JIMD Reports
DOI 10.1007/8904_2015_435

RESEARCH REPORT

The Frequencies of Different Inborn Errors of Metabolism in Adult Metabolic Centres: Report from the SSIEM Adult Metabolic Physicians Group

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Received: 16 November 2014 / Revised: 19 March 2015 / Accepted: 23 March 2015 / Published online: 9 October 2015

Communicated by: Francois Feillet, MD, PhD

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Electronic supplementary material: The online version of this chapter (doi:10.1007/8904_2015_435) contains supplementary material, which is available to authorized users.

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Abstract *Background*: There are few centres which specialise in the care of adults with inborn errors of metabolism (IEM). To anticipate facilities and staffing needed at these centres, it is of interest to know the distribution of the different disorders.

Methods: A survey was distributed through the list-serve of the SSIEM Adult Metabolic Physicians group asking clinicians for number of patients with confirmed diagnoses, types of diagnoses and age at diagnosis.

Results: Twenty-four adult centres responded to our survey with information on 6,692 patients. Of those 6,692 patients, 510 were excluded for diagnoses not within the IEM spectrum (e.g. bone dysplasias, hemochromatosis) or for age less than 16 years, leaving 6,182 patients for final analysis. The most common diseases followed by the adult centres were phenylketonuria (20.6%), mitochondrial disorders (14%) and lysosomal storage disorders (Fabry disease (8.8%), Gaucher disease (4.2%)). Amongst the disorders that can present with acute metabolic decompensation, the urea cycle disorders, specifically ornithine transcarbamylase deficiency, were most common (2.2%), followed by glycogen storage disease type I (1.5%) and maple syrup urine disease (1.1%). Patients were frequently diagnosed as adults, particularly those with mitochondrial disease and lysosomal storage disorders.

Conclusions: A wide spectrum of IEM are followed at adult centres. Specific knowledge of these disorders is needed to provide optimal care including up-to-date

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knowledge of treatments and ability to manage acute decompensation.

Abbreviations

ACE	Angiotensin-converting enzyme
CESD	Cholesteryl ester storage disease
CPEO	Chronic progressive external ophthalmoplegia
CPT1	Carnitine palmitoyltransferase 1
CPT2	Carnitine palmitoyltransferase 2
GSDb	Glycogen storage disease
IEM	Inborn errors of metabolism
LCHAD	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
MCAD	Medium-chain acyl-CoA dehydrogenase deficiency
MELAS	Mitochondrial myopathy, encephalitis, lactic acidosis and stroke-like episodes
MERRF	Myoclonic epilepsy with ragged red fibres
MIDD	Maternally inherited diabetes and deafness
MMA	Methylmalonic aciduria
MPS	Mucopolysaccharidosis
MSUD	Maple syrup urine disease
MTHFR	Methylenetetrahydrofolate reductase deficiency
MTP	Mitochondrial trifunctional protein deficiency
NAGS	*N*-Acetyl glutamate synthase deficiency
OTC	Ornithine transcarbamylase deficiency
PKU	Phenylketonuria
SCAD	Short-chain acyl-CoA dehydrogenase deficiency
SSIEM	Society for the Study of Inborn Errors of Metabolism
TMAU	Trimethylaminuria
VLCAD	Very-long-chain acyl-CoA dehydrogenase deficiency
X-ALD	X-linked adrenoleukodystrophy

Introduction

The care of adults with inborn errors of metabolism (IEM) is an expanding subspecialty due to the improved survival of children with classical IEM, the recognition of milder forms of disease diagnosed in adulthood and late-onset disorders presenting in adulthood. Reflecting this increased interest, the Adult Metabolic Physicians working group of the Society for the Study of Inborn Errors of Metabolism (SSIEM) was formed in 2010 under the leadership of Frederic Sedel (Pitié-Salpêtrière Hospital, Paris, France) (http://www.ssiem.org/amp/welcome.asp). Clinical departments with a particular adult interest have developed in various countries, including large and well-established centres in the United Kingdom, Canada and the Netherlands and national networks such as in France the SFEIM-A – Société Française des Erreurs Innées du Métabolisme Adulte.

The prevalence of IEM in the adult population is unknown, as are the number and types of these patients being seen by metabolic physicians. How many of these patients were diagnosed and managed in childhood, as opposed to presenting with an adult-age diagnosis, is also unknown. Further information regarding the care of this patient population would thus be useful to anticipate needs for adult services, provide rationale for development of protocols and education, serve as a background for awareness amongst other physicians and identify centres with specific expertise for consultation, research and training.

Methods

All physicians who participate in the SSIEM Adult Metabolic Physicians group were contacted through e-mail in 2011 to submit anonymised patient data including diagnosis, age group at diagnosis (unknown, newborn screen, neonatal (week 1 of life), infantile (0–2 years), childhood (3–10 years), juvenile (11–16 years), adult (>16 years)) and current age. Initial data included all patients seen at each centre; hence, a number of patients with diagnoses not traditionally categorised as IEM were submitted but subsequently excluded from the analysis (excluded diagnoses list available from authors on request). Patients submitted who were younger than 16 years were also excluded. Only patients with a biochemical or genetically confirmed diagnosis were included in the analysis.

The numbers of each disorder were counted and grouped into metabolic subtypes. The median current age and age group at diagnosis for each disorder were calculated.

Updated total patient numbers were requested in 2014 to assess growth in service demand over this time. A number of French centres submitted initial limited data sets at this time which included patient numbers and diagnoses at each centre, but without current patient age or age at diagnosis.

Results

Initially 15 centres responded to our survey with data on 4,998 patients. With the addition of data from the French centres that are organised through a dedicated national society (the SFEIM-A, 1,694 patients), data was available on a total of 6,692 patients (Supplementary Table S1). Five hundred and ten patients were excluded from analysis for diagnoses not within the IEM spectrum (e.g. bone dysplasias, haemochromatosis) or for age less than 16 years (Supplementary Table S2), leaving 6,182 patients for final analysis. Two hundred and thirty-six separate diagnoses

Table 1 Submitted patient numbers from each clinical centre. Patients in the 2011 column were included in age and age at diagnosis analysis. Patients in the 2014 column were included in total patient numbers for each diagnosis

Centre location	Number of patients with confirmed metabolic diagnoses in 2011	Number of patients with confirmed metabolic diagnoses in 2014
London, United Kingdom	1,418	1,940
Vancouver, Canada	753	795 (estimated)
Rotterdam, Netherlands	551	564
Amsterdam, Netherlands	540	600
Sydney, Australia	499	583
Nijmegen, Netherlands	291	447
Auckland, New Zealand	278	358
Hamburg, Germany	132	155
Lille, France	124	126
Udine, Italy	117 (submitted in 2013)	117
Tours, France	106	100
Paris, France (Dr Mochel)	76	93
Doha, Qatar	71	95
Grenoble, France	35	43
Verona, Italy	7	12
Paris (Pitié-Salpêtrière hospital minus Dr Mochel patients), France		734
Paris (Necker Hospital), France		385
Angers, France		113
Marseille, France		98
Strasbourg, France		97
Reims, France		92
Bordeaux, France		63
Nancy, France		53
Dijon, France		49
Caen, France		10

Table 2 Thirty most frequent diagnoses and ages, including French patients added in 2014 in the total number, but not in the analysis of median age and age range which were not available for French patients. Four thousand eight hundred and seventy-one patients are included in this group of thirty diagnoses

Disorder	Number	Median age	Age range	Percentage of total patients
PKU	1,274	34	16–83	20.6
Fabry	544	45	19–82	8.8
Mitochondrial – CPEO	263	59.5	18–85	4.3
Gaucher	261	48	17–90	4.2
Mitochondrial	253	49	19–84	4.1
Homocystinuria	244	35	16–84	3.9
X-ALD	237	47	16–82	3.8
GSD II	220	55	18–83	3.6
Galactosaemia	165	29	18–64	2.7
Mitochondrial – MELAS	159	42	19–71	2.6
TMAU	146	44	20–79	2.4
GSD V	145	51.5	20–80	2.3
OTC	136	33	20–79	2.2
Hypophosphataemic rickets	87	36	18–79	1.4
MSUD	69	27	16–52	1.1
GSD III	60	38	21–67	1.0
GSD Ia	59	29	20–59	1.0
Niemann-Pick C	56	35	18–59	0.9
Mitochondrial – POLG	50	50	20–67	0.8
MCAD	48	23	18–49	0.8
MMA	48	25	19–44	0.8
Niemann-Pick B	45	39	0–60	0.7
MPS I	45	33.5	18–59	0.7
CPT2 deficiency	43	36	20–77	0.7
Carnitine transporter deficiency	40	31	17–61	0.6
Mitochondrial – MERRF	36	42	22–66	0.6
Porphyria	36	53	18–82	0.6
Porphyria – acute intermittent	35	51	25–81	0.6
MPS IV	35	35	19–59	0.6
Alkaptonuria	32	52	20–86	0.5

were documented, although in some disorders there was the potential for diagnostic overlap or ambiguity; for example, 12 patients were labelled with hyperhomocystinaemia, 244 were labelled with homocystinuria and a single patient was labelled as homocystinuria and MTHFR deficiency. The number of patients submitted from each centre varied from 7 to 1,418 (Table 1).

As expected, the most frequent disorder was phenylketonuria (PKU), representing 1,274 (20.6%) cases. The median age of PKU patients was 34 years, and diagnosis was predominantly via a newborn screening programme (413 of 499 (82.8%) patients with age of diagnosis data). Forty-six PKU patients were diagnosed as juveniles (13) or adults (33). The next most common diagnosis was Fabry disease (544 patients, 8.8%), followed by CPEO (263 patients, 4.3%) and Gaucher disease (261 patients, 4.2%). The 30 most common diagnoses are listed in Table 2.

Table 3 Number of patients grouped by disease categories, as defined in Saudubray et al. (2012). The urea cycle disorders are counted amongst the aminoacidopathies. The patient numbers for the lysosomal storage disorders do not include the mucopolysaccharidoses or peroxisomal disorders as they are counted in separate disease categories. A more detailed table is available in Supplementary Table S4

Disorder type	Number
Aminoacidopathy	2,061
Lysosomal	1,220
Mitochondrial	867
Peroxisomal	258
Glycogen storage	370
Fatty acid oxidation	221
Mucopolysaccharidoses	141
Porphyrias	101
Vitamin and cofactor	93

Disorders of amino acid metabolism (2,061 patients) were the most frequent when data were analysed according to types of disease (Table 3). Lysosomal storage disorders were the next most prevalent (1,220 patients) and were predominately Fabry (544), Gaucher (261) and Pompe (220) diseases. The broad group of mitochondrial disorders was strongly represented with 867 patients. Within these 867 patients, 253 did not have their phenotype described further, 162 had MELAS, 263 had CPEO, 23 had MIDD, 19 had Kearns-Sayre and other mitochondrial phenotypes were present to lesser degrees. The age group at onset was documented for 377 of these mitochondrial patients, and of these 317 were diagnosed in adulthood. Out of 258 patients with peroxisomal disorders, 237 had X-ALD. Patient numbers for each condition within the urea cycle disorders (201), disorders of fatty acid oxidation (225), mucopolysaccharidoses (141) and glycogen storage diseases (370, excluding Pompe) are shown in Table 4.

Data for the age group at diagnosis was available for 2,022 patients, all of whom were submitted in the initial group of cases (Table 5). Many were diagnosed as adults (925 patients, 45.7%), with the known remainder predominantly diagnosed via newborn screening (455 patients, 22.5%), although this number is largely patients with PKU (413 patients). Mitochondrial diseases accounted for the largest number of adult diagnoses (317 patients) followed by Fabry disease (137 patients) and then homocystinuria (45 patients).

Of the conditions that may present with fatal decompensations at any time of life, 29 patients with OTC deficiency were diagnosed as adults (age at diagnosis was available for 46 patients); however, patient gender was not

Table 4 Patient numbers for each diagnosis in the urea cycle disorders, fatty acid oxidation disorders, mucopolysaccharidoses, glycogen storage diseases (excluding GSD II) and total lysosomal disorders. Some disorders are divided into separate categories, depending on the amount of diagnostic detail submitted by the clinician; e.g. 11 patients with citrullinaemia may be type I or type II, but were not specified in the data submitted. Patient numbers include the French data from 2014

Disorder	Number of patients
Urea cycle	
OTC deficiency	136
Argininosuccinic aciduria	31
Citrullinaemia	11
Arginase deficiency	8
CPS	7
NAGS	4
Citrullinaemia type I	2
Fatty acid oxidation	
MCAD	48
CPT2 deficiency	43
Carnitine transporter deficiency	40
VLCAD	32
LCHAD	19
CPT1 deficiency	15
GA2	13
SCAD	7
MTP deficiency	4
Mucopolysaccharidoses	
MPS I	45
MPS IV	35
MPS III	20
MPS VI	17
MPS II	16
MPS IIIA	5
MPS IIIB	2
MPS VII	1
Glycogen storage diseases	
GSD V	145
GSD III	60
GSD Ia	59
GSD	25
GSD Ib	24
GSD IX	14
GSD IIIa	12
GSD VI	9
GSD IIIb	5
GSD IV	4
GSD VII	4
GSD IIId	1
GSD VIII	1

(continued)

Table 4 (continued)

Disorder	Number of patients
Total lysosomal	
Sphingolipidoses	965
Peroxisomal disorders	258
Pompe disease	220
Mucopolysaccharidoses	141
Oligosaccharidoses	30
Cystinosis	28
CESD	10
Ceroid lipofuscinoses	7

Table 5 Patient age group at diagnosis. French data submitted in 2014 was not included in this analysis

Age group at diagnosis	Number of patients	% of total with data (2022)
Unknown	2,466	n/a
Adult	925	45.7
Newborn screen	455	22.5
Juvenile	334	16.5
Infantile	255	12.6
Neonatal	44	2.2
Childhood	9	0.4

requested and so the proportion of these that are female is not known. Where age at diagnosis was submitted, all of the acute porphyrias were diagnosed in adulthood. Others with potentially unstable conditions were generally diagnosed in infancy or early childhood, although five patients with MSUD and two patients with MMA were diagnosed as juveniles.

Conditions where some form of treatment is available, whether dietary, enzyme replacement or other pharmacological means, were represented by 4,649 (75%) patients (Supplementary Table S3). Disorders in which bone marrow transplant may be offered, such as metachromatic leukodystrophy, were not included in this "treatable" cohort, although we appreciate that an argument could be made to include them.

Discussion

This paper is the first analysis of patient data from a group of clinical centres with a dedicated interest in adult patients with IEM. It demonstrates the wide spectrum of disease seen and is striking for the large numbers of patients that were diagnosed as adults and the growth in demand for these services in a relatively short period of time. We recognise that this data set is limited due to its ascertainment biases and as such does not represent a true picture of the burden of IEM in adults; however, it does make apparent that IEM in adults is far from restricted to PKU, mitochondrial disease and the lysosomal disorders.

Disease Frequencies

Newborn screening for PKU was instituted in many countries in the late 1960s and early 1970s, and this in combination with its relatively high prevalence (1 in 10,000 in Australia) makes it unsurprising that it is the most common disorder in this cohort. All centres saw patients with PKU, although the proportion varied widely. The frequency of mitochondrial patients is perhaps lower than expected as various studies have indicated that around 1 in 7,000 adults have a mitochondrial disorder (Schaefer et al. 2008). Given this prevalence we might have expected to see similar numbers of mitochondrial and PKU patients, however various factors likely account for this discrepancy – many patients will be seen by neurologists or other specialty facilities (such as that at Newcastle upon Tyne in the United Kingdom), as well as an incomplete diagnostic rate in adults. As our study only included patients with confirmed diagnoses, patients with "possible" or "probable" mitochondrial disease (a group which is expected to be significantly larger than the group of patients with a confirmed molecular diagnosis of mitochondrial disease) are not included in our data.

This data set is a "snapshot" of the patients that adult metabolic physicians care for and is a useful tool for service planning and building an awareness of the significant burden of adult metabolic disease. It is not however a comprehensive description of the epidemiology of these patients. For example, the number of patients with MCAD (48) is less than expected from prevalence data (1 in 4,900 (Sander et al. 2001) to 1 in 25,000 (Carpenter et al. 2001)). Fifty percent of MCAD patients remain undetected in the absence of screening (Wilcken et al. 2007), with the risk of death in this group about 5–7% in the first 6 years and very low thereafter (Wilcken 2010), although there are case reports of previously undiagnosed adults dying (Lang 2009). Thus, a good proportion of unscreened MCAD patients would be expected to reach adulthood undiagnosed. Some diagnosed MCAD patients would not be transitioned to adult services as a result of being lost to follow-up, and some may have been transitioned to alternative services such as adult endocrinology. The sample is also biased by the relative expertise and historical interests of each centre; for example, many of the Pompe patients come from the Rotterdam centre (106 of the 220

patients), and other centres see fewer patients. Similarly, 120 of the 146 TMAU patients and 70 of the 87 hypophosphataemic rickets were seen at the Charles Dent Metabolic Unit in London. Data was submitted from the European, Canadian and Asia-Pacific centres only; hence, our data may be different from patient populations seen at centres in the United States and elsewhere.

Age Group at Diagnosis

Age group at diagnosis was available for approximately 2,000 patients and showed that more than 40% were diagnosed in adulthood. This demonstrates the importance of adult physicians being aware of metabolic diseases as a diagnostic possibility. Mitochondrial disorders may present with any combination of organ dysfunctions and at any stage of life and may therefore be seen by nearly any type of specialist physician, although neurologists are perhaps the most likely to be involved given the strong representation of MELAS and CPEO patients in this group. Fabry disease was also diagnosed almost exclusively in adulthood (137 of 147 patients with age at diagnosis data), and given its prevalence in hypertrophic cardiomyopathy, stroke and end-stage renal failure cohorts (Rolfs et al. 2005; Gaspar et al. 2010; Palecek et al. 2014), its importance to adult physicians is noteworthy. It is, however, important to realise that a diagnosis of Fabry disease can be difficult. The availability of enzyme replacement therapy since 2,000 has triggered screening for this disorder, showing a steep rise in prevalence of genetic and enzymatic diagnoses. Traditionally, the prevalence of classical Fabry disease is estimated to be around 1 in 40,000 (Desnick et al. 2007), but this has changed to almost 1 in 3,000 in newborn screening programmes (Spada et al. 2006). Since most mutations in the *GLA* gene are private (Garman 2007), the pathogenicity of newly identified variants is not always clear. Many individuals picked up during screening do not fulfil the classic criteria, and hence, there may be an overestimation of cases (van der Tol et al. 2014).

Increasing Service Demands

Since these data was originally collected in 2011, each of these clinical centres has experienced growth in patient numbers (Table 1). The numbers listed in Table 1 include only those patients with confirmed metabolic diagnoses. Similar to paediatric services, many of the adult centres follow a large number of patients who are either in the process of undergoing diagnostic evaluation or in whom the results of such evaluation are inconclusive (such as patients with "possible" or "probable" mitochondrial disease) and these patients need also to be considered in the human resource requirements of adult clinics. The proportion of patients requiring ongoing follow-up but in whom a confirmed diagnosis had not yet been reached varied from 15% to 50% in those centres where it was known – these patients were not included in our analysis. Increasing awareness of adult metabolic services is responsible in part, as is ongoing transition of paediatric patients.

We are aware that there is a sizable population of paediatric metabolic patients who have been diagnosed by tandem mass spectrometry newborn screening. In New South Wales, Australia (population approximately 7.2 million), around twenty-five new patients with IEM are diagnosed each year and the oldest of these patients is 15 years. This approaching cohort of transitioning paediatric patients needs to be considered in future service planning.

There are an increasing number of previously rare metabolic defects, like carnitine transporter deficiency, being diagnosed in adult women when their infants have positive results on expanded newborn screening panels (Vijay et al. 2006). Although it is likely that many of these women will be asymptomatic for life, there are case reports suggesting that this disorder in adult women may be associated with adverse health consequences such as pregnancy loss (El-Hattab et al. 2010) and cardiomyopathy (Lee et al. 2010). These patients will need to be followed to clarify the long-term health consequences of these disorders, and thus, the expanded newborn screening panels adopted in many countries around the world have immediate resource implications for adult centres.

The majority of patients described in this cohort potentially have some form of treatment available to them; although in some localities ultra-expensive therapies like enzyme replacement may be unavailable. Given that many adult patients with IEM can be offered therapy, it would seem sensible that treatment be guided by physicians with expertise in these rare disorders. It should also not be forgotten that amongst these diseases are those that, even though extremely rare, can be well treated if diagnosed early, such as tyrosinaemia type II (5 patients) and cobalamin E deficiency (1 patient).

These data are also helpful in designing training programmes for physicians who wish to care for adults with inborn errors of metabolism. Training programmes need to include exposure to acute metabolic medicine, such as patients with decompensated urea cycle defects. However, such physicians also need expertise in adult neurology, allowing for the evaluation of myopathies, leukodystrophies, ataxic disorders and progressive cognitive impairment, and experience in general internal medicine to allow them to care for patients with lysosomal storage diseases (who require a wide range of common adult therapies such as ACE inhibitors, statins, antiplatelet agents and therapies for osteoporosis).

Conclusion

Our data show the wide range of paediatric and adult-onset IEM seen in these clinical centres. The increase in adult patient numbers is important to recognise, as it indicates an increasing need for specialty services to be available to these patients. Specialised knowledge of these disorders is needed to provide optimal care, including up-to-date monitoring and treatments and the ability to manage acute decompensation. We consider that care for this growing adult IEM patient population is important, as the vast majority of these people participate fully in society and the consequences of failed care can be catastrophic. This study also demonstrates useful collaboration between members of the SSIEM Adult Metabolic Physicians group and provides information that will hopefully pave the way for future cohort studies and clinical trials in adults with these rare disorders.

Acknowledgement The authors would like to dedicate this work to the memory of Dr Philip Lee, a pioneer in the care of adult patients with IEM.

Compliance with Ethics Guidelines

Conflict of Interest

Sandra Sirrs, Carla Hollak, Martin Merkel, Annalisa Sechi, Emma Glamuzina, Miriam Janssen, Robin Lachmann, Janneke Langendonk, Mauro Scarpelli, Tawfeg Ben Omran, Fanny Mochel, members of the SFEIM-A Study Group and Michel Tchan declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was not obtained for each participant in this study.

Author Contributions

Sandra Sirrs, Carla Hollak and Martin Merkel planned the study and reviewed the draft article.

Annalisa Sechi, Emma Glamuzina, Miriam Janssen, Robin Lachmann, Janneke Langendonk, Mauro Scarpelli, Tawfeg Ben Omran, Fanny Mochel and members of the SFIEM-A Study Group submitted patient data and reviewed the draft article.

Michel Tchan planned the study, analysed the data and wrote the draft article.

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