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ORIGINAL RESEARCH

An Exploration of Genetic Test Utilization, Genetic Counseling, and Consanguinity within the Inborn Errors of Metabolism Collaborative (IBEMC)

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Abstract The Inborn Errors of Metabolism Collaborative (IBEMC) includes clinicians from 29 institutions collecting data to enhance understanding of metabolic conditions diagnosable by newborn screening. Data collected includes hospitalizations, test results, services, and long-term outcomes. Through evaluation of this data, we sought to determine how frequently genetic counseling had been provided, how often genetic testing was performed, and also determine the consanguinity rate in this population. A data query was performed with the following elements abstracted/analyzed: current age, metabolic condition, whether genetic counseling was provided (and by whom), whether genetic testing was performed, and consanguinity. Genetic counseling was provided to families 95.8% of the time and in 68.6% of cases by a genetic counselor. Genetic testing was performed on 68.0% of subjects, with usage highest for fatty-acid-oxidation disorders (85.1%). The rate of consanguinity was 2.38%. Within this large national collaborative there is a high frequency of genetic counseling, though in one-third of cases a genetic counselor has not been involved. Additionally, while metabolic conditions have historically been diagnosed biochemically, there is currently high utilization of molecular testing suggesting DNA testing is being incorporated into diagnostic assessments - especially for fatty-acid-oxidation disorders where the underlying genotype helps predict clinical presentation.

Keywords Newborn screening · Inborn errors of metabolism · Genetic counseling · Genetic testing · Consanguinity

Introduction

The Inborn Errors of Metabolism Collaborative (IBEMC) is a group of clinicians from 29 member institutions across the United States, who have joined together to improve the understanding of metabolic conditions identified by newborn screening (NBS). The ultimate goal of the IBEMC is to improve long-term outcomes for individuals identified with NBS-screened conditions. Member institutions collect and enter data into a database regarding these individually rare but collectively common conditions. Examples of data elements collected include hospitalizations, lab test results, provision of genetic counseling, clinic visits, and long term outcomes. Through evaluation of data contributed to this large national collaborative, we sought to determine how genetic services were being utilized in this patient population. We examined how frequently genetic counseling had been provided to families with metabolic genetic conditions identified by newborn screening, and how often genetic testing had been performed either to confirm a diagnosis or for other purposes. Secondarily, we wanted to determine whether trends in genetic testing following newborn screening have changed over

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time and also to determine the rate of consanguinity in this population as compared to historic data previously reported.

Methods

The Inborn Errors of Metabolism Information System (IBEM-IS) was established in 2007 by the IBEMC to allow for the capture and management of longitudinal data from individuals identified with an inborn error of metabolism (Berry et al. 2010). Data contained in the IBEM-IS are collected and managed using REDCap electronic data capture tools hosted at Michigan Public Health Institute (MPHI) (Harris et al. 2009). Individuals in the dataset include those who have metabolic disorders identifiable by newborn screening, i.e. both individuals who were clinically diagnosed with an inherited metabolic disorder prior to the availability of newborn screening for that condition, and those who were detected through NBS once it was available. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies. Prospective informed consent is obtained before initiating study participation and data collection. At each member institution, after a subject is enrolled and given a unique patient identifying number, an initial enrollment survey is completed through researcher abstraction of information from clinical documents produced surrounding the clinical visit, followed by ongoing interval surveys completed in the same fashion at subsequent clinical encounters (Berry et al. 2010).

For this retrospective study, a data query from the IBEM-IS was performed for 1585 subjects consented and enrolled prior to April 28, 2014. Subjects were removed from further analysis if the metabolic condition for the subject was missing from the dataset (9 individuals, one of whom had genetic counseling), or if the total number of responses to questions relating to genetic counseling or genetic testing for a specific metabolic condition numbered less than four. For this analysis, 8 conditions (3-methylglutaconic aciduria, type 1, arginase deficiency, tetrahydrobiopterin deficiency, carnitine/acylcarnitine translocase deficiency, holocarboxylase synthetase deficiency, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, malonic academia and 2-methylbutyryl-CoA dehydrogenase deficiency), involving 23 subjects, were removed from analysis for this reason. 1553 subjects (97.9%) remained for evaluation. The following elements were abstracted for analysis:

- Current Age
- Metabolic Condition
- Was genetic counseling provided?
- If genetic counseling provided, by whom?
- Was molecular genetic testing performed?
- Reported Parental Consanguinity

Results

Among the 1553 subjects, 48% were female, 52% were male. At the time of the data extraction on April 28, 2014, the average age was 10.8 years and the median age was 7.8 years, with the youngest being two months old and the oldest being 61 years old.

In this dataset, 1123 subjects had yes/no values entered for the question "Has the family received genetic counseling?" Of these, 1076 (95.8%) reported genetic counseling had been provided (Table 1, further sorted by diagnostic category). The initial data set was expanded after data collection was initiated and a question not included in the original data elements asks *who* provided the genetic counseling, with data available for 210 subjects, representing 20% of the total data set. In 144 (68.6%) cases, as reported by data abstraction of medical record documentation of genetic counseling, a genetic counselor was involved in the counseling while in 66 cases (31.4%) the counseling was provided by a physician, nurse practitioner, dietician, or medical student. Thus, while the majority of families are receiving genetic counseling, in about 1/3 of cases a genetic counselor did not provide the service.

Genetic test utilization was also assessed. Regarding genetic testing for metabolic conditions, 691 (68.0%) of 1017 subjects who had yes/no answers to the genetic testing question had undergone DNA testing, with usage especially high for fatty acid oxidation disorders (Table 1). Genetic testing was performed greater than 90% of the time for three conditions: carnitine palmitoyltransferase I (*CPT1*) deficiency, very long-chain acyl-CoA dehydrogenase (*VLCAD*) deficiency, and long-chain 3-hydroxyacyl-CoA dehydrogenase (*LCHAD*) deficiency. Genetic testing was least likely to be performed for the diagnoses of 3-methylcrotonyl-CoA carboxylase deficiency (*3-MCC*), tyrosinemia, and hyperphenylalaninemia – PKU (Table 1).

The average ages of individuals in the database who have had genetic testing is younger than those who have not (8.70 years vs. 12.10 years, $p < 0.001$). The average age of enrolled subjects/families who have received genetic counseling is older than the average age of people enrolled who have never received genetic counseling (9.96 years vs. 6.77 years, $p = 0.003$) (Table 2). It should be noted that the dataset does not include the ages at which individuals/families received genetic testing or genetic counseling, only the current ages at the time of this data query.

Finally, as most metabolic conditions diagnosable by newborn screening are autosomal recessive, the data set includes basic information on consanguinity. In the dataset, consanguinity was reported in 26 of 1093 cases (2.38%). Degree of relationship was not ascertained.

Table 1 Summary of genetic counseling and testing by disorder category and disorder

Disorder Class	Disorder Name	# Responses to question of genetic counseling	# of genetic counseling performed	Rate of genetic counseling performed	# Responses to question of genetic testing	# of genetic testing performed	Rate of genetic testing performed
Fatty Acid Oxidation	Class Total	424	409	96.5%	395	336	85.1%
	CPT-1	4	4	100.0%	4	4	100.0%
	LCHAD	16	15	93.8%	15	14	93.3%
	VLCAD	65	64	98.5%	60	55	91.7%
	CPT-2	11	10	90.9%	8	7	87.5%
	SCAD	39	38	97.4%	37	32	86.5%
	MCADD	247	238	96.4%	234	200	85.5%
	GA-II	7	7	100.0%	5	4	80.0%
	TFPD	10	10	100.0%	10	8	80.0%
	Carnitine uptake disorder	25	23	92.0%	22	12	54.6%
Galactosemia		125	123	98.4%	108	79	73.1%
Biotinidase		148	140	94.6%	142	88	62.0%
Organic Acid Conditions	Class Total	163	159	97.5%	150	89	59.3%
	MMA	11	11	100.0%	11	9	81.8%
	IVA	18	17	94.4%	14	11	78.6%
	BKT Deficiency	4	4	100.0%	4	3	75.0%
	MMA + Hcy	14	13	92.9%	12	9	75.0%
	GA-1	28	27	96.4%	28	19	67.9%
	2M3HBA	8	8	100.0%	6	4	66.7%
	IBD	6	6	100.0%	6	4	66.7%
	PA	45	44	97.8%	40	20	50.0%
	3-MCC deficiency	29	29	100.0%	29	10	34.5%
Amino Acid Disorders	Class Total	263	245	93.2%	222	99	44.6%
	Citrullinemia Type 1	9	9	100.0%	7	6	85.7%
	HCY	11	11	100.0%	11	6	54.6%
	MSUD	32	32	100.0%	29	15	51.7%
	ASA	14	14	100.0%	15	7	46.7%
	Tyrosinemia	9	9	100.0%	7	3	42.9%
	Hyperphenylalaninemia-PKU	188	170	90.4%	153	62	40.5%
Grand Total		1123	1076	95.8%	1017	691	67.9%

2M3HBA 2-Methyl-3-hydroxybutyric academia; *3-MCC* 3-methylcrotonyl-CoA carboxylase deficiency; *ASA* Argininosuccinic aciduria; Biotinidase = Biotinidase deficiency; *BKT* ß-Ketothiolase Deficiency; Carnitine Uptake Dis. = Carnitine Uptake Disorder; Citrulinemia = Citrulinemia type 1; *CPT-1* Carnitine palmitoyltransferase I, *CPT-2* Carnitine palmitoyltransferase II; *GA-1* Glutaric acidemia type 1; *GA-2* Glutaric acidemia type 2; Galactosemia = classical galactosemia; *HCY* Homcystinuria; *IBD* Isobutyryl-coenzyme A dehydrogenase deficiency; IVA = Isovaleric academia; *LCHAD* Long-chain 3-hydroxyacyl-CoA dehydrogenase; *MCAD* Medium-chain acyl-CoA dehydrogenase; *MMA* Methylmalonic academia; *MMA + HCY* Methylmalonic acidemia with homocystinuria (Cbl C,D); *MSUD* Maple syrup urine disease; Hyperphenylalaninemia = classic PKU + benign hyperphenylalaninemia; Propionic Acidemia = Propionic Acidemia; *SCAD* Short-chain acyl-coA dehydrogenase; Tyrosinemia = Tyrosinemia; *VLCAD* Very long-chain acyl-CoA dehydrogenase deficiency; *TFP* Trifunctional proteindeficiency

Table 2 T-tests of average age at time of data extraction

	N	Mean age	Std. deviation	Std. Error mean	Mean difference	Sig. (2-tailed)	Std. error difference
Genetic counseling							
NO	47	6.77	6.80	0.99	−3.18	.003	1.33
YES	1071	9.96	9.03	0.28			1.03
Genetic Testing							
NO	324	12.10	10.71	0.60	3.41	.000	0.60
YES	688	8.70	7.85	0.30			0.67

Discussion

Based on data collected from 29 medical centers participating in the NIH-funded Inborn Errors of Metabolism Collaborative (IBEMC), genetic counseling has been provided to the vast majority of the patients in the registry (95.8%) and does not vary greatly by condition (Table 1). Genetic counseling is essential for family understanding, knowledge, satisfaction, and compliance (Bjorvatn et al. 2007; Rutherford et al. 2014). Similar rates of genetic counseling were found by Livingston et al. 2011 when they studied rates of genetic counseling for metabolic disorders tracked by newborn screening programs in Minnesota, Missouri, and Rhode Island (Livingston et al. 2011). This is in stark contrast to recent data reported from the ABOUT study where this group investigated the rate of genetic counseling for women undergoing *BRCA* genetic testing, and found that only 36.8% of received genetic counseling (Armstrong et al. 2015). Evidence suggests that genetic counseling is provided more frequently in clinics providing care for inherited metabolic conditions than in other fields of genetics (Hinton et al. 2014; Livingston et al. 2011). This may be because patients with rare inherited metabolic disorders are seen regularly by specialist providers for routine follow-up, often at academic medical centers, while other genetic testing (e.g. *BRCA* testing) is provided in a broader variety of settings.

Genetic counseling in the IBEMC has most often been provided by a genetic counselor, approximately two-thirds of the time. When not provided by trained genetic counselors, genetic counseling has not only been provided by physicians and nurse practitioners, but also by dieticians and medical students. Most IBEMC member institutions have access to genetic counselors at their institution, though not all report that they have immediate access within their Inborn Errors of Metabolism clinic. Thus access to counseling services may be an issue for some of these patients. Given the complexity of many conditions identified by NBS, continued NBS expansion, and increased utilization of genetic testing for metabolic conditions, we encourage all metabolic clinics to have genetic counselors as members of the multidisciplinary care team. Counselors in this capacity are invaluable to assist the family in understanding genetic information and its implications, as well as addressing the impact on the family, allowing other team members the time to focus on medical management and dietary issues. This need will only grow as molecular testing moves to a position as a primary screening technique as is being explored now through grants funded by the NICHD/NHGRI newborn sequencing program (NHGRI 2016).

In our study, when comparing categories of metabolic conditions identified by newborn screening, we found that fatty acid oxidation disorders have the highest rates of utilization of genetic testing while amino acid disorders have the lowest. It is worthwhile to note that fatty acid disorders such as LCHAD, VLCAD, and MCAD deficiencies are examples of metabolic conditions for which genotype/phenotype information is available that suggests a correlation between underlying genotype and anticipated clinical presentation and clinical course. In particular, molecular genetic testing is needed in order to discriminate between isolated LCHAD and mitochondrial trifunctional protein (an enzyme complex in the inner mitochondrial membrane) deficiencies. These disorders overlap significantly clinically, but mutations in different subunits affect the three enzymatic activities, long-chain 3-hydroxyacyl-CoA dehydrogenase, 2-enoyl hydratase and 3-keto acyl-CoA thiolase, differently. The common c.1528 G > C mutation in *HADHA* leads to isolated LCHAD deficiency while mutations in *HADHB* result in trifunctional protein deficiency, as do other mutations in *HADHA* (Choi et al. 2007). Thus, given the predictive and applicable nature of the molecular findings, it is not surprising that these conditions are among those with the highest utilization of genetic testing. Additional conditions for which molecular testing is performed routinely in clinical practice may be added to this list as our understanding of genotype/phenotype correlations advances.

Younger individuals with inborn errors of metabolism are more likely to have had molecular genetic testing performed than older individuals. The average age of patients in our study who received genetic testing is 8.70 years, which is 3.4 years younger than those who had not received genetic testing. This may reflect a recent increase in use of genetic testing following newborn screening, especially for conditions

in which testing may assist with diagnostic confirmation. This trend will likely continue given the potential for molecular genetic testing to become an integral part of the newborn screening diagnostic workup, whereas in decades past the diagnostic workup relied more heavily on biochemical testing given limited availability and clinical applicability of molecular testing.

Several studies in the United States and Canada have described rates of cousin marriages from a low of 0.076% to as much as 1.3–1.5% (Bennett et al. 2002; De Braekeleer and Ross 1991; Lebel 1983), which is lower than that observed in other world cultures where some degree of consanguinity is more common (Hamamy et al. 2011). Within the IBEM-IS, the rate of consanguinity is likely highest in isolated populations at increased risk for recessive conditions due to the presence of founder mutations, including several identifiable by NBS. To our knowledge, the degree to which consanguinity contributes to autosomal recessive metabolic genetic disease in the United States overall has not been well studied. With a consanguinity rate of 2.38% for all metabolic conditions diagnosable by newborn screening in the IBEM-IS, we are able to provide an additional benchmark for current and future comparisons within a population ascertained by presence of recessive conditions. For comparison, previous studies from other countries have reported consanguinity rates of 5.2% for biotinidase deficiency in Brazil, 74.2% for organic acidemias in Syria, 84% for homocystinuria in Qatar, and 86.9% for 46 different metabolic disorders in Libya (AlObaidy 2013; Borsatto et al. 2014; El Bashir et al. 2015; Shennar et al. 2015). Given that not all families enrolled in the IBEM-IS may be comfortable reporting consanguinity to care providers, it is possible that the 2.38% figure found in our study is an underestimate.

In summary, within the IBEMC there is very high frequency of genetic counseling for metabolic conditions, though in one-third of cases a genetic counselor was not the primary counseling professional. Additionally, while metabolic conditions have historically been diagnosed by biochemical methods, there is now high utilization of DNA testing for these conditions across this country, suggesting this is being incorporated into diagnostic assessments. Finally, the rate of consanguinity for conditions diagnosable by newborn screening is between 2%–3%.

Given the high rates of genetic counseling and DNA testing for inborn errors of metabolism found in our study, we propose that Metabolic Genetics & Newborn Screening is an area of genetic medicine which may be ideal for future evidence-based studies, both by member institutions of the IBEMC and others, particularly on the value of genetic counseling (McAllister et al. 2011). For this area of genetic medicine, the identifiable metabolic pathway, the apparently straightforward autosomal recessive inheritance pattern, the opportunity to explain recurrence risk, and an often effective treatment approach make this an ideal field to explore the effectiveness of genetic counseling and education to determine if an extrinsic difference is being made toward long term outcomes for individuals identified with genetic diagnoses and their families (McAllister and Dearing 2015; McAllister et al. 2011). Analysis of patient understanding, satisfaction, decision-making and compliance in centers with genetic counselors integrated into the system as compared to those where genetic counselors are not available, for example, might yield support for better approached to patient management.

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Compliance with Ethical Standards

Conflict of Interest Quinn P. Stein, Cate Walsh Vockley, Mathew J. Edick, Shaohui Zhai, Sally J. Hiner, Rebecca S. Loman, Laura Davis-Keppen, Taylor A. Zuck, Cynthia A. Cameron, and Susan A. Berry declare that they have no conflict of interest.

Human Studies and Informed Consent 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 obtained from all patients for being included in the study.

Animal Studies No animal studies were carried out by the authors for this Article.

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