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.