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RESEARCH REPORT

Barriers to Transplantation in Adults with Inborn Errors of Metabolism

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Abstract *Background:* Transplantation in patients with inborn errors of metabolism (IEM) may be used as rescue therapy for acute decompensation, organ replacement, or disease-modifying therapy. We sought to quantify the use of transplantation in adults with IEM.

Methods: A 10-question online survey was sent through the email list of adult IEM physicians maintained by the Society for the Study of Inborn Errors of Metabolism and posted on the website of the Society of Inherited Metabolic Diseases.

Results: Thirteen centers from five continents responded. These centers, ranging in size from <50 adult patients (three centers) to >500 (two centers), reported 57 adult patients who had undergone transplantation. 29/57 (51 %) came from the two largest centers and 27/57(47 %) were renal transplants for Fabry disease (FD). Only seven transplants were identified as being done for acute decompensation. Eight of thirteen centers had not had patients with IEM passed over on the transplant list but four of these eight had not referred a patient for transplantation. 4/13 centers had patients passed over on the transplant list and reasons cited included: (a) transplant team not comfortable with underlying disease, (b) cognitive impairment in patient raised concerns about compliance, (c) multisystem disease makes single organ transplantation inappropriate, and (d) not at enough risk of life-threatening decompensation.

Conclusions: Excluding renal transplantation for FD, there is low use of transplantation in adults with IEM. Some barriers to transplantation reported by adult centers could be improved with development of educational and management modules for both transplant and metabolic programs.

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Introduction

Organ transplantation has been used as a therapeutic modality for many inborn errors of metabolism (IEM). Transplantation can be done to provide organ replacement therapy as in the case of patients with renal failure from Fabry disease (FD) (Weidemann et al. 2010) or methylmalonic aciduria (MMA) (McGuire et al. 2008). It can be a life-saving therapy for patients with acute metabolic decompensation from unstable conditions like maple syrup urine disease (Mazariegos et al. 2012) and urea cycle defects (UCD) (Morioka et al. 2005). Finally, it can be used to modify the disease course of progressive IEMs, particularly those with involvement of the central nervous system (such as Krabbe disease, metachromatic leukodystrophy, adrenoleukodystrophy, and mucopolysaccharidoses) where alternative treatment strategies are limited (Boelens et al. 2010). Recently, there has been a move to increase the availability of adult specialty clinics to allow the transition

of patients from the pediatric to the adult health care system. We sought to quantify the use of transplantation as a therapeutic modality in adults with IEM.

Methods

A 10-question online survey was sent out through an email list maintained by a representative of the Society for the Study of Inborn Errors of Metabolism (SSIEM) of physicians who identify their interest as the care of adults with IEM. The survey link was also posted on the Society for Inherited Metabolic Disorders (SIMD) website. The survey asked for details of center size (number of adult patients followed), location, and if the center had referred patients for transplantation (and, if so, indications for the procedure). Centers were also asked if they had referred a patient for transplantation who subsequently had been rejected by the transplant team or passed over while on the transplant waiting list (and, if so, indications for this decision). The survey was available for completion for 2.5 months before data were collected for analysis.

Results

Thirteen centers from five continents responded and details of their responses are shown in Table 1. These centers, ranging in size from <50 adult patients (three centers) to >500 (two centers), reported 57 adult patients who had undergone organ transplantation. 29/57 (51 %) of the transplant recipients were from the two largest centers and 27/57(47 %) of transplants were renal transplants for Fabry disease (FD). As expected, most transplants (38/57 or 67 %) were performed because of organ failure. Surprisingly few transplants were performed for acute metabolic decompensation (porphyria $N = 2$, UCD $N = 5$, four of which were at a single center), given that these centers collectively follow thousands of patients. A small number transplants were performed in patients with the intention of modification of disease course (metachromatic leukodystrophy (2), and Krabbe (1)) although, as the reasons for transplantation were not specified in all cases (adrenoleukodystrophy $N = 6$, GSD $N = 1$, and MNGIE $N = 1$), it is possible that some of the remaining cases were transplanted with the intention of modifying the disease course. One patient received a bone marrow transplant for myelodysplasia in the context of Gaucher disease.

Eight of 13 centers had not had patients with IEM passed over while on the transplant list but four of these eight had never referred a patient for transplantation so this may represent a referral bias. 4/13 centers had patients who were passed over while on the transplant list and reasons cited included: (a) transplant team not comfortable with underlying disease, (b) cognitive impairment in patient raised concerns about compliance with post-transplant care, (c) involvement of other organ systems by the IEM made single organ transplantation inappropriate, and (d) candidate considered to be not at enough risk of life-threatening decompensation to justify organ transplantation.

Discussion

Our study, the first to explore this area, reveals that transplantation for acute metabolic decompensation, or as a disease-modifying therapy, is infrequent in centers looking after adults with IEM. The majority of transplants were done for end-stage renal disease and such transplants (which are primarily organized by consultant nephrologist rather than the IEM center) are done for symptom management (such as end-stage renal disease regardless of cause) rather than to modify disease course. Only seven patients were reported to have received transplantation for acute metabolic decompensation (in relatively common IEM such as porphyria and UCD) despite the fact that the 13 centers who responded to our survey were caring for thousands of adults with IEM. In considering the barriers to transplantation in this patient population, they can be categorized into four groups: (a) patient-specific factors, (b) lack of evidence on treatment outcomes, (c) factors resulting from organ allocation policies, and (d) factors specific to the metabolic and transplant programs.

1. Patient-specific factors – when comparing pediatric patients with IEM with adults, it may be reasonable to assume that those patients who survive to adulthood have less severe disease and therefore are less likely to require a transplant for survival. While it is true that the survival rate of patients presenting over the age of 12 years with conditions like urea cycle defects and symptomatic hyperammonemia is much higher than those with earlier onset presentations (Enns et al. 2007), mortality rate is high in patients with severe symptoms of an IEM regardless of age. For example, 25 % of female OTC patients who present with coma (Enns et al. 2007) and 29 % of adults with acute presentations of MCAD (Lang 2009) will die. These publications (Enns et al. 2007, Lang 2009) reflect a publication bias in that they focus on symptomatic cases and many adult patients with IEM such as MCAD will be asymptomatic. However, it is clear from these publications that adults with severe symptoms of their IEM may have poor outcomes. Importantly, the IEM literature suggests that earlier transplantation results in improved neurologic outcomes in patients with urea cycle defects (McBride

Table 1 Summary of responses regarding organ transplantation from adult centers

	Location	Number of adults with IEM[a] followed at that center	Number of transplant procedures performed	Indications for transplantation				Number of patients with nonperformance[b] of transplantation
Centers with no patients receiving transplants	Europe	51–100	0	Not applicable				None reported
	Europe	51–100	0	Not applicable				None reported
	Europe	101–250	0	Not applicable				None reported
	Asia	101–250	0	Not applicable				None reported
	Australia	251–500	0	Not applicable				1
Organ				Kidney	Liver	HSCT[c]	Other	
Centers with patients who received transplants	Europe	<50	3	Fabry (2; combined with heart)		Gaucher with myelodysplasia (1)	Heart Fabry disease (2; combined with kidney)	None reported
	Europe	<50	2			MNGIE[d] (1)	Unknown (1)	None reported
	Europe	<50	2		GSD[e] (2)			None reported
	South America	51–100	10	Fabry (1); Porphyria (1)	UCD[f] (1); Porphyria (1)	ALD[g] (6)		2
	North America	251–500	8	Fabry (3); MMA[h] (1); cystinosis (1)	Porphyria (1)		Heart Fabry (2); GSD (1)	3
	Europe	251–500	3	Fabry (2)			Heart GSD (1)	3
	North America	>500	6	Fabry (1)	UCD (4)	Krabbe (1)		4
	Europe	>500	23	Fabry (19); MMA (1); Gaucher (1; combined with lung)		Metachromatic leukodsytrophy (2)	Lung Gaucher (1; combined with kidney)	None reported

[a] Inborn error of metabolism

[b] Nonperformance of transplantation refers to patients who are referred to the transplant service and rejected or are placed on the list and repeatedly bumped

[c] Hematopoetic stem cell transplantation

[d] Mitochondrial neurogastrointestinal encephalopathy

[e] Glycogen storage disease

[f] Urea cycle defect

[g] Adrenoleukodystrophy

[h] Methylmalonic aciduria

et al. 2004), maple syrup urine disease (Mazariegos et al. 2012), and some lysosomal storage diseases (Wynn et al. 2009). Finally, the burden of comorbid disease which may precipitate metabolic decompensation is higher in adults than in children (Summar et al. 2005; Lang 2009). These data suggest that severity of symptoms, rather than age of symptom onset, should be the main factor in considering transplantation.

2. Lack of evidence on therapy outcomes – there are no systematic studies available which assess the efficacy of transplantation in adults with IEM. Adults are included in many case series (for example, see Morioka et al. 2005; Summar et al. 2005; Mazariegos et al. 2012) and there is not a suggestion in these series that the outcomes are worse for the adults than for the children but data are not analyzed separately to make that determination. Such analysis is required as the risks of transplantation in adults (who have comorbid disease) will differ from those in children. Also, data on natural history of many IEM in adults are completely lacking making it difficult for clinicians to weigh the risks and benefits of transplantation. Finally, the lack of information on prognostic factors in adults makes it difficult to ascertain which patients are most likely to benefit from organ allocation. A registry which collects data on adults with IEM who have undergone transplantation might be one strategy by which evidence could be collected on the outcomes of transplantation in these patients.
3. Organ allocation policies – organs from cadaveric donors are a limited resource and existing organ allocation protocols, created to prioritize patients with end-stage organ failure, may disadvantage patients with IEM. If we consider liver transplantation, both the United Network for Organ Sharing (www.UNOS.org) and Eurotransplant (www.Eurotransplant.org) use the Model for End-Stage Liver Disease (MELD) scoring system to prioritize patients for liver transplant. The MELD score is based on INR, creatinine, and bilirubin so a patient without a defect in hepatic synthetic function, i.e., without end-stage cirrhosis, would have a low MELD score. It became clear that the MELD score does not adequately reflect the need for transplantation in some conditions including hepatocellular carcinoma, and IEM (Bernardi et al. 2011). To address this problem, a working group developed a short list of genetic conditions (including familial hyperoxaluria and familial amyloid polyneuropathy) to which exceptions to the MELD system are accepted (Freeman et al. 2006) and "unusual metabolic diseases" are included, although few are named as exceptions. A "Share-15" policy was adopted in the US (where 15 % of the organs were to be shared amongst patients with MELD scores below 15) but as programs used these organs for patients on their list with higher MELD scores (Washburn et al. 2011), this did not have the desired effect. In our study, some centers had experienced patients being withdrawn from the transplant list because they were not "sick enough" and this is understandable when one considers the limitations and restrictions of the current allocation process. Finally, as patients with IEM have a low incidence of comorbid disease, they might be expected to have better long-term survival than patients with other diseases like chronic hepatitis who are at risk of numerous extra-hepatic morbidities or recurrence of the primary liver disease (e.g., hepatitis C where graft recurrence is almost universal). Indeed, patient survival in large series patients with UCD undergoing liver transplantation was significantly higher than in patients undergoing liver transplantation for other reasons at that same center (Morioka et al. 2005). Age and need for life support are two powerful predictors of survival after liver transplantation (Dutkowski et al. 2011) and patients with IEM are likely to be younger, to be stable between episodes of decompensation, and to have fewer comorbid diseases than patients with end-stage liver disease or cancer and thus might be predicted to have improved survival after receiving liver transplantation relative to those with other diseases such as chronic hepatitis or hepatocellular carcinoma. Modifications to the allocation process could be made to adjust for these disparities and allow patients with IEM to be appropriately prioritized within the organ allocation ranking system. Such modifications could weight variables such as: (a) likelihood of recurrent acute decompensation, (b) risk of neurological injury with recurrent decompensation, and (c) expected life span after transplantation (to reflect age and comorbid diseases).
4. Program-specific factors – in our survey, 5/13 centers had not referred a patient for transplantation. Half of all the transplants reported in our survey were renal transplants for Fabry disease, a situation in which one could expect that the referral for transplantation would arise not from the metabolic center but from the nephrologist caring for the patient with end-stage renal disease. In centers that had referred patients for transplant assessment, patients were sometimes rejected because the transplant team was not familiar with the condition. This suggests that education of both metabolic and transplant centers about the use of transplantation in IEM, and ongoing discussion regarding referred patients and potential patient referrals, may increase the rate of referrals to transplant programs. Also, qualitative research which evaluated the functioning of transplant program committees at different centers (Volk et al. 2011) suggested subjective parameters such as the perception that the patient was "too

well" or concerns about psychosocial barriers including psychiatric disease and social supports affected decisions made by the program committee as to whether or not to list the patient for transplantation. In our survey, metabolic centers had experienced patients being rejected or passed over because they were perceived to be "too well" (even though they may be at risk of dying or neurologic compromise with the next disease exacerbation) or due to concerns about compliance with post-transplant immunosuppressive medications due to cognitive impairment. However, patients with IEM, even with cognitive impairment, may be capable of, and familiar with, following a very complex regime of tight nutritional control, use of metabolic formulae, and multiple medications and, in such patients, a transplant, by relaxing their dietary restrictions, may actually make it easier for them to comply with a treatment program. Thus, guidelines and education around the role that these subjective factors play in making a decision around listing a patient for transplantation may be helpful for transplant programs. Also, education, as well as a realization for the need for advocacy on behalf of these patients, would be helpful for metabolic centers to more effectively address these valid if subjective concerns which influence transplant program committee internal decisions.

Our study is limited by participation bias. We were interested in the perceptions of physicians caring for adults with IEM about transplantation and this study was not intended to be a survey of transplant outcomes. We recognize that not all centers caring for adults with IEM may have received the link to the survey and we have no way of ascertaining how many centers which did receive the link to the survey chose not to participate. Also, we cannot ensure that those centers who did respond included all patients under their care who had received transplants. Further, we cannot exclude that the study was free of the nonresponse or voluntary response bias that may have reflected a physicians experience or lack of experience with transplantation in their centers. However, despite these sources of potential bias inherent to any survey sampling, we believe that this study has highlighted some of the factors which IEM physicians feel may limit a patient's access to transplantation and may be an important starting point to further investigate barriers to the use of transplantation in the adult population with IEM.

Conclusions

The use of transplantation for acute metabolic decompensation or to modify the disease course in adults with IEM is uncommon. There is an urgent need to collect data on the outcomes of adult patients with IEM who undergo transplantation so as to allow clinicians to define prognostic factors and the risk:benefit ratio of considering organ transplantation for some indications. Some of the barriers to the use of transplantation may also be modified through the use of educational materials for transplant and metabolic programs and evaluation of guidelines which underlie organ allocation processes.

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Take Home Message

Barriers exist to the use of transplantation as disease-modifying therapy in adults with IEM.

Competing Interests

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Ethics Approval

No ethics approval was needed for this study.

Contributions

All authors contributed to the study design, data interpretation, and preparation of the manuscript. Dr. Sandra Sirrs serves as guarantor for this manuscript.

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