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Mediterranean Society of Myology
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Founders: Giovanni Nigro and Lucia Ines Comi

Four-monthly

G. CONTE ACADEMY - NAPOLI

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EDITORIAL

Myology: the passion of a lifetime

When fifty–five years ago I met for the first time a patient affected by a muscle disease, I was unable to make a diagnosis. This was the main cause to convince me to take part in a meeting on muscular diseases, organised in Trieste by a group of people affected by this kind of disorders or interested in studying them, headed by the unforgettable and untiring Federico Milcovich.

I could never imagine how large could be the field that I was approaching, but from the first moment, muscle diseases came into my life as the most important subject.

Each day, more and more, new social, medical and scientific aspects have emerged, and every day I have seen new progress and encountered new obstacles.

It 's impossible to summarize all the events I attended, the people I met and the institutions that I visited. I can only mention the names of the Associations more familiar to me, having the opportunity to contribute to their birth, such as the Mediterranean Society of Myology, founded in Ischia, Naples in 1993, the World Muscle Society, founded together with Victor Dubowitz and Luciano Merlini in Bologna in 1995, the European Neuromuscular Center founded in Baarn (Netherlands) in 1999, the Italian Association of Myology in Bologna in 2000, or to their growth as it happened for the Unione Italiana Lotta alla Distrofia Muscolare (UILDM) of which I was National President for seven years and President of its Scientific Committee, and during that period I also brought the Telethon marathon from France to Italy.

Beside scientific Associations, many important scientific journals were founded and new and valuable journals have been added recently, all having Myology as the most important subject.

To Myology I dedicated most of my professional 55 years of life, and now, getting ready to leave the world of Myology, I asked friends of MSM and AIM (and obtained) to realize my dream of holding in Naples the Joint Congress of the two Societies in May 2015, as the last Congress I will chair.

Giovanni Nigro

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ORIGINAL ARTICLES

Mitochondrial disease heterogeneity: a prognostic challenge

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Mitochondrial diseases are a heterogeneous group of progressive, genetically transmitted, multisystem disorders caused by impaired mitochondrial function. The disease course for individuals with mitochondrial myopathies varies greatly from patient to patient because disease progression largely depends on the type of disease and on the degree of involvement of various organs which makes the prognosis unpredictable both within the same family and among families with the same mutation. This is particularly, but not exclusively, true for mitochondrial disorders caused by mtDNA point mutations, which are maternally inherited and subject to the randomness of the heteroplasmy. For this reason, the prognosis cannot be given by single mitochondrial disease, but should be formulated by any single mitochondrial disease-related event or complication keeping in mind that early recognition and treatment of symptoms are crucial for the prognosis. The following approach can help prevent severe organ dysfunctions or at least allow early diagnosis and treatment of disease-related complications.

Key words: multisystem disorders, clinical heterogeneity, intrafamilial variability, dual genetic control

Introduction

Definition

Mitochondrial diseases are a heterogeneous group of progressive multisystem disorders caused by impaired mitochondrial function. Mitochondria are subcellular organelles endowed with their own DNA (mitochondrial DNA or mtDNA) which is only maternally transmitted to all progeny. The most important mitochondrial role is the provision of energy in the form of adenosine triphosphate (ATP), which occurs through different metabolic pathways. One of these pathways, known as respiratory chain, depends on both nuclear DNA (nDNA) and mtDNA. This dual genetic control and the fact that mitochondrial diseases encompass defects in any of the multiple metabolic pathways that are contained within the mitochondrion account for the great heterogeneity, complexity and severity of clinical manifestations and disease classification.

Brief molecular classification of mitochondrial disorders (1, 2)

1. Disorders due to mutations in mtDNA (maternally inherited point mutations, sporadic large scale deletions).
2. Disorders due to mutations in nDNA (Mendelian/autosomal inheritance) that can affect five components of mitochondrial biology:
   a. genes encoding subunits of the respiratory chain;
   b. genes encoding mitochondrial assembly proteins;
   c. genes affecting mtDNA translation;
   d. genes controlling the phospholipid composition of the mitochondrial inner membrane (MIM);
   e. genes involved in mitochondrial dynamics.
3. Defects of mtDNA maintenance (Mendelian inheritance, but clinically similar to primary mtDNA defects).

Demographics

The prevalence of mitochondrial disorders in the general population is not known also because of the clear-cut separation into two main genetic groups: mtDNA point mutations and mtDNA deletions.

The prevalence is estimated around 1 in 5000 in patients tested for deletions and for common mutations of mtDNA which account for 5-40% of cases, depending on the study (3, 4).

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In an investigation made in the North East of England from 1990 to 2004 to define the prevalence of mtDNA disease in adults with suspected mitochondrial diseases, 9.2 in 100,000 people were found to have clinically manifest mtDNA disease, making this one of the commonest inherited neuromuscular disorders. The m.3243A_G mutation was the most common pathogenic mtDNA mutation (40%), associated with extreme phenotypic variation. A further 34% of adults were affected with Leber's hereditary optic neuropathy [LHON]) caused by the m.11778G_A or m.3460G_A point mutations Single large-scale deletions of mtDNA represented 13%, and the m.8344A_G mutation a further 4%, of disease cases. The remaining 9% of affected adults harbored other mtDNA point mutations (5).

Clinical features

It would be excessively reductive to confine the description of mitochondrial disorders to just one or two mitochondrial diseases because there is a quite consistent number of typical, genetically different, mitochondrial syndromes each of them characterized by a peculiar set of clinical signs and symptoms.

The following tables, courtesy of Prof. Di Mauro (1, 2) aim at providing a schematic and at the same time exhaustive description of the main clinical features of key mitochondrial disorders in compliance with their molecular and functional classification.

When speaking about mtDNA-related mitochondrial disorders it is worth reminding that there are thousands of copies of mtDNA instead of the two alleles of each nu-

Table 1. Signs and symptoms of six key mitochondrial diseases due to mtDNA mutations.

Tissue or factor	Sign or symptom	Δ-mtDNA-associated disease		tRNA-associated disease		ATPase 6-associated disease	
		KSS	Pearson	MERRF	MELAS	NARP	MILS
CNS	Seizures	–	–	+	+	–	+
	Ataxia	+	–	+	+	+	+/–
	Myoclonus	–	–	+	+/–	–	–
	Psychomotor retardation	–	–	–	–	–	+
	Psychomotor regression	+	–	+/–	+	–	+
	Hemiparesis/hemianopia	–	–	–	+	–	–
	Cortical blindness	–	–	–	+	–	–
	Migraine-like headaches	–	–	–	+	–	–
	Dystonia	–	–	–	+	–	+
PNS	Peripheral neuropathy	+/–	–	+/–	+/–	+	–
Muscle	Weakness	+	–	+	+	+	+
	Ophthalmoplegia	+	+/–	–	+/–	–	–
	Ptosis	+	–	–	+/–	–	–
Eye	Pigmentary retinopathy	+	–	–	–	+	+/–
	Optic atrophy	–	–	–	–	+/–	+/–
	Cataracts	–	–	–	–	–	–
Blood	Sideroblastic anaemia	+/–	+	–	–	–	–
Endocrine	Diabetes mellitus	+/–	–	–	+/–	–	–
	Short stature	+	–	+	+	–	–
	Hypoparathyroidism	+/–	–	–	–	–	–
Heart	Conduction block	+	–	–	+/–	–	–
	Cardiomyopathy	+/–	–	–	+/–	–	+/–
Gastrointestinal	Exocrine pancreatic dysfunction	+/–	+	–	–	–	–
	Intestinal pseudo-obstruction	–	–	–	–	–	–
ENT	Sensorineural hearing loss	–	–	+	+	+/–	–
Kidney	Fanconi syndrome	+/–	+/–	–	+/–	–	–
Laboratory testing	Lactic acidosis	+	+	+	+	–	+/–
	Muscle biopsy (Ragged-Red Fibers)	+	+/–	+	+	–	–
Inheritance	Maternal	–	+/–	+	+/–	+	+
	Sporadic	+	–	–	–	–	–

clear autosome. For this reason, in most mtDNA-related diseases, mutated and wild-type mitochondrial genomes coexist, a situation known as heteroplasmy. The degree of heteroplasmy determines both the manifestation and the severity of the disease because a critical number of mutated mtDNAs is needed for clinical symptoms to manifest (threshold effect). This pathogenic threshold varies in different tissues according to their dependence on oxidative metabolism, explaining why brain and skeletal muscle are so often affected ("mitochondrial encephalomyopathies") even if every organ and tissue can virtually be affected (multisystem disorders). Also, because the number of mutated mtDNAs can distribute in different proportions in different tissues and organs as well as in the same tissues from one generation of cell to the next (mitotic segregation), both genotype and clinical phenotype of mtDNA-related disorders may vary in different individuals of the same generation and, in some tissues, in the same individual with time (1, 6, 7).

Diagnosis

Mitochondrial disorders should be suspected anytime an individual presents clinical involvement of more than one tissue and/or organ (multisystemic nature of these diseases) especially when both central and peripheral nervous system are affected ("mitochondrial encephalomyopathies"). Serum lactate increase helps reinforce the diagnosis and prompts further diagnostic procedures.

Blood: Serum creatine kinase levels are mildly elevated in most mitochondrial disorders. Increased serum lactate and consequent lactic acidosis is a hallmark of mitochondrial disorders, especially in pediatric cases, but it is not invariably present and, also, not necessarily severe.

CSF: Increased CSF lactate is a pathognomonic marker in mitochondrial encephalopathies.

Neurophysiology: Myopathic and/or mainly axonal polyneuropathic patterns can be evidenced. Degree of severity is quite variable, depending on the underlying disease.

Skeletal muscle biopsy: This diagnostic procedure represents the gold standard for the diagnosis of mitochondrial disorders. Apart from the histological reaction for Gomori Trichrome, which shows proliferation of (pathologic) mitochondria in affected fibers (Ragged Red Fibers), valuable diagnostic clues are given by the histochemical reactions for COX (cytochrome c oxidase, complex IV of respiratory chain) and SDH (succinate dehydrogenase, complex II of the respiratory chain) used alone or in combination. COX is frequently lacking or reduced in skeletal muscle fibers from patients with both mtDNA-related and nDNA-dependent mitochondrial disorders whereas SDH, which is entirely encoded by nDNA, is unaffected by deleterious mutations affecting mtDNA and therefore stands as an excellent marker of mitochondrial proliferation ("ragged blue" fibers). Also, ultrastructural studies may show evidence of mitochondria proliferation and alterations (enlarged mitochondria with abnormal cristae and paracrystalline inclusions).

Biochemistry: Measurement of the activities of respiratory chain complexes can provide important diagnostic clues depending on whether respiratory chain deficiency is confined to one, two or all complexes. Studies can be performed on both frozen muscle tissue or fibroblast cultures.

Genetics: Maternal inheritance or sporadic (mtDNA defects), autosomal dominant or recessive (nDNA defects). Defects are detected by PCR, Southern Blot, sequence analysis of mtDNA or candidate nuclear genes, whole-exome or mito-exome sequencing.

Imaging: Increased lactate detectable by brain 1H-MRS; strokes that do not conform to the distribution of major brain vessels and commonly affect the occipital or parietal lobe in MELAS (TC and MR).

Prognosis

Although once considered rare, accumulating evidence suggests that mitochondrial disorders are relatively common, primary disorders of the respiratory chain affecting up to 1 in 5000 people (3, 4).

The prognosis for patients with mitochondrial myopathies varies greatly from patient to patient because disease progression largely depends on the type of disease and the degree of involvement of various organs. Indeed, the prognosis of mitochondrial diseases relies on disease type, degree of heteroplasmy (mtDNA point mutations), duration, possible complications, consequent outcomes, and prospects for recovery. These variables affect both quality of life and survival rate and are by their nature unpredictable.

Also, a distinction is due between pediatric and adult cases, the former being usually more dramatically affected and severe. In the last years many efforts have been done to find more effective treatments if not a real cure to improve both quality of life and survival rate in affected children, the purpose being to try to guarantee fairly normal lives at least in selected cases. Many children, however, still have to face major disabilities and a poor prognosis, survival rate ranging between few months and teenage years.

Adult onset disorders are less aggressive, but can result in drastic changes from an active lifestyle to a debilitating illness in a short amount of time.

Genetic counseling for families with ascertained mitochondrial diseases is another important part of the prognostic puzzle and faces the same uncertainties and

dilemmas. Also, in the case of mutations in mitochondrial DNA, the degree of heteroplasmy will influence the clinical presentation of the disease and its unpredictability is a major drawback in family preconception counseling. When the mutation causing the mitochondrial disease is not yet identified, counseling about recurrence risks in future pregnancies is even more difficult (8).

Given the progressive, often multisystem, nature of mitochondrial disease, patients' needs should be assessed in detail at the time of diagnosis and monitored at regular intervals thereafter to guarantee the best prognostic outcome (9). It is important to underline that any acute or chronic symptoms or complications consequent to mitochondrial disorders should be approached and treated in the same way they would be treated when due to non-mitochondrial causes (i.e. insulin for diabetes) and that the same principle is true for the prognosis. In other words, the prognosis cannot be given by single mitochondrial disease, but should be formulated by any single mitochondrial disease-related event or complication. It is true, of course, that a patient with mtDNA macrodeletion and isolated CPEO has a much better prognosis than one with a fully expressed MELAS or MERFF syndrome, but this does not affect the concept that mitochondrial disorders are prognostically unpredictable. Therefore, as for many other pathologic conditions, especially those with a progressive course, the principle is that the earlier you diagnose a complication, the better you treat it and the more successful the prognosis will be. This is particularly true in cases with cardiac involvement (see below). In mitochondrial disorders caused by mtDNA point mutations, which are maternally inherited and subject to the randomness of the heteroplasmy, signs, symptoms and organ involvement are highly heterogeneous from an individual to another, which accounts for a very high degree of both inter- and intra-familial variability. This is why, in these cases, each affected subject will have a different prognosis. For example, MELAS and MERFF point mutations are associated with several, extremely variable clinical pictures, and the majority of patients do not have full-blown MELAS or MERRF syndrome. In particular, subjects with MELAS point mutations who never have a stroke, or with MERRF point mutation without myoclonic epilepsy, have a totally different, and much better, prognosis compared with individuals affected with the entirely manifested syndrome caused by the same mutation (10-12). Regarding mitochondrial disorders due to nuclear gene mutations (autosomal dominant or recessive inheritance) the mutation-related clinical picture is somehow more predictable, but still a certain degree of intrafamilial variability in terms of both manifestations and related severity is to be expected. Again, early recognition and treatment of symptoms are crucial for the prognosis.

The following approach can help prevent severe organ dysfunctions or at least allow early diagnosis and treatment of disease-related complications.

Cardiac assessment: Cardiac arrhythmias are quite common and require routine electrocardiography monitoring because progression to high-grade atrio-ventricular block is often unpredictable, (i.e. KSS, MELAS, MILS). Supraventricular and ventricular tachyarrhythmias have been reported in patients with mtDNA disease, particularly in children. Also, echocardiography and/or cardiac MRI should be performed periodically even in asymptomatic subjects because hypertrophic cardiomyopathy, most commonly associated with mt-tRNA gene mutations, can become clinically evident only at an advanced stage and evolve to dilated cardiomyopathy if not treated. Cardiopathy is also a feature of nDNA defects especially mutations in respiratory chain ancillary proteins, often in association with Leigh disease (Table 2) (13). In addition, as demonstrated by a clinical study of a large population of pediatric patients with mitochondrial disorders (14) cardiac function in mitochondrial patients deteriorates rapidly regardless of the associated RC defect. Early and aggressive supportive treatment might increase the chances of survival even if mortality in subjects with cardiac complications remains higher than in individuals with predominant neuromuscular manifestations. In detail, pediatric patients with cardiomyopathy had an 18% survival rate at 16 years of age whereas patients without cardiomyopathy had a 95% survival at the same age.

Ophthalmology assessment: Ptosis, strabismus, ophthalmoplegia, retinal hyperpigmentation, optic atrophy, visual field defects and nystagmus are often part, alone or in combination, of the mitochondrial clinical picture. Strict periodic eye examination along with specific techniques like optical coherence tomography are necessary when the optic nerve is directly involved (i.e. LHON and optic atrophy-plus syndrome, OPA1) to monitor the subtle progression of this highly disabling degeneration (15, 16).

EEG monitoring: epilepsy is a frequent complication of many mitochondrial disorders (MERRF, MELAS, MILS, autosomal encephalopathies) and seizure control is a main goal to prevent progressive cortical brain damage and thus guarantee a satisfactory quality of life. Periodical EEG monitoring allows identification of any brain electrical abnormalities and their correction by appropriate therapeutic adjustments.

Respiratory assessment: periodical spirometry and nocturnal saturimetry allow early detection of any respiratory dysfunction and early adoption of measures to prevent hypoxia. This is extremely important to avoid hypoxia-related symptoms, namely headache, fatigue,

Table 2. Disorders due to mutations in nDNA.

Mutations in respiratory chain subunits
• Leigh syndrome
Mutations in respiratory chain ancillary proteins
• Leigh syndrome with cytochrome *c* oxidase deficiency (***SURF1***)
• Leigh syndrome and cardiopathy (*SCO2, COX10, COX14, COX15, COA5, FAM36A, TACO1*)
• Leigh syndrome and hepatopathy (*SCO1*)
• GRACILE syndrome
• Defects of mitochondrial protein importation: Mohr–Tranebjaerg deafness–dystonia syndrome (***TIMM8A)***; spastic paraplegia-13 *(HSP60)*
Defects of mtRNA translation
• Fatal neonatal lactic acidosis *(MRPS16, MRPS22, RMND1)*
• Spastic paraplegia *(SPG7)*; dominant hereditary ataxia (*AFG3L2*)
• Infantile hepatocerebral syndrome (*GFM1*); infantile encephalomyopathy (*TUFM*)
• Myopathy, lactic acidosis, sideroblastic anaemia (*PUS1*); reversible hepatopathy (*TRMU*)
• Leukoencephalopathy, brainstem and spinal cord involvement, lactic acidosis (*DARS2*)
• Late-onset Leigh syndrome with COX deficiency (*TACO1*)
Defects of the MIM lipid milieu
• Barth syndrome (*TAZ*)
• Sengers syndrome (*AGK*)
• Megaconial encephalomyopathy (*CHKB*)
• MEGDEL (*SERAC1*)
• Childhood myoglobinuria (*LPIN1*)
Defects of mitochondrial dynamics
• DOA; DOA-plus (*OPA1*)
• Charcot–Marie–Tooth type 2A (*MFN2*)
• Charcot–Marie–Tooth type 4A (*GDAP1*)
• Fatal infantile encephalomyopathy (*DRP1, MFF*)
Representative implicated genes are indicated in parentheses. Abbreviations: DOA, dominant optic atrophy; GRACILE, growth retardation, aminoaciduria, cholestasis, iron overload, and early death; MEGDEL, 3-methylglutaconic aciduria with sensorineural deafness, encephalopathy, and Leigh-like syndrome.

nausea, dyspnoea and, ultimately, seizures, all of them contributing to deteriorate quality of life.

Physiotherapy assessment: Abnormalities of tone, posture, power, and balance often complicate mitochondrial disease in patients of all ages. Life-improving solutions include, for example, the use of special seats to support hypotonic infants/children and unable them to keep an upright posture, develop axial tone and have a more comprehensive visual engagement with their environment. Also, management of spasticity and dystonia with splinting, botulinum toxin, and pharmacotherapy can advantage affected individuals at many disease stages and lower the risk of falls. It is very useful to perform functional assessment of the patients at home because this approach can reveal their main areas of difficulties and help plan personalized health care support such as mobility and hygiene aids. Management of respiratory problems, including prevention of aspiration pneumonia, is another important issue that the physiotherapist has to care for (9).

Specific treatments of mitochondrial diseases

Therapy for mitochondrial diseases is unfortunately scarcely adequate and sometimes palliative, but pharmacological treatments and surgical remedies are useful in prolonging and improving the lives of patients with mitochondrial diseases, which equals the concept of prognosis to that of chronic morbidity.

Specific pharmaceutical drugs have failed to show clear efficacy in treating mitochondrial diseases effectively, but improvement in fatigue and relief of myalgia have been reported with use of coenzyme Q10 and its analogue idebenone. Also, coenzyme Q10 replacement therapy at higher doses can benefit patients with coenzyme Q10 deficiency whereas Riboflavin can be effective in some patients with complex I deficiency. Some evidence has been reported of successful use of arginine for both acute treatment and prophylaxis of stroke-like episodes (2, 17, 18).

Treating symptoms of mitochondrial diseases

The difficulty in developing disease-modifying drugs to cure mitochondrial diseases has led to a focus on symptomatic treatments aiming at improving patient health which ultimately results in a better prognosis at least in terms of life quality if not, in some cases, of life span.

Lactic acidosis

It is one of the main symptoms especially in children. Acute episodes are corrected with sodium bicarbonate and dichloroacetate, but chronic use is not recommended because it is not effective and, also, it can cause peripheral neuropathy (17, 21).

Diabetes mellitus

Diabetes mellitus is a frequent complication of mitochondrial diseases, especially in patients with mitochondrial DNA mutations (22). Disease control relies on dietary advice, physical exercise, weight control and drug treatment in the same way as in non-mitochondrial diabetes. Metformin should be avoided in patients with mitochondrial disease because there is a risk of precipitating or exacerbating lactic acidosis.

Electrolyte disturbances

Hyponatraemia and hypokalaemia are not uncommon in children with mitochondrial diseases with renal involvement and both proximal and distal renal tubular acidosis have been identified (23). Their prompt investigation and treatment help avoid life-threatening adrenal crises.

Epilepsy

Seizures frequently complicate both pediatric and adult cases of mitochondrial disorders, the most common types being myoclonic and focal epilepsy. Common antiepileptic drugs are often effective and enable good seizure control. Levetiracetam, lamotrigine, carbamazepine, and clonazepam, alone or in combination, are most frequently used. It is recommended not to use sodium valproate and barbiturates which inhibit the respiratory chain and have occasionally been shown to precipitate hepatic failure in affected children (24, 25).

Table 3. Defects of mtDNA maintenance.

Mutated gene	mtDNA depletion	Multiple mtDNA deletions
TK2	Infantile or adult myopathy SMA phenocopy	Adult autosomal recessive PEO
DGUOK	Infantile hepato-cerebral syndrome	Adult myopathy ± PEO
PEO1	Hepato-cerebral syndrome Infantile-onset spinocerebellar ataxia	Adult autosomal dominant PEO-plus
SUCLA2	Infantile encephalomyopathy	—
SUCLG1	Infantile encephalomyopathy Methylmalonic aciduria	—
RRM2B	Infantile encephalomyopathy	Adult autosomal dominant or autosomal recessive PEO-plus
MPV17	Infantile hepatocerebral syndrome Navajo neurohepatopathy	Adult autosomal recessive PEO-plus
TYMP	Mitochondrial neurogastrointestinal encephalomyopathy	Mitochondrial neurogastrointestinal encephalomyopathy
POLG	Hepato-cerebral syndrome (Alpers syndrome)	Adult autosomal dominant or autosomal recessive PEO-plus; SANDO; MIRAS
POLG2	—	Adult autosomal dominant PEO
ANT1	—	Adult autosomal dominant PEO-plus
OPA1	—	DOA; PEO-plus
MFN2	—	DOA-plus
GFER	—	Congenital cataract, encephalomyopathy
MGME1	—	PEO, muscle wasting, proximal weakness, profound emaciation, respiratory failure

Abbreviations: DOA, dominant optic atrophy; MIRAS, mitochondrial recessive ataxia syndrome; mtDNA, mitochondrial DNA; PEO, progressive external ophthalmoplegia; SANDO, sensory ataxic neuropathy, dysarthria and ophthalmoparesis; SMA, spinal muscular atrophy. MGME1, mitochondrial genome maintenance exonuclease 1

Cardiomyopathy and arrhythmias

In patients with cardiomyopathy, early administration of β blockers and an angiotensin converting enzyme inhibitor (or angiotensin II receptor antagonist) is helpful in delaying disease progression, which explains why early diagnosis is fundamental. Rhythm disturbances include Wolff -Parkinson-White syndrome and various degrees of conduction block (from right bundle branch block to complete atrioventricular block) which can require radiofrequency ablation and/or implantation of pacing devices. Rhythm disturbances are easily identifiable on the electrocardiogram which, once again, stresses the importance of strict disease monitoring from the very early phases. Occasionally, cardiac involvement is the only, or earliest, manifestation of mitochondrial disease, leading to rapid cardiac deterioration and, when possible, cardiac transplantation before a diagnosis of mitochondrial disease is considered. After cardiac transplantation, survival depends both on the immune-mediated reaction to the new organ and on the degree of the disease-dependent multi-organ involvement (26-29).

Respiratory failure

Respiratory insufficiency can dominate the clinical picture especially in the late disease stages, the origin being either central or peripheral (weakness of diaphragm and/or respiratory muscles). In the latter cases, non-invasive positive pressure ventilation can help patients with their breathing and relieve them from hypoxia side effects (9).

Ocular disease

The most debilitating ocular problem in mitochondrial disorders is optic neuropathy which can be almost isolated, as in patients with LHON, or part of a multisystem involvement. In both cases, given the progressive nature of the neuropathy, this disabling disturbance is very difficult to treat. Visual aids should be used as much as possible to preserve residual visual activity.

Regarding eyelid ptosis, corrective ptosis surgery can dramatically improve both visual field and appearance, but the intervention is very delicate and subject to complications. For this reason, it should be performed only by dedicated ophthalmologists who are able to plan both timing and technique of surgery. Alternatively, surgically adjustable frontalis slings or less invasive ptosis props might be preferred to ptosis surgery (30).

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Far field R-wave sensing in Myotonic Dystrophy type 1: right atrial appendage versus Bachmann's bundle region lead placement

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Aim of the present study was to investigate far field R-wave sensing (FFRS) timing and characteristics in 34 Myotonic Dystrophy type 1 (DM1) patients undergoing dual chamber pacemaker implantation, comparing Bachmann's bundle (BB) stimulation (16 patients) site with the conventional right atrial appendage (RAA) pacing site (18 patients). All measurements were done during sinus rhythm and in supine position, with unipolar (UP) and bipolar (BP) sensing configuration. The presence, amplitude threshold (FFRS trsh) and FFRS timing were determined. There were no differences between both atrial sites in the Pmin and Pmean values of sensed P-wave amplitudes, as well as between UP and BP sensing configurations. The FFRS trsh was lower at the BB region in comparison to the RAA site. The mean BP FFRS trsh was significantly lower than UP configuration in both atrial locations. There were no significant differences in atrial pacing threshold, sensing threshold and atrial lead impedances at the implant time and at FFRS measurements. Bachmann's bundle area is an optimal atrial lead position for signal sensing as well as conventional RAA, but it offers the advantage of reducing the oversensing of R-wave on the atrial lead, thus improving functioning of standard dual chamber pacemakers in DM1 patients.

Key-words: far field, oversensing, far field R-wave sensing, myotonic dystrophy type 1, atrial lead, Bachmann's bundle

Introduction

Myotonic Dystrophy type 1 (DM1), or Steinert's disease, is the most common muscular dystrophy in adult life, with an incidence of 1:8000 births (1, 2). It is an autosomal dominant disorder caused by an abnormal expansion of an unstable trinucleotide repeat in the 3-prime untranslated region of DMPK gene on chromosome 19 (3, 4). The phenotype is characterized by myotonia and muscle weakness, but multisystem involvement is frequent. Cardiac involvement is noticed in about 80% of cases, and it often precedes the skeletal muscle one. Paroxysmal atrial arrhythmias (atrial fibrillation, atrial flutter, atrial tachycardia) frequently occur in DM1 patients (5, 6), but the atrioventricular block is the first and most clinically significant cardiac disease in this group of patients (7). To prevent cardiac sudden death, implantation of a pacemaker (PM) is required in 3-22% of cases (8, 9). Considering the high risk of supraventricular arrhythmias in this particular class of patients, optimal atrial sensing is an important prerequisite for proper pacemaker function. During conventional right atrial appendage (RAA) stimulation, the bipolar (BP) atrial electrogram amplitudes were shown to be lower in AF and atrial flutter (10); this aspect requires higher atrial programmed sensitivity, thereby increasing the risk of sensing of ventricular depolarization in the atrial channel (FFRS). It has been shown that Bachmann's bundle (BB) stimulation is a safe and feasible procedure with low rate of sensing and pacing defects (11, 12). However, BB pacing does not provide significant benefit for the prevention of paroxys-

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mal atrial fibrillation in DM1 population (13-15). No data are available concerning the effects of the different atrial lead placement on the far field R-wave sensing (FFRS) characteristics in DM1 patients. Aim of the present study was to investigate FFRS timing and characteristics in 34 DM1 patients undergoing dual chamber pacemaker implantation, comparing Bachmann's bundle stimulation (16 patients) with the conventional right atrial appendage (RAA) pacing site (18 patients).

Methods

Study population

The study involved 34 patients (age 51.4 years ± 8.5; 23M:11F), with a genetic established diagnosis of Myotonic Dystrophy type 1, undergoing dual chamber PM implantation from January 2007 to December 2013, in the Arrhythmologic Unit of Department of Cardio-Thoracic and Respiratory Sciences, Second University of Naples. The indications for PM implantation were: a)first-degree atrioventricular blocks with a pathological infra-Hissian conduction (16 patients); b) symptomatic second- or third-degree atrioventricular blocks, respectively in 14 and 4 patients. Before PM implantation a comprehensive cardiac examination including physical examination, 12-lead electrocardiogram (ECG), 24-h ECG Holter monitoring, echocardiogram and invasive electrophysiological study (EPS) was performed. No statistically significant differences in the electrical parameters (P wave amplitude, pacing threshold and lead impedance) were observed at implantation.

Device characteristics and programming

Standard techniques for implantation of a dual-chamber PM system (Medtronic Kappa D901, or Adapta ADDR01, Medtronic Inc., Minneapolis, MN, USA) were used. Percutaneous subclavian vein cannulation was performed in all cases;the right ventricular lead was first positioned in the apex, under fluoroscopic guidance. All patients received the bipolar atrial screw-in pacing lead CapSureFixw 5076 (Medtronic Inc., Minneapolis, MN, USA). The electrode surface material consisted of titanium–nitride alloy with an electrode surface area of 4.2 mm^2 for the helix and of 22 mm^2 for the ring electrode. There was 1-mg of dexamethasone in the electrode tip, which eluted after lead implantation. The distance between the two electrodes was 10 mm. The atrial pacing lead was positioned in the right atrial appendage or on the right side of the interatrial septum, in the region of Bachmann's bundle. All the devices were programmed in DDDR mode. The lower rate was set to 60 bpm. Rate adaptive pacing was used with a maximum rate of 130 bpm. Mode switches were programmed to occur for atrial rates > 200 bpm, persisting for more than 8 ventricular beats. The devices used in this study were programmed to detect episodes of atrial tachycardia, and to record summary and detailed data, including atrial and ventricular electrogram.

Study protocol

The study population was retrospectively subdivided into 2 groups according to the location of the atrial lead: right atrial appendage (18 patients) or Bachmann's bundle region (16 patients). Patients with foramen ovale, atrial septal aneurysm, severe mitral stenosis, left atrial enlargement or receiving prior surgery (coronary bypass or valvular heart surgery) that involved the right atrium (RA) or taking anti-arrhythmic medications were excluded from the study. All measurements were performed with patients in the supine position. The minimum (Pmin), maximum (Pmax) and mean (Pmean) sensed P-wave amplitude were established in each patient, both in unipolar (UP) and bipolar (BP) atrial lead sensing configuration, by the automatic P-wave amplitude test. Pmean is the result of the arithmetic average between Pmax and Pmin values. The results between the two atrial stimulation sites were statistically compared. Using the same test, the FFRS after sensed R-waves was evaluated, at the highest available testing atrial sensitivity (0.1 mV), with the simultaneous recording of RA intracardiac electrogram (IEGM), marker channels and surface ECG. During the test the presence of the atrial sense marker coincident with the R-wave was monitored, and if FFRS occurred, the IEGM was frozen and displayed at the programmer screen, at a sweep speed of 100 mm/s. Then, using an electronic calliper system (with an accuracy of 3 ms) the interval between the beginning of the QRS complex on the surface ECG and the first atrial FFRS marker was measured to determine FFRS timing. Subsequently, the automatic P-wave amplitude test was repeated with the atrial sensitivity gradually decreasing step by step, until no FFRS was seen (as indicated by the absence of atrial sense marker coincident with the R-wave). The FFRS threshold (FFRS trsh) was defined as the minimal atrial sensitivity at which no FFRS occurred (Figure 1). If FFRS was not present at the most sensitive setting of 0.1 mV, FFRS trsh was assumed to be 0.1 mV.

Statistical analysis

The χ^2-test was used to analyze differences between categorical variables. For normally distributed continuous variables, Student's t-test was applied. If variables did

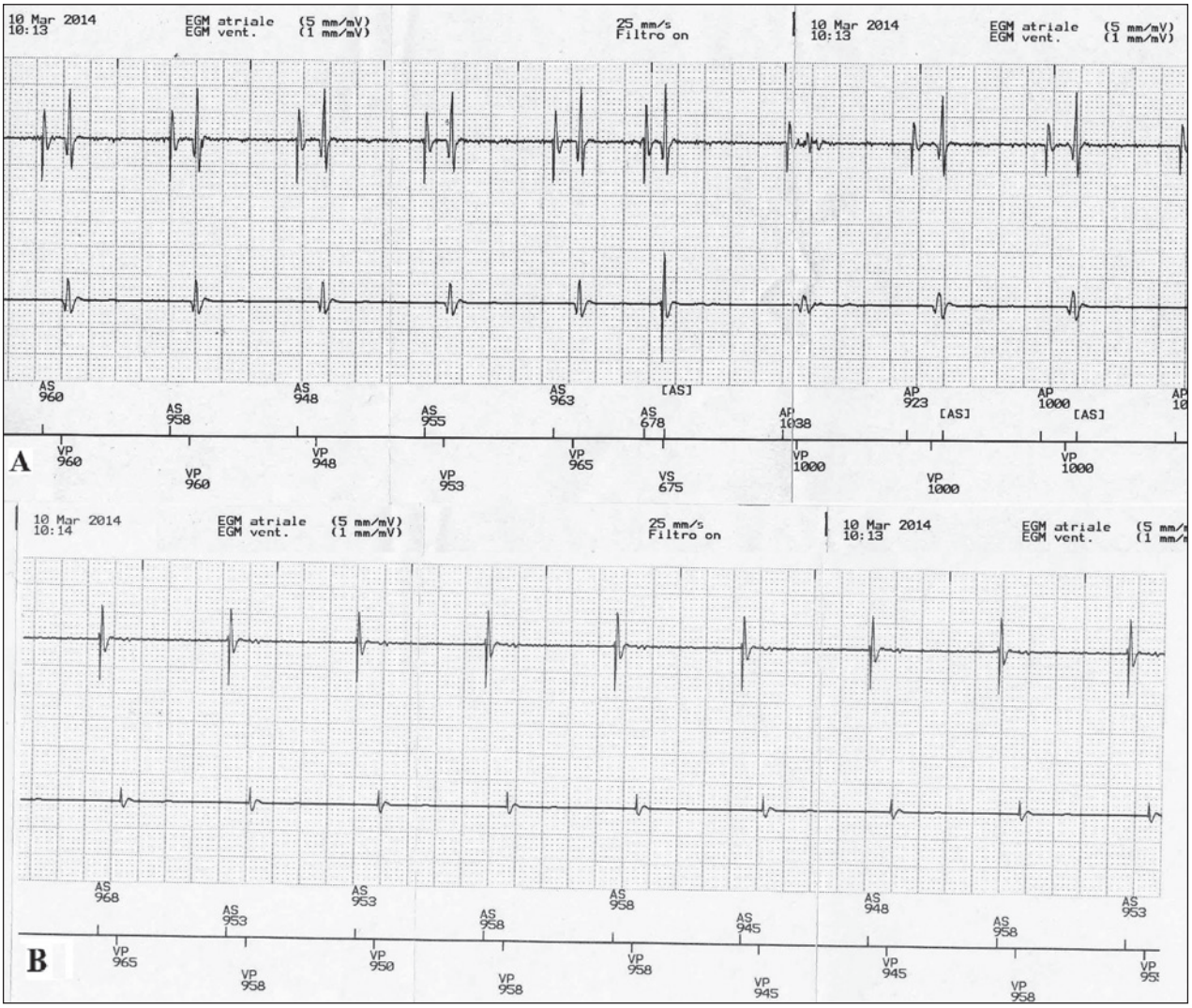

Figure 1. A) At the programmed sensitivity of 0.1 mV with BP sensing configuration the FFRS after sensed and paced R-wave is present during the automatic P-wave amplitude test, as indicated by the atrial sense marker corresponding to the R-wave. B) With the atrial sensitivity setting of 1.2 mV FFRS is no longer observed during the test.

not follow normal distribution, the Mann–Whitney U-test was performed for comparisons of independent variables. Wilcoxon signed rank test was used for comparisons of related variables. STATISTICA software (version 7.1, StatSoft, Inc.) was used to calculate statistics. $P < 0.05$ was set as statistically significant.

Results

Data are presented as means and standard deviations, or medians and ranges, when appropriate. Table 1 shows the pacing and sensing parameters, at the time of FFRS measurements in the 2 study groups: Group RAA (n:18; age 54.1 ± 6 years; 12 M:6 F) with atrial lead positioned in the right atrial appendage, and Group BB (n: 16; age 48.5 + 6.8 years; 11 M:5 F) with atrial lead positioned in the Bachmann's bundle region. There were no statistically significant differences between age and sex composition of the 2 groups and the medications intake. No differences were observed between the two atrial stimulation sites regarding the Pmin and Pmean values of sensed P-wave amplitudes, as well as between UP and BP sensing configurations. Table 2 shows the FFRS characteristics in both right atrial stimulation sites. Significant differences were observed in terms of FFRS trsh, between the two study groups, but not in terms of FFRS timing. The FFRS trsh was lower at the BB region compared to RAA site. The mean BP FFRS trsh was significantly lower than UP configuration in both atrial locations ($P < 0.02$).

Table 1. Electrical measurements of the atrial lead in the two study groups.

Sensing configuration	Parameters	RAA group	BB group	P-value
UP	Pacing threshold (V)	0.7 + 0.2 (0.4 – 1.5)	0.9 + 0.3(0.3 – 1.7)	ns
	Pacing impedance (Ohm)	602 + 235 (227 –984)	676 + 288 (275 – 1001)	ns
	P min (mV)	2.1 + 1.3(0.6 – 4.6)	2.8 + 1.0 (0.5 – 4.9)	ns
	P mean (mV)	3.4 + 1.3 (0.6 – 5.1)	3.2 + 1.1 (0.8 – 5.1)	ns
BP	Pacing threshold (V)	0.8 + 0.4 (0.3 – 2.6)	0.6 + 0.5 (0.2 – 3.0)	ns
	Pacing impedance (Ohm)	721 + 233 (315 –1080)	751 + 304 (301 – 1099)	ns
	P min (mV)	2.3 + 1.2 (0.5 – 4.3)	2.5 + 1.6 (0.6 – 4.8)	ns
	P mean (mV)	3.3 + 1.5 (0.8 – 4.9)	3.0 + 1.4 (0.9 – 5.2)	ns

Data are presented as mean ± standard deviation and range.

Legenda: Pmin: the minimal, and Pmean: the mean amplitude of sensed P-wave; UP: unipolar; BP: bipolar; RAA: right atrial appendage; BB: Bachmann's bundle.

Discussion

Optimal atrial sensing is an important prerequisite for proper pacemaker functions. It is especially important in DM1 patients with frequent paroxysmal atrial tachyarrhythmias, in whom automatic mode switch algorithms are involved in the prevention and termination therapies for atrial fibrillation. This aspect requires a higher atrial programmed sensitivity with the risk of sensing of ventricular depolarization in the atrial channel (FFRS), that interferes with advanced diagnostic and therapeutic functions of modern dual chamber devices, including ICD (16-18). However, with the ability to program the post ventricular atrial blanking (PVAB) time in modern devices, FFRS-related consequences can be easily solved. Nevertheless, it should be emphasized that long atrial blanking periods may decrease the sensitivity of arrhythmias detection, especially atrial flutter, if every other flutter wave will not be sensed. Thus, for reliable AF detection, the programming of short PVAB time is recommended as well as a higher atrial sensitivity setting is necessary to detect low AF amplitude. In the heart conduction system, Bachmann's bundle is a branch of the anterior internodal tract that resides on the inner wall of the left atrium. It is a broad band of cardiac muscle that passes from the right atrium, between the superior vena cava and the ascending aorta (19). During the normal sinus rhythm, BB is the preferential path for the conduction of cardiac impulse from right to left atrium. We have previously shown (11, 12) that in DM1 patients undergoing dual chamber pacemaker implantation, the insertion of the atrial lead in the interatrial septum is a safe procedure, presenting a low rate of sensing and pacing defects. However, it seems not to be able to prevent the onset of paroxysmal atrial fibrillation in this population (13-15). Lewicka-Nowak et al. showed that the BB stimulation is affected by a low rate of FFRS compared to conventional RAA pacing, with a high atrial programmed sensitivity (20). These results were explained by Kirchoff's law, which states that the electrical potential, at any location, is inversely related to its distance from the current source (21). It has also been reported that the BP atrial sensing configuration is clearly superior in rejecting FFRS compared with the UP configuration, both in BB region and RAA site (20-24). Furthermore, it has been observed that atrial oversensing is more frequent and the amplitude of far field R-waves greater with a longer tip-to-ring spacing; reducing the inter-electrode distance, it decreases the incidence of FFRS and increases the ratio between the P-wave and FFRS amplitudes. DM1 patients are a high-arrhythmic risk population (9, 25-28), probably related to

Table 2. Far field R-wave sensing (FFRS) characteristics at both right atrial stimulation sites.

Sensing configuration	Parameters	RAA group	BB group	P-value
UP	FFRS trsh (mV)	0.9 ± 0.4 (0.5 – 3.1)	0.5 ± 0.1(0.1 – 1.3)	P < 0.05
	R-T1 (msec)	33 ± 21 (16 – 88)	30 ± 19 (12 – 77)	ns
BP	FFRS trsh (mV)	0.6 ± 0.3 (0.4 – 2.0)	0.3 ± 0.1 (0.1 – 1.1)	P < 0.05
	R-T1 (msec)	39 ± 18 (28 – 76)	44 ± 22 (24 – 85)	ns

Data are presented as mean ± standard deviation and range

Legenda FFRS trsh: FFRS threshold; R-T1: FFRS timing; UP: unipolar; BP: bipolar.

the heterogeneity of ventricular repolarization (6), proven by the increase of QTc and JTc dispersion, as reported in congenital (29-32) or acquired (33-35) heart diseases and in other neuromuscular disorders (36-40). Considering the high risk of supraventricular arrhythmias in DM1 patients, an optimal atrial sensing is an important prerequisite for proper pacemaker functions.

At our knowledge, this is the first paper investigating the effects of the different atrial lead positioning on the FFRS characteristics in DM1 population. We observed that the atrial lead positioning in BB region significant decreases the FFRS threshold compared to RAA atrial lead placement, and that BP sensing configuration significantly improves FFRS threshold compared to UP sensing configuration, in both placements.

A possible explanation for these results is that FFRS is only related to the distance from the atrial lead placement and the point of ventricular activation, and to the inter-electrode distance; furthermore it does not depend on the degree of fibrosis, hypertrophy of the atrial myocytes and fatty acid infiltration, which are generally the histopathological cardiac pattern observed in patients with DM1. In conclusion, we report that in DM1 patients, Bachmann's bundle area is an optimal atrial lead position for signal sensing as the conventional RAA. Furthermore based on our experience, it offers the advantage of reducing the oversensing of R-wave on the atrial lead, thus improving the functions of standard dual chamber pacemakers in DM1 patients.

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Sleep breathing disorders and nocturnal respiratory pattern in patients with Glycogenosis type II

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Patients affected by glycogenosis type II frequently present sleep-disordered breathing. The presence of symptoms suggestive of sleep breathing disorders was investigated, by a questionnaire, in 10 patients, affected by adult or juvenile forms of glycogenosis type II. Diurnal respiratory function, diaphragm weakness and nocturnal respiratory pattern were evaluated at the enrolment. In patients presenting sleep disordered breathing, the same parameters were re-evaluated after treatment with assisted non invasive ventilation. Out of 10 patients, 5 presented symptoms suggestive of sleep-disordered breathing at the baseline, 2 a pattern of sleep apnea syndrome and 3 nocturnal hypoventilation. All patients presented diaphragmatic weakness. No correlation was found between forced vital capacity values (FVC) in sit position and nocturnal respiratory disorders. Five patients with respiratory disorders were treated with non invasive ventilation. All patients – after one month of treatment - showed an improvement in symptoms with reduced diurnal hypersomnia (ESS < 10), absence of morning headaches and nocturnal awakenings, and reduced nicturia regardless the modality of ventilation. We recommend that all patients with glycogenosis type II, once diagnosed, are carefully monitored for the development of respiratory involvement, even in the absence of reduced FVC values and in the early stages of the disease, to receive appropriate therapy.

Key words: glycogenosis, apnoea, hypopnea, hypoventilation, non invasive ventilation

Background

Patients with glycogenosis type II, also known as Pompe disease, are susceptible to the development of sleep disordered breathing (SDB). Sleep, with its reduction in ventilatory responses (1, 2), represents a major stress to weakened respiratory muscles and an opportune time to asses the ventilatory reserve. Sleep disordered breathing is found in 40-70% of patients with neuromuscular diseases (3, 4), but relates poorly to daytime functional variables (5). Recognition of nocturnal hypoventilation is of particular importance because it contributes to the development of respiratory failure (6). Unfortunately, a simple relationship between awake measurements of respiratory function and nocturnal breathing events has not been found (7-10). Symptoms suggestive of SDB are often underestimated, particularly in patients with neuromuscular diseases (4, 11). The presence of symptoms such as morning headaches and daytime hypersomnia may interfere heavily on the quality of life of these patients. The treatment of respiratory disorders can therefore have a strong impact on improving their quality of life (12-14).

Aims of the study were: 1) to evaluate respiratory function, nocturnal respiratory pattern and presence of symptoms suggestive of sleep-disordered breathing in a group of 10 patients, affected by Glycogenosis type II; 2) to investigate the relationship between diurnal respiratory function, diaphragmatic dysfunction and nocturnal breathing patterns; 3) to assess the improvement in symptoms after treatment with non invasive ventilation (NIV).

Patients and methods

Ten patients affected by adult or juvenile form of glycogenosis type II (Table 1) aged 41,2 ± 13,3 were progressively enrolled. All patients – at the enrolment – filled in a questionnaire on the presence of the following symptoms: a) excessive daytime sleepiness; b) choking or gasping

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Table 1. Baseline characteristics of patients.

Patient	Age	FVC%	FEV1%	DW	SYM	CO2>45	AHI	T90
1	21	74	75	N	N	N	3	6
2	48	73	68	N	Y	N	14	8
3	28	67	70	N	N	N	4	1
4	50	62	61	Y	Y	N	6	32
5	49	61	61	Y	Y	Y	5	44
6	27	63	62	N	Y	N	16	9
7	31	66	66	N	N	N	4	0
8	57	58	58	N	N	N	2	6
9	43	49	49	Y	Y	Y	5	30
10	58	57	57	N	N	N	2	6

Legend
Y: yes; N: no; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; DW: diaphragm weakness; SYM: symptoms; AHI: Apnea/Hypopnea per hour; T90: % time with arterial oxygen saturation less than 90%

during sleep; c) recurrent awakenings from sleep; d) unrefreshing sleep; e) daytime fatigue; f) morning headaches; g) nicturia and h) impaired concentration.

All patients underwent a respiratory investigation including pneumological examination, measure of ventilator capacity, arterial blood gas determination and polysomnography. Ventilatory capacity was investigated by vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), measured by a hand-held spirometer (SpirolabIII, MIR). Measurements were obtained both in sitting and supine positions to evaluate diaphragm weakness. The best of tree consistent efforts (< 5% variability) was used. The reduction in lung function was classified according to ATS/ERS criteria. The defect was considered *mild* for values of FEV1 > 70% of the expected, *moderate* for values between 60 to 69%, *moderately-severe* for values between 50 to 59%, *severe* for values between 35% to 49%, and *very severe* for values < 35% of the expected, according to age, height and weight. Arterial blood gas tension was determined in the arterial blood of the earlobe, by automated blood gas analyzer (OMNI 6 MODULAR SYSTEM AVL).

Overnight polysomnography was performed in all patients, without oxygen supplementation. Sleep stages, electroencephalogram, electro-oculogram, submental electromyogram, electrocardiogram, oro-nasal flow and respiratory movement sensors, as far as oxyemoglobin saturation were recorded using a computerized work station (SOMNO lab, Weinmann). Sleep stages and respiratory parameters were scored manually. Analyses were performed using the American Academy Sleep Medicine scores. The sleep disorders breathing was sub-classified into two distinct syndromes, namely, 1) obstructive sleep apnea-hypopnea syndrome (OSAHS), and 2) sleep hypoventilation syndrome (SHVS). OSAHS was diagnosed when sleep monitoring demonstrated 5 or more apneas/hypopneas episodes/hour during sleep (AHI > 5). SHVS was diagnosed in presence of $PaCO_2$ values > 10 mmHg on waking in the morning, compared with awake supine values, and/or in presence of sustained hypoxemia with arterial oxygen saturation [SaO_2] < 90% for more than 30% of the registration period, during sleep (T90 > 30%), not related to apnea or hypopnea episodes. Patients showing SDB were addressed to ventilatory assistance and treated by continuous positive airway pressure (CPAP autoset spirit, ResMed) or non invasive ventilation (NIV with VSIII ResMed) in pressure support, with synchronised tidal volume. Parameters were set individually. Nasal masks were preferentially used, unless special needs of the patient. In this case, a facial mask was used. These patients were re-evaluated by the same parameters, 30 days after the treatment. No patient was in enzyme replacement therapy (ERT).

Results

Diurnal respiratory function

All patients presented restrictive ventilatory defect. Two had a mild reduction of respiratory capacity; 4 patients presented a moderate reduction; 3 a moderate-severe, and 1 had a severe reduction. Diaphragm weakness (DW, postural drop of VC ≥ 20 %) was present in 3/7 patients.

Arterial blood gas analysis

Two patients presented diurnal hypercapnia > 5,9 kPa (45 mmHg).

Sleep disordered breathing

Five patients presented hypersomnia (ESS > 10), morning headaches, sleep disturbance, nicturia and im-

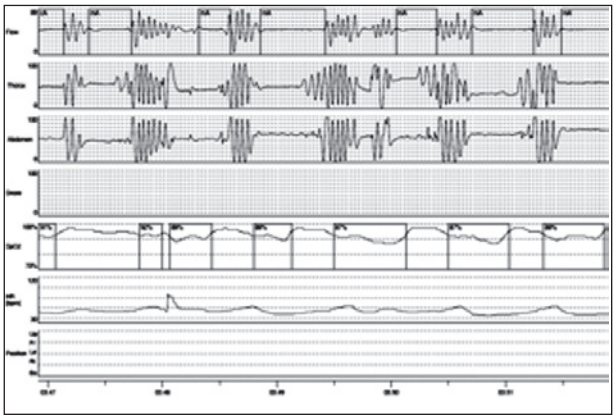

Figure 1. Apnea.

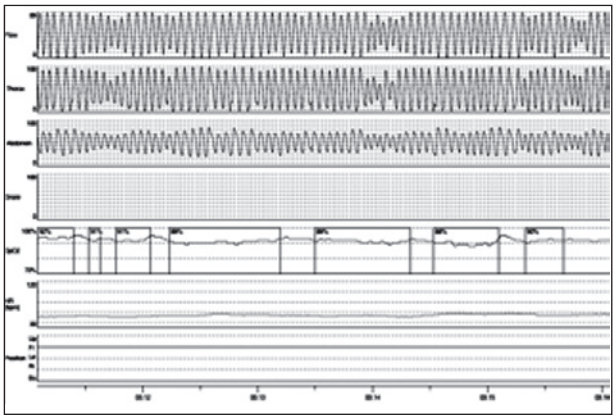

Figure 2. Desaturazione.

paired concentration. Of these, three patients complained awakenings and choking or gasping during sleep. ***SDB*** was found in five patients, three with diaphragm weakness, two without. Two subjects had findings consistent with sleep apnea syndrome (OSAHS: AHI > 5; T90 < 20%) (Fig. 1); in three patients with diaphragm weakness, REM sleep hypopneas with REM sleep hypoventilation and continuous sleep stage-indipendent hypoventilation (SHVS: AHI ≤ 5; T90 > 30%) were found (Fig. 2). The 5 patients presenting sleep disordered breathing, started therapy with non invasive positive pressure ventilation: 2 patients were well adapted with CPAP while 3 needed pressure support ventilation with target volume. After one month of treatment, all treated patients reported an improvement in symptoms with reduced diurnal hypersomnia (ESS < 10), absence of morning headache and nocturnal awakenings, reduced nicturia (Table 2), regardless of the modality of ventilation.

Discussion

The presence of sleep disordered breathing is too often overlooked in patients with neuromuscular diseases until the development of awake respiratory failure. Part of the problems lies in the difficulty of identifying symptoms associated with sleep breathing disorders in these patients., as they may maintain a good daytime function with minimal symptoms, despite significant apneas and severe nocturnal oxygen desaturation (15).

In our series, 5 patients (50%), had symptoms suggestive of sleep disordered breathing confirmed by an altered nocturnal breathing pattern. Three patients had diaphragmatic weakness and presented nocturnal hypoventilation with a pattern of latent chronic respiratory insufficiency. Two patients had a nocturnal breathing pattern type apnea/hypopnea. The role of diaphragm in these disease is fundamental. If the diaphragmatic strength is preserved but the upper airway or intercostal muscles are weak, then obstructive events are likely to predominate. On the other hand, when patients have severe diaphragmatic dysfunction, suppression of intercostal and accessory muscles during sleep will produce hypoventilation and abnormalities in gas exchanges (14). The presence of sleep hypoventilation is particularly important to be diagnosed, because it usually precedes the development of diurnal respiratory failure (15). Furthermore, in patients with neuromuscular diseases OSAHS may be responsible for significant daytime disability such as excessive daytime sleepiness and cognitive dysfunction. To recognize an altered nocturnal breathing is of particular importance because it represents an early sign of respiratory dysfunction. Many factors such as obesity, scoliosis, ability to

Table 2. Mechanical ventilation in patients treated.

Patient	Mode of MV	Mask	Time of ventilation per day	Difference in ESS score
1	PSV/VT	Full Face	8	-8
2	PSV/VT	Nasal	8	-7
3	PSV/VT	Nasal	6	-5
4	CPAP	Nasal	6	-8
5	CPAP	Nasal	5	-7

PSV/VT:pressure-support ventilation with target volume; CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale.

arouse from sleep, and other compensatory mechanisms can contribute to influence the severity of SDB and gas exchange defects. In such cases an early investigation of presence of SDB and its monitoring after the beginning of therapy, is recommended. Failure to recognize and treat SBD may contribute to unnecessary disability or even to premature death in these patients (16, 17). Treatment with NIV, accepted by all patients with good compliance, is able to reduce symptoms reported by patients (morning headaches, nicturia) and also improve the quality of life of patients, while reducing the frequency of hospitalizations and increasing their life expectancy (18-22), even in patients not receiving ERT. Therefore we recommend that all patients with Glycogenosis type II or Pompe Diseases, once diagnosed, are carefully monitored for the development of respiratory involvement, even in the absence of reduced FVC values and in the early stages of the disease, to receive appropriate treatment.

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CASE REPORT

Adenosine-induced sinus tachycardia in a patient with Myotonic Dystrophy type 1

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We report the case of a 32-year-old man with Myotonic Dystrophy type 1 showing adenosine-induced sinus tachycardia during transesophageal electrophysiological evaluation.

Key words: sinus tachycardia, adenosine, proarrhythmic effect, myotonic dystrophy

Case report

A 32 year old man with Myotonic Dystrophy type 1 (DM1) was referred to our observation for recurrent palpitations at rest, lasting a few minutes. The medical history was negative for family sudden death, dizziness or syncope. Physical examination revealed a blood pressure of 120/70 mmHg, clear lungs and normal heart sounds. Haematological examination, except for CK values, urinary analysis and thyroid function were all normal. He had no other medical pathologies in the past, and denied intake of alcohol, tobacco or any medications.

Muscle involvement was characterized by slight weakness and atrophy of facial, axial, semi-distal, and distal compartments. No abnormalities of other organs and systems including eye, endocrine system, central nervous system, gastrointestinal system, respiratory apparatus and heart were present. Electrocardiographic (ECG) examination showed a sinus rhythm of 75 bpm, normal atrioventricular conduction (PR: 160 ms), mild slurred QRS upstroke in leads V3-V4, no ST segment or T wave changes (Fig. 1). Neither chest x-ray nor color-doppler echocardiography revealed any cardiac structural or functional abnormality. 24-hours ECG Holter monitoring and treadmill stress test did not show arrhythmias. He underwent transesophageal electrophysiological evaluation: the atrioventricular node refractory period was 240 msec. During the test was not used anesthesia. The patient was conscious during the entire test and his O2 saturation, measured by a pulse oximeter, was consistently 98-99%. Programmed atrial stimulation up to triple extrastimuli did not induce supraventricular arrhythmias. Intravenous adenosine (12 mg) was performed to slow AV conduction and unmask unapparent pathways. After a single-bolus, rapidly followed by saline flush, a sinus tachycardia at a frequency of 145 beats/min, was observed, self-terminating in approximately 50 seconds, without any change in QRS morphology (Fig. 2). After the second adenosine bolus, carried out about 5 minutes

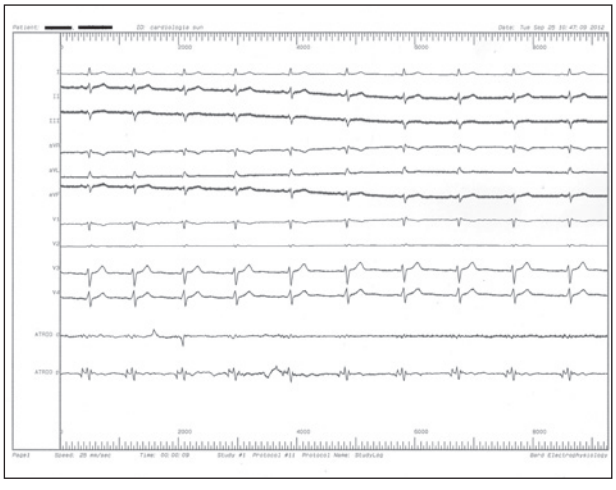

Figure 1. Basal electrocardiogram.

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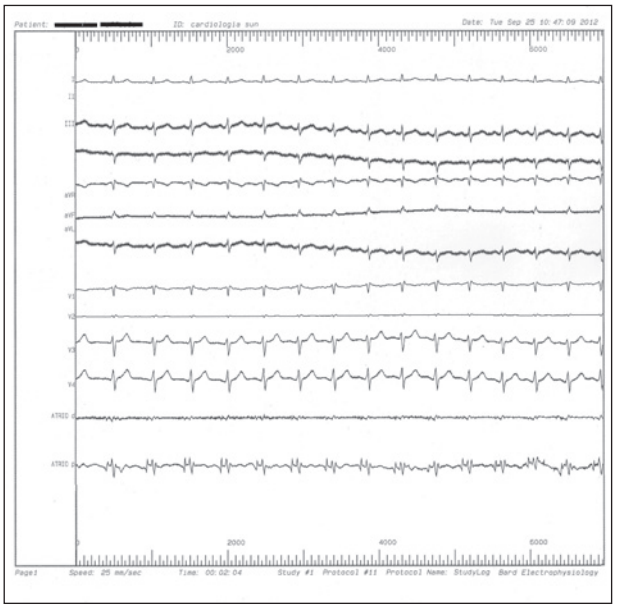

Figure 2. Adenosine induced synus tachycardia.

later, a similar effect was observed. The patient remained conscious and asymptomatic during the entire period of tachycardia.

Discussion

Myotonic dystrophy type 1 (DM1) is a serious autosomal-dominant hereditary disease with an estimated incidence of 1 in 8000 births. The phenotype is characterized by myotonia and muscle weakness, but a multisystemic involvement with highly variable clinical manifestations is very frequent. Cardiac involvement, that often precedes the skeletal muscle one, occurs in 80% of DM1 patients and represents the second most common cause of death, after respiratory causes (1). Arrhythmic risk in DM1 patients may be related to the heterogeneity of ventricular repolarization (2, 3), expressing by an increase in QTc and JTc dispersion, as reported in other congenital (4-8) or acquired (9-11) heart diseases and in neuromuscular diseases (12-16). Adenosine is an endogenous nucleoside whose actions were first investigated by Drury & Szent-Gyorgyi in 1929 (17). They described a slowing of sinus rate and a reduction of conduction through the atrioventricular node in the hearts of laboratory mammals. The adenosine test seems to have a good sensitivity for unmasking accessory pathways (18), because it extends the atrioventricular node refractory period, favoring the anterograde conduction. The electrophysiologic effects of adenosine on a specific AV bypass tract, depend on the type of cell that characterize the tract: nodal type cells (with decremental conduction) or atrial myocytes. In sinu-atrial nodal cells, the activation of a potassium outward current, results in a reduced rate of phase IV depolarization, thereby slowing sinu-atrial node automaticity. In the AV node, adenosine prolongs post-repolarization refractoriness and suppresses excitability of cells in the N region of the node, resulting in an AV nodal conduction block of variable degree.

Some authors reported serious adverse events related to the adenosine infusion, including supraventricular and life threatening ventricular arrhythmias (19, 20). To date, while the association between adenosine infusion and ventricular arrhythmias is well known (21), little is known about the adenosine induced supraventricular arrhythmias. The possible mechanisms underlying pro-arrhythmic effect of adenosine are summarized in Table 1.

The most common pro-arrhythmic effect of adenosine is the induction of atrial fibrillation (AF) (19). This is probably owing to the shortening of atrial refractoriness, that favours the induction of reentrant arrhythmias. Because the signal transduction pathways activated by adenosine and acetylcholine, converge on the same potassium channels and produce similar electrophysiologic effects in the atrial myocardium, adenosine-induced and vagus nerve–dependent AF are mechanistically similar.

Table 1. Mechanisms underlying pro-arrhythmic effect of adenosine.

Type of arrhythmia	Underlying mechanisms
Atrial fibrillation/atrial flutter	Shortening of atrial refractoriness Sympathetic activation
Rapidly conducted atrial flutter/atrial fibrillation	Sympathetic activation
Orthodromic atrioventricular reentry tachycardia	Critical prolongation of anterograde AV nodal and retrograde activation of the atrium via an accessory pathway
Pre-excited atrial fibrillation/atrial flutter	Critical prolongation of anterograde AV nodal and retrograde activation of the atrium via an accessory pathway
Sinus tachycardia/atrial tachycardia	Reflex sympathetic discharge Direct sympathetic activation by stimulation in the carotid body chemoreceptors

Both adenosine and vagus nerve activation cause a spatially and temporally heterogeneous shortening of atrial refractoriness (22).

A dangerous increase of the ventricular rate in patients with atrial flutter (23, 24), atrioventricular reentry tachycardia (25), narrow QRS complex tachycardia (26), and 'mild sinus tachycardia' following a brief period of bradycardia (27) have also been reported. The case here shown is the first report of sinus tachycardia induced by intravenous adenosine infusion in a DM1 patient without previous bradycardia, supporting the hypothesis of Biaggioni el al. (28) that adenosine may be responsible of a direct increase in circulating catecholamine levels and of sympathetic nerve traffic, by sympathetic stimulation in the carotid body chemoreceptors. However, in our patient, no bradycardia during the entire test was observed, as transesophageal electrophysiological evaluation was performed under continuous ECG monitoring. We are aware that the relation between adenosine infusion and sinus tachycardia is anecdotal, but we believe that all possible and unexpected pro-arrhytmic effects of antiarrhytmic drugs should be taken into account in clinical practice, particularly in patients affected by neuromuscular disorders.

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2013 GAETANO CONTE PRIZE LECTURE

GNE myopathy: a personal trip from bedside observation to therapeutic trials

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Based on the Gaetano Conte prize lecture delivered at the 11th meeting of the Mediterranean Society meeting (Athens 2013).

The trip is not over yet as definite therapy for GNE myopathy is not yet available. Also the exact mechanisms by which GNE defects lead to isolated muscle disease in humans are not fully recognized. But in the Gaetano Conte lecture of 2013 I have tried to describe how much a progress was made in several research laboratories and clinical institutes in the investigation of this unique myopathy.

Introduction

This is a personal review of the history and current status of a rare myopathy that spans my 35 years' career in the neuromuscular field, starting from a bedside observation to ongoing therapy trials. As a neurologist in training I returned from Newcastle UK after a WHO sponsored fellowship period at the Muscular Dystrophy Laboratories under Professors John Walton and Frank Mastaglia. Soon after my return in late 1979 I was called for a consultation to a hospitalized man who was at his 60's. I found him sitting in his wheelchair at the hospital corridor playing with his little granddaughter: he extended his legs straight forward and she was riding on them at the ankles. This was a very unusual feature for a person with progressive myopathy that required major strength in the quadriceps (usually the muscle first involved in most muscular dystrophies and acquired myopathies). By 1982 I identified 9 patients with this unique syndrome of quadriceps sparing myopathy who all were Jews of Iranian (Persian) origin. They all had adult onset myopathy, with modest elevation of serum CPK and biopsy that showed various numbers of muscle fibers containing 'rimmed' vacuoles. I termed this disorder quadriceps sparing myopathy (QSM) and sent it to be published in a special issue (foreschrift) honoring Sir John Walton's departure from Newcastle to Oxford in 1982. It took until 1984 to be published in the *Journal of Neurological Sciences* (1), by then I already accumulated 27 such patients (added as an addendum in that publication). Few reports of a similar disorder were published in the following two decades from other countries. Because of the similarities in the histological feature of the QSM with the sporadic IBM, the disease carried the term hereditary inclusion body myopathy (HIBM) or IBM2 (2). The understanding that this is not only a unique clinical entity but a well-defined genetic disease came from the work of Stella Mitrani-Rosenbaum, with whom I continue to collaborate for the past 20 years, who by 1995 linked the Persian Jewish QSM to chromosome 9 (3). This led to a special meeting in Napoli in 1996 where the diagnostic criteria for this recessive myopathy were set by a group of experts from around the world and published in a special issue of Acta Myologica (4). In 2001 Iris Eisenberg, a PhD student in Prof Mitrani-Rosenbaum's laboratory, identified mutations in the gene encoding N-acetylglucosamine epimerase/N-acetylmannosamine kinase (termed *GNE*) as the disease causing defect (5). The linkage data and later the identified gene defects helped in determining that what was thought to be a different disorder previously described in Japan as distal myopathy with rimmed vacuoles (DMRV or Nonaka's myopathy (6)) is in fact the same condition (7). A consortium of researchers working on various aspects of this disease has decided recently to unify the name for this myopathy and call it GNE myopathy (8).

I will review some issues related to GNE myopathy with a personal perspective.

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Clinical features

These have not changed much since the original descriptions. It usually starts at the third decade of life but few cases were reported with onset in the early teens and some had late onset in the 5th decade. The typical onset in the vast majority of patients is distal weakness in the legs (drop foot). The disease is usually slowly progressive spreading to the proximal musculature and the upper limbs but patients may maintain independent walking for many years relying on the hip strength. A major determinant of early loss of ambulation is quadriceps weakness. Although most patients retain the quadriceps sparing feature through several decades, about 5% have various degrees of weakness in this muscle early on. However, the unique clinical pattern of strong quadriceps in spite of major involvement in other leg muscles is still the best clinical hint for the diagnosis of GNE myopathy and is unequalled in any other neuromuscular disorder. Unusual patterns of onset in proximal lower limb musculature and even in the upper limbs is still associated with quadriceps relative or total sparing. The cause of the quadriceps sparing remains one of the enigmas of this condition (9). The understanding of what preserves this muscle could be of major help to future therapy.

Genetic features

To date, several dozens of mutations in the *GNE* were associated with this myopathy. A clear phenotypic-genotypic correlation has not emerged although recently in the cohort of patients from Japan heterozygous patients seem to have a more severe course (10). This observation remains to be confirmed in other countries. There are, however, several important genetic data that emerge from the various reports of patients with this recessive myopathy. While the mutations are spread along the various exons of the *GNE* gene, most of them are missense mutations. Apart from few ethnic clusters (see Epidemiology) most patients are compound heterozygotes, carrying usually two missense mutations or a combined missense and nonsense mutations. No patient with two nonsense mutations was described. Since *GNE* knockout is lethal in mice it is presumed that such condition is also nonviable in humans. It is my personal belief that *GNE* double nonsense genotype results in a completely different disorder, possibly not only limited to muscle but this remains to be proven. Another enigma in GNE myopathy is the finding of homozygous person for the common mutation in Persian Jews (with other affected members in the family) who has no myopathy at age 78 years. We are currently working to understand this unusual situation in recessive disorders, because it can provide yet another clue for the disease pathogenesis and its therapy.

Epidemiology

The largest ethnic cluster of GNE myopathy is in the community of Jews originating from Iran and neighboring Middle Eastern countries (11). They all share homozygosity to a specific *GNE* mutation (M743T using the new nomenclature- see (8)). With about 150 patients identified in Israel and about 50-70 in other countries (mainly the USA) this large cohort represent a prevalence of 1:1500 in this community with an estimated carrier rate of 1:20-30 (11). A similar number of patients but in a much larger and mixed population was recorded in Japan (under the term DMRV) but in this country the overall prevalence is smaller. Although two mutations are more common (considered to be founder mutations) numerous patients are either compound heterozygotes to those or to a combination with other mutations. This is a unique situation where a rare myopathy is more frequently reported in two countries but the epidemiology of the mutations is so different in them. Is it more awareness in the two countries from which the original descriptions emerged? The disease has been reported from numerous other countries (Asian and Europeans) and is certainly a world-wide disorder, thus recognition may not be the sole explanation to this variable epidemiology. It should be pointed out that no patient was reported from South America but again this maybe a result of lack of awareness and diagnostic methods. Estimates of the total number of patients are difficult as only few patients are currently identified in China and India, but it should still be regarded as a rare disease with several hundred to possible few thousands of patients.

Pathophysiology

GNE is encoding a bi-functional enzyme in the sialic acid synthetic pathway. As a result, one could consider it to be a 'metabolic myopathy' with reduced product (hyposialylation). However, when summarizing the biochemical investigations in this myopathy one is faced with few more enigmas. GNE activity is only partially reduced in patients ranging from 30-60% reduction. Such range of reduction is not expected to cause a phenotype in the 'classical' metabolic myopathies. Testing overall sialylation of muscle showed that it is only marginally reduced in some patients and more severe in others (12, 13). Searching for specific muscle glycoconjugate (protein or lipid) did not reveal a crucial hyposialylated metabolite that could determine the disease pathophysiology.

The HIBM research laboratory at Hadassah has spent a lot of time and effort in determining other 'unknown' functions of GNE that could be part of the pathophysiology of this myopathy (14). While some other functions

may have been identified, the process by which a *GNE* defect leads to muscle disease remains to be fully elucidated. I believe that the lack of normal GNE in muscle is contributing to the degenerative disease process in GNE myopathy, not only through the metabolic pathway.

In trying to develop a mouse model for GNE myopathy it became clear, yet again, that mice are not human. An attempt to develop a knock-in model with the common Middle Eastern mutation resulted in a different lethal disorder in early life (few days) due to a kidney disease (15). Adding yet another enigma to the story, our laboratory has managed to produce a line of mice homozygous for this mutation who do not show any kidney or muscle disease after more than 12 months of life (16). What was rescued here and whether it is similar to the protective effect in our elder subject homozygous for this mutation is currently unknown. Clearly an answer to this puzzling issue carries a promise for therapy.

One cannot ignore though the role of hyposialylation in *GNE* defects. Both the knock in model and the transgenic model for the D176V (currently termed D207V) common Japanese mutation produced in the Tokyo laboratory could be treated with sialic acid or its metabolic precursors with major improvement (15, 17). These observations set the stage for the current and future therapy trials.

Therapy

GNE myopathy has currently no proven effective therapy. However, an important human trial based on the hypothesis of reduced sialic acid as a major contributor to the myopathy pathogenesis was initiated by Ultragenyx Pharmaceutical (18). 46 patients have completed 24 weeks of treatment with oral slow release sialic acid preparation (SA-ER). Preliminary results show that the serum levels of free sialic acid doubled. Modest positive effect was seen in changing the progressive weakness course in the upper limbs with statistically significant slowing over this short period. Results of 48 weeks SA-ER treatment are pending. A phase 1 trial with a metabolic derivative (ManNAc) was also completed and a phase 2 trial is pending at the NIH- USA. Will such metabolic correction, 'bypassing' the defect, suffice to arrest the progression or restore the muscle function? At this stage there is no clear answer to this question but efforts are continued.

If indeed the lack of normal GNE in muscle is of major importance to the disease process, then gene therapy will have to be applied. Under Prof Mitrani-Rosenbaum, the laboratory at our Institute is devoting its major effort toward such therapy, using viral mediated gene delivery to muscle. A construct based on AAV8-human wild type *GNE* driven by MCK promoter has been designed. Such a construct has been injected into normal mice intravenously and yielded a persistent intramuscular human GNE mRNA. An experiment to determine whether this construct will be able to prevent or reverse the myopathy in the Japanese transgenic mouse model is underway.

Acknowledgment

The research into GNE myopathy in Jerusalem was generously and consistently supported through almost two decades by several patients' support groups and individual donations as well as by Hadassah Chapters from Southern California (especially NDF of Los Angeles). Their continuous support is a crucial factor in our success.

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MEMORIES BY A MYOLOGIST

How we developed, at the Centre/Institute for Neuromuscular Diseases, differential diagnostics of Spinal Muscle Atrophies / Amyotrophic Lateral Sclerosis (SMA/ALS) and tried to influence the development of the disease

Anica Jušić

Retired Neurology Professor

In our research, we placed the emphasis on delimiting fatal diseases against those that have some similar symptoms, but can be improved, even completely cured. More often we succeeded in differentiating the local compressive factor. In our search for early symptoms, we also found physiological, although quite unusual EMG phenomena. High amplitude neural potentials confirmed the malignant disease diagnosis. The spinal angiography discovered arterial pathology, while CT demonstrated localised hydromyelia. Amyotrophic syndromes caused by chronic led intoxications represented a separate group. Patients would recover significantly on d-penicillamine. We applied it successfully in amyotrophic syndromes with laboratory confirmed copper metabolism disorders. A very significant therapeutic effect was obtained in a patient with SMA without similar laboratory, even in recidivism. Exceptionally, we were able to achieve significant remission with corticosteroids, too. The remaining patients, differentiated as certainly fatal, represented a separate group. We tried to elaborate the special psychosocial and ethical problems connected with its outcome in "round table discussions". The first one was in 1989, at the workshop with King Engel, and the second in 1990, on the Fourth Yugoslav Symposium on Neuromuscular Diseases. In 1990, I visited Cicely Saunders and the St. Christopher's hospice in London, and in 1994 I started to organised hospice movement in Croatia.

Key words: amyotrophic syndromes, d-penicillamine, Hospice Movement in Croatia

Introduction

"The Motor Neurons Disease" (MND) – with its more frequent form Spinal Amyotrophy (SMA) and its rarer form Amyotrophic Lateral Sclerosis (ALS) – was, along with Myasthenia Gravis, the disease I was mostly occupied with. It is still an incurable, fatal disease. However, there are similar clinical forms, which have an entirely different prognosis regarding the speed of spontaneous development, in which the differential diagnostic analysis and therapeutic attempts result with some results. Moreover we have in medicine the diagnosis "*ex iuvantibus*". When we are dealing with a deadly disease, even the least likely alternative must be taken into account, and we have to help, even slightly and temporarily. In this report I put the emphasis on differential diagnostics, as precise as possible, primarily obtained by electroneurography and electromyography, the methods I menaged in the best way.

Differential diagnosis

While still in the early phases of our development of sensory neurography, we had a paper published in Lon-

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don (1). Atrophy of hand muscles with high neural potential proximally, point to MND. In our plurisegmental electrophysiological analises, besides the basic disease, we also succeeded to differentiate the local compressive syndrome, in which the neurolysis represents stopping the deterioration of at least one muscle group (2). The positivity of ischemic test of chronic tetany (3) in typical spinal amyotrophy was unusual. A colleague who had to follow up its appearence as part of his master's thesis, did not finish his work.

During the primary EMG analysis, we were looking, first of all, for differential diagnostic phenomena, in size and frequency of outburst of motor units potentials., In m. Quadriceps (4) we used to find positive " gigantic" potentials. The finding surprised us, so we followed up patients who complained of becoming tired easily. In some, getting tired stopped, but the finding remained. In the end, we found it even in entirely healthy but musculous persons.

The lack of neural potentials (5) in patients with spinal amyotrophy with a lot of fasciculations and cramps, pointed to a very bad prognosis. As a part of a master's thesis (6), the value of neurophysiological techniques in assessment of seriousness of the disease and prognosis of the outcome were worked out. During these detailed analyses, I discovered the phenomenon of variations in innervation zones (6), which I interpreted first as a pathological phenomenon. Very quickly, however, it became clear that, besides variations in motor innervation, there exist also variations in sensory innervation, and we reported on that, in a number of publications.

We dealt with hereditary forms of spinal amyotrophy and the so called pseudomyopathic histology test results (8, 9), as well as cardiological pathology in ECG (10). Unfortunately, at that time we did not have access to genetic research.

By spinal angiography, we used to single out the origins of certain form of spinal amyotrophy as a consequence spinal circulation pathology (11, 12) or, by a CT scan in a young person, hydromyelia with the monomelic amyotrophy syndrome (13).

Our joint research with the Institute for Medical Research and Work Medicine JAZU (the Yugoslav Academy of Sciences and Arts) was very importante. We analysed the patients intoxicated by led, with amyotrophic syndrome (14). With d-penicillamine (Metalcaptase) therapy and eliminating the exposition, we managed to stop the progression, even achieved recovery. The research brought me to direct exchange of experiences with Pamella Fullerton, Middlesex Hospital, London, who was at that time considered to be the leading expert in this area.

In the seventies, we repeatedly had patients with Wilson disease, which we also treated with d-penicillamine (Metalcaptase) We applied the group of differential diagnostic laboratory tests for this disease on some SMA/ALS patients as well. The positive results were published (15-17).

In 1977, in one patient with SMA (18) without copper metabolism disorder, or led intoxication, we applied d-penicillamine, because the disease progressed relatively fast. The result was satisfactory, even in recidivism. Applied on other patients with the same diagnosis, the results varied. In 1979 we (19) published correlation with concentration of D-DALK, according to which, the worst results were achieved with its highest concentrations.

We worked out some "rules of the game" in application of corticosteroides on Myasthenia Gravis, and we achieved a relatively low percentage of complications, so we attempted this therapy on SMA/ALS, too. We described the effects on three cases with more or less pronounced signs of immunological processes also in biopsy of skin or muscles. The results were of various intensity and duration (20). The best result was achieved in two young women with asymmetric atrophy of arm muscles and significant humoral signs of autoimmune process (21). We started also with specific liquor analysis (22).

Malignant forms of ALS in terminal stage

Every now and then, the patients were differentiated as suffering of malignant disease for sure. It was especially painful to follow up and listen to younger, lonely patients with bulbar symptomatology. I could not help them, and I could not keep them on the ward, either. There was a shortage of beds and pressure from those coming for comprehensive differential diagnostics.

I started looking for a solution. The first step was the scientific workshop on ALS. I organised it as a full-day event, in english, in the great hall at the Rebro hospital, with guests from Los Angeles, V. Askanas and K.W. Engel, the co-directors of the Centre for Neuromuscular Diseases of the Neurological Clinic at the Good Samaritan hospital.The round table discussion, entitled "Procedures in Terminal Stadium of Amyotrophic Lateral Sclerosis" was central. The solutions that K.W. Engel offered were for rich patients and a rich public health system.

The discussion on the same subject was repeated at the Fourth Yugoslav Symposium on Neuromuscular Diseases, 1990 in Zagreb. Title was "Medicolegal aspects of terminal stages in neuromuscular diseases". The rich discussion about the principles and attitudes — legal, as well as ethical issues was recorded, and published 1999 (22).

In 1990, in search of a better solution, I went to "The First International Symposium on MND / ALS", Solihull,

England. It was only there I was referred to Cicely Saunders and St. Christopher's Hospice. I visited London, and that visit defined my main activities during next twenty years, as a retired neurologyst.

I started the hospice movement in the Republic of Croatia by establishing the Croatian Society for Hospice/ Palliative Care of the Croatian Physicians' Society, two other citizien's associations and the Regional Hospice Centre, Zagreb, supported by the Health Ministry. I published more than a hundred articles, edited several books and brochures, founded and edited the Bulletin for Palliative Medicine/Care and so on. As the President of the Committee for Palliative Care of the Ministry of Health of Republic of Croatia, I mediated the first inclusion of the basic terms of palliative care into the Croatian health legislation. Nevertheless, we did not come closer to the English, not even Polish models. As usal , the new ideas to be accepted, must be based on the change of major mentality . And that takes time... which is so precious!

Conclusion

A physician must always try to suppress particular symptoms. It is nice when he or she manages to restore patients health at least partially. The triumph is to save the life. In every patient, we try to have, as precise differential diagnostics, as possible. That is the first step and basic for eventually successfull treatment. In some cases, we were positively surprised when we found a therapeutic way out from a tragic situation. We sometimes managed to save a life as well.

In other cases we stumbled upon an unsolvable problem. What the modern hospice movement offers, as defined by Cicely Saunders, was in such cases all that was left. It should never be said: "there is nothing else we can do for you". There is a lot that can be done. One thing we can and should always give - is the psychological support.

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NEWS FROM AROUND THE WORLD

MSM

The 12nd Congress of the Mediterranean Society of Myology will be held in Naples, Italy on May 2015, from 18th to 20th. The congress will be chaired by Prof. Giovanni Nigro, President of the Mediterranean Society of Myology. The Scientific Committee, is chaired by Prof. Giovanni Nigro, cooperated by the Board of the Society: Lefkos Middleton, London; George Serratrice (Marseille); Yeuda Shapira, Jerusalem; Luisa Politano, Naples; Ekram Abdel-Salam, Cairo; Marinos Dalakas, Athens; Fayçal Hentati, Tunis; Giovanni Meola, Milan; Gabriele Siciliano, Pisa; Eduardo Tizzano-Ferrari, Barçelona; Antonio Toscano, Messina; Janez Zidar, Ljubliana and by Vincenzo Nigro, Naples; Giuseppe Novelli, Rome; Reinhardt Rüdel, Ulm.

The symposium will be in the traditional three-days MSM format with 5 selected topics:

- Spinal Muscular Atrophies
- Nuclear Envelop Diseases
- Heart involvement in NeuroMuscular Disorders
- Infiammatory Myopathies
- Next Generation Sequency and NeuroMuscular Disorders
- New therapeutic approach in NeuroMuscular Disorders

During the General Assembly of the Society, the new Board of the Society will be elected.

Further information is available in the website of the Organizing Secretariat www.fclassevents.com

GCA

During the Gala dinner of the 12nd Congress of the Mediterranean Society of Myology to be held in Naples, Italy on May 18th –20th, the 2015 Gaetano Conte Prizes will be assigned for both basic research and clinical research.

AIM

The 15th Congress of the Italian Association of Myology will be held 8 in Naples, Italy on May 2015, from 18th to 20th, closely linked to the Congress of the Mediterranean Society of Myology. The Scientific Committee is chaired by Prof. Giovanni Nigro, cooperated by the Board of the Society: Maurizio Moggio, Milan; Antonio Toscano, Messina; Claudio Bruno, Genua; Paola Tonin, Verona; Angela Berardinelli, Pavia; Massimiliano Filosto, Brescia; Giovanni Marrosu, Cagliari; Lucia Ovidia Morandi, Milano; Elena Pegoraro, Padua; Gabriele Siciliano, Pisa and by Luisa Politano and Vincenzo Nigro, Naples.

The local Organizing Committee is chaired by Luisa Politano and Vincenzo Nigro with the cooperation of Liberato Berrino, Gerardo Nigro, Orlando Paciello, Alberto Palladino, Luigia Passamano, Raffaele Russo, Cira Solimene, Paola D'Ambrosio, Roberta Petillo, Esther Picillo, Marianna Scutifero, Antonella Taglia and Emanuela Viggiano. Further information will be available in the website of the Society www.miologia.org and of the Organizing Secretariat www.fclassevents.com

WMS

The 20th International WMS Congress will be held in Brighton, UK from 30th September to 4th October, 2015. The Congress will be held in the traditional WMS format with three selected topics. One day of the symposium will be dedicated to each of the selected topics addressing emerging discoveries in the field of:

1. Muscle metabolism in health and disease
2. Immune mediated Peripheral Nerve, Neuromuscular Junction, and Muscle Disorders
3. Advances in the treatment of Neuromuscular Disorders

Abstracts will also be welcome on advances across the neuromuscular field. Further information is available in the website of the Society www.wms2015.com

FORTHCOMING MEETINGS

2014

September 15-17

6th International Biobanking Congress. Seattle, Washington. Website: *www.healthtech.com/biobanking*

October 7-11

19th World Muscle Society Congress. Berlin, Germany. Website: *www.world musclesociety.org*

October 18-22

ASHG Annual Meeting. San Diego, CA,USA. Website: *www.ashg.org*

October 21-24

ESBB Annual Meeting. Leipzig, Germany. Website: *www.esbb.org/leipzig*

2015

May 18-20

12th Mediterranean Society of Myology Congress. Naples, Italy. Information: *giovanni.nigro@unina2.it; luisa.politano@unina2.it*

May 21-23

15th Congress of the Italian Society of Myology. Information: *giovanni.nigro@unina2.it; luisa.politano@unina2.it*

June 6-9

The European Human Genetics Conference, Glasgow, United Kingdom. Website: *www.esgh.org*

September 30th – October 4th

20thWorld Muscle Society Congress. London/Brighton, UK. Website: *http://www.worldmusclesociety.org*

October 6-10

American Society of Human Genetics ASHG Annual Meeting. Baltimore, MD, USA. Website: *www. www.ashg.org*

2016

April 3-7

The European Human Genetics Conference. Kyoto, Japan. Website: *www.esgh.org*

September 4-9

International Congress of Human Genetics 2016. Yokohama, Japan. Website: *www.esgh.org*

October 20-24

ASHG Annual Meeting. Vancouver, Canada. Website: *www.ashg.org*

October (to be announced)

21st World Muscle Society Congress. Granada, Spain. Website: *http://www.worldmusclesociety.org*

2017

October 17-21

ASHG Annual Meeting. Orlando, Florida, USA. Website: *www.ashg.org*

21st World Muscle Society Congress. London/Brighton, UK. Website: *www.world musclesociety.org*

2018

October 16-20

ASHG Annual Meeting. San Diego, CA,USA. Website: *www.ashg.org*

2019

October 22-26

ASHG Annual Meeting. Toronto, Canada. Website: *www.ashg.org*

2020

October 27-31

ASHG Annual Meeting. San Diego, CA,USA. Website: *www.ashg.org*

Retraction statement

The article published in the May 2014 issue (Acta Myologica • 2014; XXXIII: 22-33)

2013 GAETANO CONTE PRIZE LECTURE

A gating model for wildtype and R1448H Nav1.4 channels in paramyotonia

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has been withdrawn upon request of the authors.

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