Molecular Genetics and Metabolism Reports 10 (2017) 92–95

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Clinical characteristics of adult patients with inborn errors of metabolism in Spain: A review of 500 cases from university hospitals

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ARTICLE INFO

Article history:
Received 23 August 2016
Received in revised form 26 January 2017
Accepted 26 January 2017
Available online 3 February 2017

Keywords:
Inborn errors of metabolism
Adulthood
Clinical characteristics

ABSTRACT

Patients with inborn errors of metabolism (IEMs) have become an emerging and challenging group in the adult healthcare system whose needs should be known in order to implement appropriate policies and to adapt adult clinical departments. We aimed to analyze the clinical characteristics of adult patients with IEMs who attend the most important Spanish hospitals caring for these conditions. A cohort study was conducted in 500 patients, categorized by metabolic subtype according to pathophysiological classification. The most prevalent group of IEMs was amino acid disorders, with 108 (21.6%) patients diagnosed with phenylketonuria. Lysosomal storage disorders were the second group, in which 32 (6.4%) and 25 (5%) patients had Fabry disease and Gaucher disease respectively. The great clinical heterogeneity, the significant delay in diagnosis after symptom onset, the existence of some degree of physical dependence in a great number of patients, the need for a multidisciplinary and coordinated approach, and the lack of specific drug treatment are common features in this group of conditions.

1. Background

Inborn errors of metabolism (IEMs) are a group of rare disorders caused by genetic mutations that affect activator proteins or co-factors for enzymes, protein transport, carrier systems, or recognition markers [1,2]. From a pathophysiological viewpoint, IEMs may be divided into defects in the synthesis or catabolism of complex molecules, defects in intermediary metabolism, and deficiencies in energy production or utilization [3]. In consequence, they may involve multiple organs and systems.

More than seven hundred IEMs are known today, and the number is constantly increasing because of the identification of new metabolic disorders using sophisticated techniques. Although they are considered as rare diseases, their cumulative incidence is about one in every 5000 live births [4].

Prevalence of IEMs in the adult population is unknown in many countries, as are the number and types of these patients who are currently seen by different specialized physicians.

In the past, such rare conditions were considered pediatric diseases due to low survival rates of affected infants. In addition, in the past decade IEMs were mostly seen by pediatricians, even beyond adolescence [5]. However, apart from IEMs that may occur in adulthood, early treatment of patients diagnosed with neonatal screening tests, greater survival of some IEMs diagnosed in childhood, and improved treatment have resulted in an increasing number of adult patients with IEMs in recent years.

Because of this growing number of patients in adult healthcare departments and the complex clinical management they require, as well as the inadequate understanding of these conditions in adulthood, IEMs have become an emerging and challenging group of diseases in the adult healthcare system.

The Spanish central government recently appointed the referral centers for adult patients with IEMs in Spain [6]. However, in order to maximize the quality of medical care, the clinical characteristics and requirements of this group of patients should first be known to plan suitable public health policies, to adapt adult care services and

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http://dx.doi.org/10.1016/j.ymgmr.2017.01.011

healthcare providers to this new situation, and to design appropriate training schemes for physicians who wish to care for adults with IEMs.

This study was intended to report the clinical characteristics of adult patients with IEMs who attend the most important Spanish centers caring for these conditions.

Table 1
Specific diagnosis of IEM listed by their frequency.

IEM type	Number of patients	Percentage
PKU	108	21.6
Porphyria cutanea tarda	43	8.6
Porphyria – acute intermittent	34	6.8
Other mitochondrial diseases	33	6.6
Fabry	32	6.4
Gaucher	25	5
GSD V	24	4.8
MELAS	20	4
Homocystinuria	12	2.4
Pompe (GSD II)	8	1.6
Hereditary fructose intolerance	8	1.6
Hereditary coproporphyria	8	1.6
Alpha-mannosidosis	7	1.4
Morquio A (MPS IVA)	7	1.4
GSD Ia	7	1.4
Kearn Sayre disease	7	1.4
OTC	6	1.2
GSD III	6	1.2
Variegate porphyria	6	1.2
Carnitine primary deficiency	5	1
MADD	5	1
Galactosemia	5	1
Niemann-Pick A-B	4	0.8
Niemann-Pick C	4	0.8
MCAD	4	0.8
3-MCCD-A	4	0.8
Cystinuria	4	0.8
Glutaric acidemia type I	4	0.8
Alkaptonuria	3	0.6
Morquio B	3	0.6
Hunter (MPS II)	3	0.6
CPT-2	3	0.6
Tyrosinemia type I	3	0.6
Methylmalonic acidemia	3	0.6
Other porphyria	3	0.6
Aspartylglycosaminuria	2	0.4
Hurler/Scheie (MPS IH/MPS IS)	2	0.4
Sanfilippo A (MPS IIIA)	2	0.4
VLCAD	2	0.4
3-MCCD-B	2	0.4
GSD Ib	2	0.4
GSD Ixa	2	0.4
Propionic acidemia	2	0.4
Glycosylation deficiency	2	0.4
MAT I/III deficiency	2	0.4
GSD VII	2	0.4
Sanfilippo B (MPS IIIB)	1	0.2
Sanfilippo C	1	0.2
Sly (MPS VII)	1	0.2
Cystinosis	1	0.2
LCHAD/TFP	1	0.2
SSADHD	1	0.2
Dihydrolipoamide dehydrogenase deficiency (E3)	1	0.2
Citrullinemia type I	1	0.2
Methylmalonic acidemia combined with homocystinuria (cblC)	1	0.2
Methylmalonic acidemia combined with homocystinuria (cblD)	1	0.2
3-HMG	1	0.2
GLUT-1 deficiency	1	0.2
GSD type unknown	1	0.2
GSD IV	1	0.2
MTHFR	1	0.2
Lysinuric protein intolerance	1	0.2
Mucolipidosis type III	1	0.2

2. Patients and methods

We designed a cross-sectional descriptive and multicentric study. Criteria for inclusion of Spanish centers in this study were: 1) institutional commitment to care for adult patients with IEMs, 2) plan for transition of pediatric patients with IEMs to adult healthcare departments when they reach the adult age, and 3) coordinated and multidisciplinary team of physicians for adults specialized in IEMs.

Once centers were selected, all responsible and coordinator physicians from each center were contacted by e-mail and requested to submit anonymized patient data from all departments involved. Only patients with a biochemically or genetically confirmed diagnosis were included in the study.

Clinical characteristics analyzed in every adult patient (over 16 years of age) with an IEM were: age (years), sex, type of IEM, main clinical department and number of clinical departments involved in care of the patient, department of origin (defined as the department where diagnosis was made before patient was sent to medical care by the adult multidisciplinary team), age at diagnosis (classified as unknown, neonatal screening, neonatal if diagnosis during first week of life, 0–2 years, 3–10 years, 11–16 years, and >16 years), delay in diagnosis from onset of symptoms (years), Barthel index as a score of physical dependence (classified as independence if 100, low dependence if 91–99, moderate dependence if 61–90, severe dependence if 21–60, and total dependence if 0–20) [7], number of hospital admissions during the previous year (2015), and use of any orphan drug as a specific drug treatment.

The numbers of each disorder were counted and grouped into metabolic subtypes according to the classical classification. A comparative analysis was performed between the subtypes.

All data were analyzed using statistical software SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL). For quantitative variables, mean was calculated as a measure of central tendency, and standard deviation as a measure of statistical dispersion. To work out the association between two qualitative variables with two categories, a Pearson's Chi-squared test and a Fisher's exact test were used. A Student's, ANOVA or non-parametric test was used to study the association between qualitative variables (with two or more categories) and quantitative variables. A value of $p < 0.05$ was considered statistically significant.

3. Results

A total of 500 adult patients with IEMs with a mean age of 39.1 (16.2) years, 278 (55.6%) women, were enrolled into the study. All of these patients were from seven Spanish university hospitals (five of which had been appointed as national referral centers in IEMs by the Spanish central government).

The most prevalent group of IEMs was amino acid disorders (Table 1), with 108 (21.6%) patients affected of phenylketonuria. Lysosomal storage disorders were the second leading group, including 32 (6.4%) and 25 (5%) patients with Fabry disease and Gaucher disease respectively.

Two hundred and sixty-five patients (53%) were diagnosed at an age older than 16 years, and only 57 (11.4%) at newborn screening programs (Table 2). However, although the overall delay in diagnosis

Notes to Table 1:
PKU = phenylketonuria; GSD = glycogen storage disease; MELAS = mitochondrial myopathy, encephalitis, lactic acidosis and stroke-like episodes; MPS = mucopolysaccharidosis; OTC = ornithine transcarbamylase deficiency; MADD = multiple acyl-CoA-dehydrogenase deficiency; MCAD = medium-chain acyl-CoA dehydrogenase deficiency; 3-MCCD-A = 3-methylcrotonyl-CoA carboxylase A subunit deficiency; CPT-2 = carnitine palmitoyltransferase 2 deficiency; VLCAD = very-long-chain acyl-CoA dehydrogenase deficiency; 3-MCCD-B = 3-methylcrotonyl-CoA carboxylase B subunit deficiency; MATI/III = methionine adenosyl transferase I/III; LCHAD/TFP = long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and trifunctional protein deficiency; SSADHD = succinic semialdehyde dehydrogenase deficiency;3-HMG = 3-hydroxy-3-methylglutaric aciduria; GLUT-1 = glucose transporter-1; MTHFR = methylenetetrahydrofolate reductase deficiency.

Table 2
List of the variables analyzed for each metabolic subtype group.

		Intoxication syndromes	Energy metabolism disorders	Lysosomal storage disorders	*p*-Value
N of patients		260 (52%)	146 (29.2%)	94 (18.8%)	
Age		38.7(15.6)	41(17.4)	40.8(16.1)	0.376
Sex	Male	108(41.5%)	60(41.1%)	54(57.4%)	
	Female	152(58.5%)	86(58.9%)	40(42.6%)	
Clinical department of origin		Pediatric	Internal medicine	Pediatric and internal medicine	
Number of clinical departments		1.9(1)	1.9(0.9)	2.7(2)	0.004
Age at diagnosis	Unknown	5(2%)	1(0.7%)	4(4.3%)	
	Neonatal screening	57(23%)	0	0	
	Neonatal	13(5%)	4(2.7%)	0	
	0–2 years	29(11.2%)	30(20.5%)	9(9.6%)	
	3–10 years	22(8.5%)	15(10.3%)	25(26.6%)	
	11–16 years	8(3.1%)	5(3.4%)	8(8.5%)	
	>16 years	126(48.5%)	91(62.3%)	48(51.1%)	
Delay in diagnosis (years)		4,4(9.1)	16.3(23.1)	7.2(10)	0.000
Barthel Index Score	Independence (100)	204(78.5%)	87(59.6%)	56(59.6%)	
	Low dependence (91–99)	21(8.1%)	32(21.9%)	15(16%)	
	Moderated dependence (61–90)	15(5.8%)	13(8.9%)	9(9.6%)	
	Severe dependence (21–60)	20(7.7%)	13(8.9%)	7(7.4%)	
	Total dependence (0−20)	0	1(0.7%)	7(7.4%)	
Hospital admissions during 2015		0.2(0.4)	0.2(0.5)	0.4(0.7)	0.011
Use of orphan drugs		57(21.9%)	14(9.6%)	43(45.7%)	

For the quantitative variables, the mean was calculated as a measure of central tendency and standard deviation as measure of statistical dispersion. In order to study the differences between quantitative variables for each disorders, a Kruskall-Wallis non-parametric test was performed (p-value < 0.05 was considered as statistically significant).

from symptom onset was important (8.6 (16.4) years), delay in diagnosis was significantly shorter in patients attending pediatric departments (3.1 (7.3) years) than in those diagnosed in adult life (14.7 (21) years) ($p < 0.05$).

One hundred and fifty-three patients (30.6%) had some degree of physical disability. Of these, 37 (7.4%) and 8 (1.6%) patients had severe and total physical dependence respectively. Physical disability was related to nervous system, bone or muscle involvement.

The pediatric department was the referring medical department for 243 (48.6%) patients, and the internal medicine department was the main and coordinator department in charge of all these patients (100%). A mean of 2.1 (1.3) adult specialties were involved in multidisciplinary healthcare, and patients had a mean of 0.2 (0.5) hospital admissions in the previous year. Patients who needed a hospital admission were by order of frequency: patients with pulmonary or urinary infections due to important involvement of the central nervous system (3 patients with Sanfilippo syndrome, 2 patients with mitochondrial disease, 1 patients with Niemann Pick type C and 1 patient with Hunter syndrome), 1 patient with ornithine transcarbamylase deficiency because of hyperammoniemia, and 1 patient with acute porphyria because of pain.

A part from patients treated with dietary measures, vitamins or cofactors (intoxications disorders, beta oxidation disorders etc), only 114 (22.8%) patients were specifically treated for IEMs with any orphan drug. However, 45.7% of patients with lysosomal storage disorders were being treated, mostly with enzyme replacement therapy.

Table 2 shows the comparative results between IEMs classified by pathophysiological group. First of all, lysosomal storage disorders are characterized by the mean higher numbers of clinical departments involved (2.7 (2), $p < 0.05$) and by hospital admissions (0.4 (0.7), $p < 0.05$). In addition, patients from this group showed a tendency with more physical dependence. On the other hand, energy metabolism disorders are the group with the longest delay in diagnosis, 16.3 (23.1) years on average.

4. Discussion

This study is the first overall description of clinical characteristics of adult patients with IEMs, with their burden of care, in Spain, showing an expected heterogeneous group of diseases having however some common features.

Despite some methodological weaknesses regarding sample representativeness (e.g. centers excluded from our study because they did not meet the criteria may represent a large population, or data from some centers may be incomplete), prevalence of some IEMs in our study was similar to that reported in other publications in medical literature [8–11] and may portray a true burden of IEMs in adult Spanish patients.

Fifty-three percent of patients were diagnosed in adult life, in agreement with a report from the Society for the Study of IEM Adult Metabolic Physicians Group [11], and 48.6% of patients were transferred from any pediatric department, showing a suitable plan for transition of these patients to internal medicine departments. However, more extensive newborn screening in intermediary metabolism (including even >20 different conditions) resulting from new healthcare policies in Spain will change this situation in the near future.

It is also worth noting that our data showed a significant delay in diagnosis, more important when this is made in adulthood. Chronic and mild phenotypes of some IEMs, lack of awareness of these conditions by adult physicians, an inadequately organized and coordinated healthcare system not based on referral centers, poor accessibility to some diagnostic techniques, and availability of few specific biomarkers may play an important role in the current situation. Resources involved before diagnosis (human resources, biochemical and genetic analyses…) are important issues in the health assistance of this group of disorders.

In addition, physical disability, and comorbidity associated with old patients (not evaluated in this article) may increment the burden of care of these patients.

As regards specific treatment, in addition to dietary management for intermediary metabolism disorders, few conditions have a specific drug treatment. Lysosomal storage disorders are the group for which a greater variety of specific drugs are available (enzyme replacement therapies, substrate reduction drugs and chaperones) [12–15], but some of them are very expensive. In addition to the cost, most of patients treated with enzyme replacement therapy may need home therapy or need to go to hospital in order to receive intravenous infusions.

This is a group of patients with a low overall number of hospital admissions. However, 30.6% of these patients had some degree of disability, and because of the mean age of our cohort, they may become important consumers of healthcare resources. In view of the foregoing, and because of the complexity that comes with these disorders, a

multidisciplinary approach is mandatory, and coordination by internal medicine may be a valid model.

5. Conclusions

Adult patients with IEMs are a heterogeneous and growing population that requires multidisciplinary and specialty approach to provide optimal care (including new treatments and the ability to manage acute decompensation). In Spain, internal medicine departments have become the main department involved, but our study shows a significant delay in diagnosis. Although some form of treatment is available for most patients, a small number of patients can be under specific drug treatment.

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