spectrum antibiotic therapy should be started early. In case of surgical emergencies requiring urgent general anesthesia, it is crucial to follow anesthesia recommendations (see Chapter 9).

✓ It is common experience to find that emergency physicians often lack sufficient knowledge and clinical experience in treating patients with neuromuscular diseases, as these are rare diseases. The problem is even more pronounced when considering the number of BMD patients to treat in emergency to reach the necessary experience and knowledge required to adequately treat these patients.

Recent international recommendations published in Lancet propose the introduction of an Emergency Card for patients with DMD. This card would provide physicians handling these patients in emergency situations with concise information on the most common complications of the disease and their treatment in urgent/emergency situations. We believe that these recommendations could also be extended to patients with BMD.

Table 4. Emergency management in BMD Patients

1 **CARDIAC COMPLICATIONS:**

BMD can lead to the development of cardiomyopathy with impaired heart contractility, arrhythmias or conduction abnormalities. These conditions can cause the following emergencies: cardiac arrest, acute heart failure, hypotension or acute pulmonary edema, and hypo- or hyperkinetic arrhythmias (the heart rate is too slow or too fast).
In these cases, it is essential:

- Immediately perform a cardiac evaluation with ECG, chest X-ray, echocardiogram and assess blood levels of natriuretic peptide and blood oxygenation using a pulse oximeter or blood gas analysis;
- Immediately start appropriate cardiology therapy i [inotropes (drugs that help the heart contract better), diuretics, vasodilators, anti-arrhythmics, etc.];
- In the presence of acute pulmonary edema, associate with NIV;
- In case of severe cardiac conduction abnormalities consider placing a pace-maker or, in the case of ventricular arrhythmia, consider implanting a defibrillator;
- In case of severe heart failure resistant to pharmacological therapy consider: VAD implantation while awaiting a heart transplant.

2 **RESPIRATORY COMPLICATIONS:**

BMD can significantly reduce the ability to breathe and to expectorate bronchial secretions and increase the predisposition to obstructive apnea. Therefore, especially in case of respiratory infections or after anesthesia, acute respiratory failure (ARF) may develop.
In case of ARF, it is essential to:

- Immediately perform a blood gas analysis of arterial blood;
- Consider the use of NIV and mechanical cough assistance;
- Perform a chest X-ray;
- Rule out cardiogenic pulmonary edema as the cause of ARF by performing an echocardiogram;
- If a respiratory infection is suspected and pulse oximetry is < 93% in room air, start broad-spectrum antibiotic therapy early.

3 In the case of **SURGICAL EMERGENCIES** requiring urgent anesthesia, it is essential to follow anesthesia recommendations.

4 The introduction of an **EMERGENCY CARD** for patients with BMD would be desirable. This would provide physicians handling these patients in emergency situations with concise information on the most common complications of the disease and their treatments in urgency/emergency situations.

Key: ECG=electrocardiogram; NIV=non-invasive ventilation; VAD=ventricular assist device; ARF=acute respiratory failure.

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NUTRITIONAL **MANAGEMENT** and **REHABILITATION**

NUTRITIONAL MANAGEMENT and REHABILITATION

The lack of specific international guidelines for individuals with Becker muscular dystrophy (BMD) inevitably leads to consulting and adapting those related to Duchenne muscular dystrophy (DMD).

EVALUATIONS TO CONDUCT AND WHY

The goal of nutritional support in BMD is to prevent undernutrition and overnutrition (overweight and obesity) through regular assessment of height and weight growth. It also aims to promote a healthy and balanced diet with optimal intake of calories, protein, fluids, and micronutrients; particularly calcium and vitamin D. Regarding specific dietary characteristics, it should be noted that the absence of solid evidence-based nutritional research specific to BMD necessitates the use of guidelines for the general population.

NUTRITIONAL STATUS ASSESSMENT: during the developmental age, at each medical visit, ideally every 6 months, nutritional status should be evaluated by recording weight and height, body composition, fat tissue distribution and dietary intake.

Weight and height hould be measured by trained personnel familiar with acquiring these measurements in neurological patient, as these patients often present with scoliosis, muscle contractures, etc., due to the specific characteristics of the disease. In the developmental age, weight and height are interpreted using growth charts, that exist for DMD but not for BMD. Their interpretation should therefore be done with caution, and only continuous monitoring can allow understanding of the nutritional status trend. In adults, weight and height measurements are used to calculate the body mass index (weight in kg/height in m2, BMI), which is interpreted according to the categories shown in the table below.

BMI	CONDITION
< 18.5	UNDERWEIGHT
18.5 - 25	NORMAL WEIGHT
25 - 30	OVERWEIGHT
30 - 40	MEDIUM DEGREE OBESITY
> 40	HIGH-GRADE OBESITY

It should be noted that these BMI value classes corresponding to a nutritional status condition have been defined for the healthy general population and therefore should be interpreted with caution and through continuous weight monitoring.

Body composition: studying body composition means analyzing body weight in terms of lean mass, with muscles being one of its main components, fat mass, where adipose tissue is the most significant storage site, and bone mineral content, from which bone mineral density can be derived, necessary for the diagnosis of osteopenia (a condition where bones are more fragile than normal) and osteoporosis (a condition where bones are more fragile than normal and prone to fracture). In BMD and more generally in neuromuscular disorders, there is a progressive loss of lean mass, an increase in fat mass, and a reduction in bone mineral density. Monitoring these components is therefore extremely useful to understand how nutritional status is changing. The evaluation of fat mass and lean mass can be done with simple methods like skin fold measurement (a method of measuring body fat using a tool, called caliper, which measures the thickness of skin folds) and body circumference measurement, or with more complex and naturally more precise methods, including noninvasive instrumental exams such bioelectric impedance analysis (BIA), and Dual X-Ray Energy Absorptiometry (DXA) for estimating lean mass and fat mass. BIA measures the body's impedance ("bioimpedance"), which is the resistance

the body offers to the passage of a low-power, high-frequency electric current for determining body composition (fat mass, lean mass, total water). It is incorporated into clinical practice due to its speed and ease of use, as well as being economical, portable, and non-invasive. However, results should be interpreted with caution as it has not been specifically tested for BMD. DXA is considered a reference method for evaluating body composition because it can distinguish between bone and non-bone tissues and provide a measurement of the amount of bone using a small doses of X-rays. The DXA scan provide data on the kilograms of lean mass, fat mass, and bone mineral mass of the whole body and its segments (upper limbs, lower limbs, and trunk). Although it is a radiological technique, the radiation dose for each exam is very low, resulting in minimal exposure for the patient. This makes it possible to perform the exam on growing individuals and it can be repeated at short intervals.

Dietary intake: estimating dietary intake means determining daily caloric intake and the consumption of macronutrients (proteins, fats, and sugars) and micronutrients (vitamins and mine-

rate). This estimation is done using a 3- or 7-day food diary, which is then analyzed using specific software. The results obtained should be compared with recommended requirements. Currently, there are no specific recommendations for patients with BMD; therefore, reference is made to the recommended intake levels for the Italian General Population (LARN). For estimating the resting energy expenditure (REE), which is essential for calculating daily caloric needs, specific formulas can be used. In particular cases of altered nutritional status, the use of indirect calorimetry is indicated. This instrumental examination accurately measures the REE. Calorimetry allows the measurement of basal metabolism, which is the amount of energy the body uses to maintain vital functions when completely at rest.

ASSESSMENT OF GASTROINTESTINAL ISSUES: Dysphagia, constipation, gastroesophageal reflux, and gastroparesis are common and often progressive in patients with BMD with severe muscle strength deficit. Preventive evaluation of dysphagia is important and should be performed regularly; screening questions, through biannual questionnaires should focus on perceived difficulty swallowing liquids and solids, the perception of food "sticking in the throat", the time required to eat an average meal, and the impact of eating on quality of life. A gastroenterologist should be consulted for managing constipation, gastroesophageal reflux, and gastrointestinal motility issues and, when necessary, for PEG placement (a tube inserted directly into the stomach through an abdominal hole) and/or daily laxative treatment. From a dietary standpoint, the adequacy of daily fiber and fluid intake should always be assessed.

Assessment of Bone health: Individuals with BMD may have fragile bone tissue due to chronic calcium loss induced by reduced mobility. Monitoring Bone health requires an annual assessment of dietary calcium intake and serum 25-hydroxyvitamin D concentration. If these are below the recommended levels for age and less than 30 ng/ml, respectively, adequate dietary intake and supplementation according to current guidelines should be provided.

NUTRITIONAL CONSEQUENCES OF PHARMACOLOGICAL TREATMENT

Exacerbations of the disease, reduced physical activity, and muscle disuse can further decrease lean mass leading to reduced functional capacity and severe consequences for morbidity and mortality.

Patients with BMD may also be treated with glucocorticoids (GC). Although the beneficial effect of GC in increasing muscle strength, delaying loss of ambulation, preserving respiratory function, and slowing muscle degeneration, through a direct anti-inflammatory effect on muscle is well known, medical and nutritional monitoring is necessary due to their side effects. Osteoporosis, hyperglycemia, diabetes mellitus, cardiovascular disease, and infections are the most frequent and more serious adverse effects of therapy. GC also promote the onset of overweight and obesity by increasing appetite and, consequently, caloric intake and increasing sodium and fluid retention, highlighting the importance of nutrition as a fundamental part of clinical management of the disease.

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PSYCHOLOGICAL, NEUROCOGNITIVE AND PSYCHIATRIC ASPECTS IN BMD

PSYCHOLOGICAL, NEUROCOGNITIVE AND PSYCHIATRIC ASPECTS IN BMD

LIVING WITH BMD

A diagnosis of BMD is an event that can have a significant impact on the lives of individuals and their families. This impact concerns not only the physical and clinical aspects of the disease, but also the psychological and relational area of the individual. Like other chronic diseases, BMD can be considered family system illness because it involves both the person directly affected and their family members (parents, partners, children...). Each person must strive to establish new balances not only after diagnosis but also during other changes throughout the life cycle.
Increasingly, the care of BMD patients and their family in clinical centers involves a multidisciplinary approach, where medical aspects interface with psychological ones, complementing each other.
Living with BMD means accessing internal resources, such as awareness, hope, the ability to live day by day, a realistic, present-oriented view of one's condition, as well as external resources represented by the family, health professionals (neurologists, psychologists, social workers...), and the work and school environment.
Sometimes managing the disease can be challenging not only in "practical" terms but also in dealing with related psychological experiences.

How is common, the following psychological symptoms may manifest:

difficulties in coping with the disease and its consequences

difficulties concentrating, attention

anxiety, restlessness, presence of intrusive thoughts, panic attacks

Sadness, mood swings, rage, feeling of helplessness and guilt

Isolation from relationships, loneliness, shame

Excessive worry about one's own physical condition

altered physical pain due to pathology and psychological condition

These psychological symptoms could appear both in the person with BMD and in their family members.

Prenatal Diagnosis

For new parents, discovering during pregnancy that their child has a diagnosis of BMD can have a profound psychological impact. Therefore, the care team, especially the psychologist, must pay particular attention to the impact of this news has on the couple to facilitate the processing process and contain potential emotional reactions.

Diagnosis in childhood and adolescence

Considering the variability of the condition, it is challenging to accurately pinpoint when the first symptoms of BMD appear, making it difficult to determine the exact timing for diagnosis. In this paragraph, we will explore the experiences related to the impact of the diagnosis and symptoms according to the developmental stage of individuals.

Childhood: the presence of physical symptoms, if they manifest early, leads the child to experience the diagnosis firsthand sometimes even before fully understanding it. During this phase, the child may exhibit restlessness, opposition, passivity and competitiveness in response to their physical limitations. These experiences should be acknowledged and managed by the family through adequate communication.
It is also possible, although lesser frequently than in children with DMD, to encounter neuropsychological issues, such attention difficulties, memory or perception problems, or behavioral issues like attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). The cognitive differences between Duchenne and Becker may stem from qualitative and quantitative variations in dystrophin, which, in the case of BMD, is partially and variably present.

Adolescence: during this phase of life, the body undergoes constant changes. If the body is perceived as damaged due to the condition, it becomes an obstacle to building a positive self-image, often leading to feelings of inferiority and inadequacy. In addition, peers continue to grow and acquire more skills, while in adolescents with BMD, the emotional and affective development may be hindered by functional difficulties, resulting in regression that particularly affects autonomy, social and emotional relationships.

Common psychological reactions may include anger outbursts, opposition, feelings of loneliness and isolation.

Adulthood: discovering BMD in adulthood can evoke ambivalent feelings. On one hand, thinking that significant symptoms were not experienced earlier in life can be seen as positive. On the other hand, the need to reconsider lifestyle and habits in a phase of life where personal identity is already established can be very challenging. Risk or protective factors may include the severity of the condition, the presence of significant symptoms, family history of neuromuscular disorders, and social support.

Family perspective: the moment parents receive the diagnosis is certainly very delicate; expectations nurtured thus far about their child's future are inevitably shattered. It could be crucial for the couple to receive support that facilitates processing their experiences and guidance that promotes awareness. Moreover, for parents, accepting their child's difficulties and helping them cope with the frustration of experiencing their limitations can be extremely complex.
For siblings, integrating their brother's diagnosis with BMD into their own experience can also be difficult. Sometimes this can trigger feelings of guilt, jealousy, shame, over-responsibility or conversely, avoidance and regressive behaviors.

Variability and unpredictability of BMD

When considering the psychological aspects related to BMD, it is important to take into account the severity of the condition on a clinical level; the experiences associated with a severe condition will differ from those of an asymptomatic one.

Moreover, symptomatic patients exhibit enormous variability, both in terms of the age of onset of the disease and the age at which symptoms manifest and walking ability is lost. Therefore, predicting the progression of the disease is extremely difficult. This unpredictability, hinders planning for the patient's and their family's future.

In the care of the individual and their family it is crucial to consider the importance of fostering autonomy, both practically in terms of daily life, and realizing personal life projects.

Psychological support interventions

Psychological interventions vary depending on the developmental stage at which the diagnosis occurred and the state of disease progression. It may be necessary to:

- provide individual and couple psychological support during genetic counselling for you and your child;
- offer individual, family and couple psychotherapy to facilitate acceptance and acquiescence of the illness, enhance the parental responsibility, promote personal resources and develop new coping strategies and support emotional distress when it arises;
- conduct screening for neuropsychological, learning and behavioral issues;
- support the management of the patient within the school, educational and social context.

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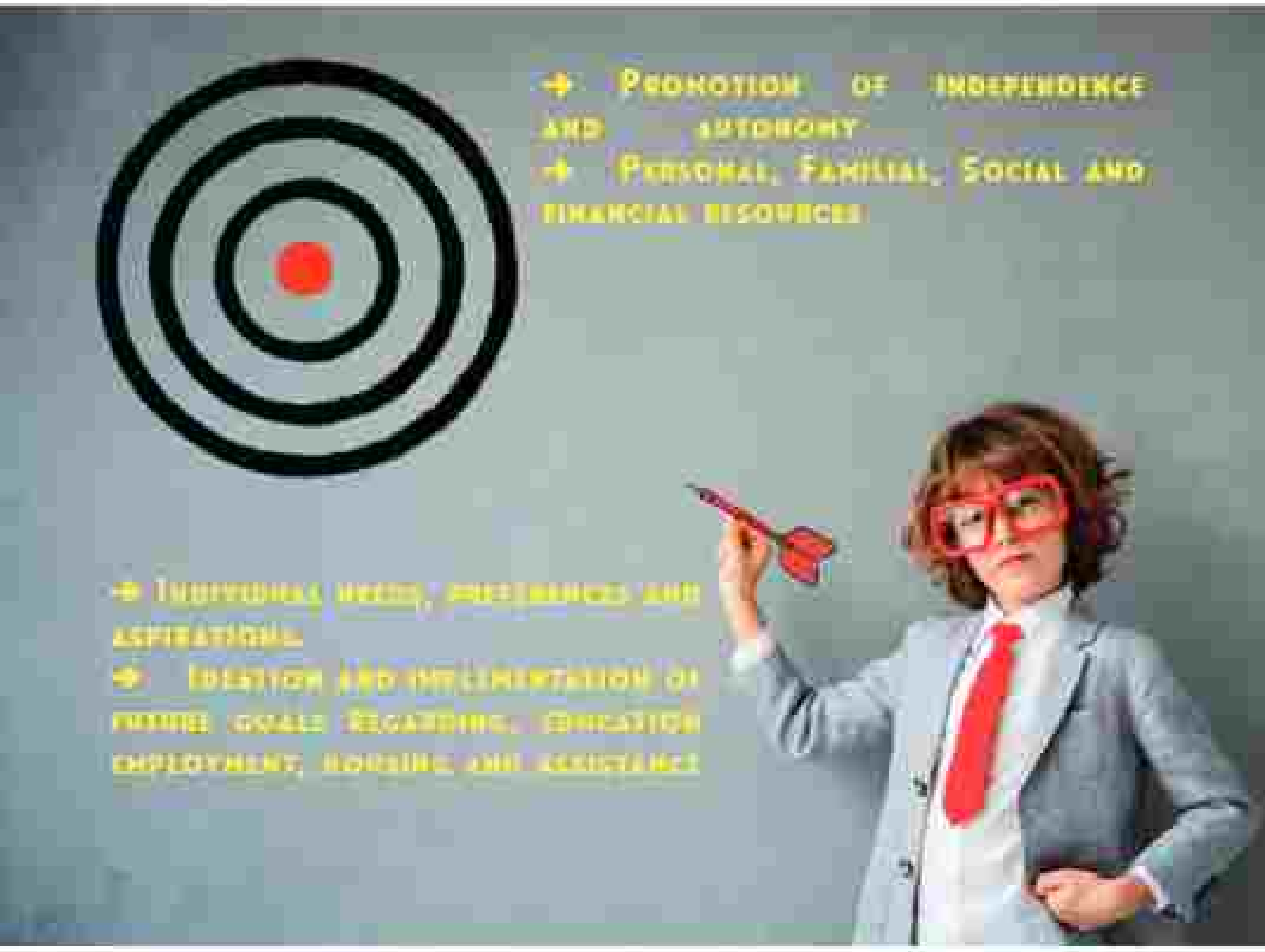
SOCIAL, WORK and ADMINISTRATIVE ASPECTS

SOCIAL, WORK, and ADMINISTRATIVE ASPECTS

The lives of patients affected by BMD can be very complex due to muscle weakness, and for this reason, in addition to clinical healthcare management, it would be appropriate to provide psychosocial support. Addressing psychosocial issues is a crucial aspect of the well-being of BMD patients, contributing to the development of independence, improving quality of life, and enhancing personal and relational resources with both primary (family), and secondary (social community) groups.
Intervention areas vary depending on age, health conditions, needs, interests and desires of the patient. Achieving the highest possible level of independence typically requires careful planning.

Fundamental aspects to focus on:



Childhood

From the moment of diagnosis, it is possible to request the activation of certain services and the recognition of benefits that can make life easier for the patient and their family.
You can request, at the clinical center where you are being treated, the certificate of rare disease (Ministerial Decree No. 279/2001) and then proceed to the local service that will issue the rare disease card to the patient.
The card contains the identification code necessary to activate exemption for all appropriate and effective treatments and monitoring of the disease, as well as for the prevention of further complications. In addition, you can request both recognition of civil disability (Law 118/1971) and disability status (Law 104/92), either personally through the INPS website or by contacting a CAF (Tax Assistance Center) or Patronato (Patronage) which will assist with the application process.
Once the certifications for disability and handicap status are obtained, you can request economic contributions and tax, employment and school-related benefits. Upon diagnosis, the physician at the reference clinical center advise the patient to undergo physiotherapy, psychomotor therapy, and/or hydrokinesitherapy, depending on the stage of disease progression. The physician prescribes the treatment and determine the most suitable activities based on the patient's needs. To access these services, you need to contact local services.

School Period

The school career is a fundamental phase for the construction of the personality and autonomy of children and adolescents. It is useful to contact local services to request a Functional Diagnosis with the aim of providing a clinical framework that guides rehabilitative, therapeutic and educational interventions, which are coordinated among the various professional involved.

Adolescence and transition to adulthood

BMD has a highly heterogeneous course, which makes the interventions to be performed very variably. There may arise the need for:

- *request aids from local services;*
- *request home care assistance from the municipality of residence*
- *work on personal relationships and integrate the young people into the social community, activating an informal support network or developing social interactions; friendships and support groups;*
- *assess the strengths, abilities, and attitude of the young person to adequately plan for future needs;*
- *develop autonomy and independence by planning suitable housing, cohabitation or independent living plans, home care;*
- *tasks; accessible sports, day care centers, communities, socio-educational centers and home educational services).*

Employment for patients with BMD is an important aspect in building their lives. It is essential to start with a careful assessment of their skills, desires and potential to plan a vocational training and guidance path.

In Italy there has long been a system establishing norms for the access of people with disabilities to the workforce, primarily governed by Law 68/1999, which identifies capabilities placement in so-called "**protected categories**". Additionally, opportunities include: training internships, competitive exams, training courses and university courses. It is beneficial in this phase to consider aids and subsidies that can assist the person in performing specific daily activities. All these interventions can be assessed by contacting the relevant social service. The social worker, considering the needs and the requirements of the young person as well as the available resources in the area, will develop a project aimed at enhancing social skills.

Duchenne Parent Project

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