Cognitive and Behavioural Outcomes of Paediatric Liver Transplantation for Ornithine Transcarbamylase Deficiency

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Abstract Ornithine Trans-Carbamylase (OTC) deficiency is the most common disorder of the urea cycle. Cognitive impairments in skills such as attention and executive function have been reported in individuals with OTC deficiency who are managed with medication. In some cases, children undergo liver transplantation (LTx) to correct the metabolic defect. The metabolic and medical outcomes of LTx are generally good. However, little is known about the impacts on cognition. In this study, four

children (three female) completed detailed neuropsychological batteries prior to ($n = 6$) and following LTx ($n = 8$ assessments). Children's age at assessment ranged from 3 to 11 years. The battery included standardised, age-referenced measures of intellectual ability (IQ), attention, memory and educational ability. Additionally, parent measures of behaviour and executive function were administered. Generally, there was little change in overall IQ following LTx. Memory and academic skills were at expected levels for the three female patients and gains were made after LTx. Children showed ongoing impairments in attention and parent rated executive function. In conclusion, the immediate effect of LTx on cognition may not appear beneficial in the short-term and impairments in IQ, attention and behaviour persisted after the procedure. However, LTx seems to enable stabilisation to premorbid function in the longer term.

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Introduction

Ornithine Trans-Carbamylase (OTC) deficiency is the most common disorder of the urea cycle, the metabolic pathway responsible for ammonia detoxification (Brusilow and Horwich 2000). The urea cycle is also the main production site of the amino acid arginine and patients with defects in the urea cycle (except for Arginase deficiency) require arginine supplementation. Arginine is a substrate for creatine and nitric oxide (NO), two metabolites that are very important for normal brain function (Bachmann et al. 2004). It is widely accepted that the effects of OTC deficiency on brain function are a result of ammonia toxicity, on one hand, and arginine deficiency, on the other (Bachmann et al. 2004; Braissant 2010). During metabolic

decompensation, ammonia levels are high and may lead to encephalopathy. Acute hyperammonaemia leads to excessive activation of the *N*-methyl-D-aspartate (NMDA) receptors, whereas chronic moderate hyperammonaemia impairs activation of the receptors (Hermenegildo et al. 1998). Hyperammonaemia also impairs axonal growth as well as medium weight neurofilament expression and phosphorylation (Braissant et al. 2002).

The cognitive function of girls and women with OTC deficiency who are mildly symptomatic or asymptomatic (i.e., have not had any episodes of hyperammonaemia) has previously been investigated (Maestri et al. 1996; Gropman and Batshaw 2004; Gyato et al. 2004). Whilst these women were of average intellectual ability overall, difficulties were demonstrated in fine motor skills, attention and executive skills, and non-verbal intelligence (Gyato et al. 2004). Women who were symptomatic performed significantly worse than asymptomatic women on verbal and non-verbal intelligence and verbal learning (Gropman and Batshaw 2004; Gyato et al. 2004). By contrast, the information regarding the neurocognitive outcome of males with OTC deficiency is limited, likely because most male patients die in the newborn period or are severely intellectually disabled and are unable to complete neuropsychological evaluations. In general, OTC deficiency with neonatal onset has been associated with significant intellectual impairment in childhood (Krivitzky et al. 2009). However, limited sample description and design details suggest these findings require confirmation.

Liver transplantation (LTx) is usually considered for patients with urea cycle defects including OTC deficiency when there are increasing difficulties or failure to maintain metabolic stability using conservative medical treatment, including diet, nitrogen scavengers and arginine supplementation. In recent years, LTx has been performed on patients with disorders of the urea cycle, including OTC deficiency, with overall very high survival rate and good metabolic outcome (Kim et al. 2013; Stevenson et al. 2009). However, the cognitive and neuropsychological outcome of these patients has not been reported in detail. Published reports have been restricted to IQ outcomes, with little change reported up to 1 year after LTx (Kim et al. 2013; Stevenson et al. 2009). Whether there is any change in other cognitive skills such as attention and memory is unknown. In other conditions with LTx as a treatment, LTx has been associated with increased risk of cognitive and academic deficits (Sorensen et al. 2014).

In this study, we present detailed longitudinal cognition and behavioural outcomes of four paediatric patients (three females) with OTC deficiency who had a LTx. In order to better characterise the long-term effect(s) of the transplantation on cognitive development and pathology, cognitive and behavioural function both pre-LTx and post-LTx is presented.

Methods

Participants

All children with OTC deficiency treated medically and transplanted at the Royal Children's Hospital, Melbourne were included ($n = 4$; female 3; male 1). The study was approved by The Royal Children's Hospital Human Research Ethics Committee (HREC #31009). Medical records were also reviewed for confirmation of diagnosis and clinical details (Table 1). All neuropsychological assessments were conducted by a trained psychologist and on an outpatient basis, in a hospital clinic, when the patients were metabolically stable.

Measures

Participants were administered a battery of standardised cognitive tests as part of their standard clinical management. All children completed an assessment prior to transplantation. The first assessment after LTx occurred within 10–21 months and the final assessment occurred 35–48 months after LTx.

Intelligence Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III; Wechsler 2002) for children under 6 years 3 months and Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV; Wechsler 2003) for children 6 years 4 months and older. Verbal IQ, Performance IQ and Full Scale IQ were calculated. The WISC-IV also has scores for Processing Speed Index (PSI) and Working Memory Index (WMI). All indexes on these scales have a mean (M) of 100 and a standard deviation (SD) of 15.

Attention Selected subtests from the Test of Everyday Attention for Children (TEA-Ch; Manly et al. 1998). Scores are scaled scores ($M = 10$, $SD = 3$). The Sky Search subtest taps selective attention and the Attention score is presented which considers the number of errors and time taken. The Score! subtest taps sustained auditory attention and the overall score was calculated. The Sky Search DT subtest is a divided attention subtest and the overall score was calculated. Patient 2 was administered the Auditory Attention subtest (NEPSY-II) as the length and demands of the TEA-Ch were inappropriate (scaled score; $M = 10$, $SD = 3$).

Memory

Visual Memory Children completed the Dot Locations subtest from the Children's Memory Scale (CMS; Cohen 1997). Immediate (Learning) and delayed recall scores were calculated (scaled scores; $M = 10$, $SD = 3$).

Table 1 Medical details of patients

ID	Age at diagnosis (Sex)	Symptoms before diagnosis	Confirmation of diagnosis ^a	Age at LTx	No. admissions for metabolic decompensation prior to transplantation
1	18 months (female)	Recurrent vomiting, behavioural issues, hyperactivity	Ammonia 350 (<50); Arginine 17 (32–142); Citrulline 16 (8–47), Glutamine 1190 (475–746); urine orotic acid +++ ^b	6 years 4 months	Metabolic decompensation: 5 Prophylactic ^c : 12
2	15 months (female)	Recurrent vomiting, unsettled, clingy, poor sleeper as infant, hyperactivity	Ammonia 160 (<50); Arginine 21 (32–142) Citrulline 23 (8–47) Urine orotic acid: 1,206.0 (<4.9) c.650delC (p.A217fsX229)	6 years 4 months	Metabolic decompensation: 36 Prophylactic ^c : 34
3	5 years 7 months (female)	Lethargy, increased sleeping time, ataxia	Ammonia 153 (<50); Glutamine 806 (475–746) Citrulline 22 (8–47); Arginine 32 (32–142) Ornithine 36 (27–96); urine orotic acid ++ ^b Uracil ++ ^b ; Plasma orotic acid 24 (<7.1)	8 years 4 months	Metabolic decompensation: 23 Prophylactic ^c : 12
4	13 months (male)	Feeding difficulties, recurrent vomiting, lethargy, irritability, 'spaced out'	Ammonia 278 (<50) Urine orotic acid 288 (<4.9) c.533C>T (p.T178M)	5 years 9 months	Metabolic decompensation: 19 Prophylactic ^c : 3

^a Ammonia and amino acid concentrations: $\mu\text{mol/L}$ (normal range)

^b ++ = 3 to 10 times the cut-off level, +++ = >10 times the cut-off level

^c Unwell but metabolically stable; no hyperammonaemia

Narrative Memory Children completed either the Stories subtest from the CMS or the Narrative Memory subtest from the NEPSY-II (Korkman et al. 2007). For Stories the immediate (learning) and delayed recall scores were calculated (scaled scores; $M = 10$, $SD = 3$). Narrative Memory from the NEPSY-II was chosen for younger children or children with significant intellectual or behavioural impairments (scaled scores; $M = 10$, $SD = 3$).

Verbal Learning Children completed either Word Pairs from the CMS or the List Memory subtest from the NEPSY-II with both using scaled scores ($M = 10$, $SD = 3$). For Word Pairs the immediate (learning) and delayed recall scores were calculated.

Academic Skills Wide Range Achievement Test 4th Edition (WRAT-4; Wilkinson 2006). The single word reading, spelling and mathematic tasks were administered to children (standard scores; $M = 100$, $SD = 15$).

Interpretation of Cognitive Scores Standard scores ($M = 100$, $SD = 15$): scores within 1 SD of the mean (i.e. 85–115) were considered 'in the average range'; Scores between 1 and 2 SD below the mean (71–84) were considered 'in the low range'; Scores ≤ 2 SD below mean (≤ 70) were considered 'in the impaired range'. Scaled scores ($M = 10$, $SD = 3$): scores <1 SD of the mean

(7–13) were considered 'in the average range'; Scores between 1 and 2 SD below mean (5–6) were considered 'in the low range'; Scores ≤ 2 SD below the mean (≤ 4) were considered 'in the impaired range'.

Parent Rating of Behaviour Behavior Assessment System for Children – Second Edition (BASC-2; Reynolds and Kamphaus 2010) was used. The Internalizing Index, Externalizing Index and Behavior Symptoms Index were calculated (T-scores; $M = 50$, $SD = 10$). Higher scores indicate more behavioural difficulties. A score of 60–69 is considered in the at-risk range and a score >70 in the impaired range, suggesting significant behavioural difficulties. The Adaptive Skills Composite was calculated (T-scores; $M = 50$, $SD = 10$). Lower scores indicate more adaptive difficulties. A score 31–40 is considered in the at-risk range and a score <30 is considered in the impaired range.

Parent Rating of Executive Function For children <6 years at assessment the Behavior Rating of Executive Function – Preschool (BRIEF-P; Gioia et al. 1996) was used. For children ≥ 6 years, the Behavior Rating of Executive Function (BRIEF; Gioia et al. 2003) was used. The total score, the Global Executive Composite, was calculated (T-scores; $M = 50$, $SD = 10$). A score >65 (>1.5 SD above M) was in the impaired range.

Results

Patients

Age at diagnosis ranged from 1 year 1 month to 5 years 7 months (refer Table 1). Prior to diagnosis, children presented with physical, developmental and behavioural problems. The male patient had a unique mosaic pattern of a severe mutation: T178M (McCullough et al. 2000), thus providing an explanation for his age at presentation, and the disorder severity, which is comparable to that of female patients. Children were 5–8 years old at transplantation.

Altogether, patients completed 14 assessments, with each child assessed at least once before LTx and twice following LTx. The age at assessment ranged from 3 to 11 years.

Cognitive Outcomes

Intelligence IQ scores are presented in Table 2. Overall, the distribution of scores was significantly skewed to lower scores in all IQ variables, with many scores in the impaired range (>2 SD below mean). The three female patients (patients 1–3), all had the highest scores at the first assessment. Scores on the most recent IQ assessment following LTx were variable with patient 3 declining and patient 1 and 2 stabilising to pre-LTx levels. All patient 4's scores were in the impaired range with little change over time.

Academic Skills Scores are presented in Table 2. Patient 4 was not assessed as he attends a specialist school with a

modified curriculum for children with intellectual disabilities. Patient 1 showed little change over time. Patient 2 and 3 improved on word reading and spelling and showed minimal change on the mathematics task.

Attention Scores are presented in Table 3. Scores on attention measures both pre- and post-LTx showed significant impairments. No specific attention domain was intact and there was little change over time. The exception to this was patient 3 who improved on sustained and divided attention tasks post-LTx.

Memory Scores are presented in Table 3. Pre-LTx visual memory was available for two patients (patient 2 and 3) and was in the low to impaired range. At the final assessment post-LTx, all scores were in the average to above average range. Scores for narrative memory varied from impaired to average. On the verbal memory subtests, improvements were seen post-LTx for patients 1–3. Patient 4 showed no change over time.

Parent Rated Behaviour Table 4 lists the behavioural results. On the behaviour measures all patients had scores indicative of behavioural problems at the pre-LTx assessment and the results following LTx were variable. Patient 1 displayed behaviour problems in all areas pre- and post-LTx. Her adaptive skills remained in the average range. Behavioural problems were noted for Patient 2 pre- and post-LTx with little change over time, however, her externalising behaviours were in the normal range at the most recent assessment. Patient 3 showed an improvement

Table 2 IQ and academic scores pre- and post-liver transplantation

	Patient 1			Patient 2				Patient 3				Patient 4		
Age (years–months)	3–7	7–3	9–0	5–2	6–2	7–2	10–3	5–2	7–5	9–4	11–3	4–8	7–6	9–9
Time pre-/post-transplant (months)	–33	17	38	–14	–2	10	48	–38	–11	12	35	–13	21	48
<i>IQ index</i>														
Full-scale IQ	80 ^a	75 ^b	75 ^b	75 ^a	70^a	58^b	73 ^b	86 ^a	64^b	74 ^b	68^b	56^a	48^b	49^b
Verbal IQ	87 ^a	67^b	71 ^b	83 ^a	75 ^a	75 ^b	69^b	90 ^a	69^b	77 ^b	75 ^b	64^a	67^b	65^b
Performance IQ	79 ^a	79 ^b	88 ^b	82 ^a	72 ^a	63^b	84 ^b	86 ^a	71 ^b	84 ^b	82 ^b	55^a	47^b	47^b
Processing Speed Index	^c	97 ^b	80 ^b	65^a	57^a	53^b	91 ^b	^c	80 ^b	75 ^b	65^b	50^a	50^b	62^b
Working Memory Index	n/a	83 ^b	88 ^b	n/a	n/a	71 ^b	71 ^b	n/a	77 ^b	83 ^b	71 ^b	n/a	65^b	59^b
<i>Academic skills (WRAT-4)</i>														
Word reading	n/a	107	102	n/a	76	69	88	n/a	92	78	91	n/a	n/a	n/a
Spelling	n/a	114	116	n/a	61	55	91	n/a	93	71	84	n/a	n/a	n/a
Math computation	n/a	91	90	n/a	76	71	75	n/a	64	61	71	n/a	n/a	n/a

WRAT-4 Wide Range of Achievement Test – 4th Edition. Bold text signifies ≥ 2 standard deviations below the mean. All scores are standard scores, $M = 100$, $SD = 15$. n/a not applicable for the child

^a Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III)

^b Wechsler Intelligence Scale of Children – Fourth Edition (WISC-IV)

^c Unable to be calculated as supplementary subtest not administered

Table 3 Attention and memory scores pre- and post-liver transplantation

		Patient 1			Patient 2			Patient 3			Patient 4	
Age (years–months)		3–7	7–3	9–0	6–2	7–2	10–3	7–5	9–4	11–3	7–6	9–9
Transplant status		<i>Pre</i>	<i>Post</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Post</i>	<i>Post</i>	<i>Post</i>
Time pre/since Tx (months)		–33	17	38	–2	10	48	–11	12	35	21	48
<i>Attention</i>												
Selective attention	Sky Search attention	–	4	1	–	–	3	1	6	3	1	1
Sustained attention	Score!	–	2	3	–	–	1	2	3	6	1	2
	Auditory Attention	–	–	–	4	3	5	–	–	–	–	–
Divided attention	Sky Search DT	–	1	1	–	–	1	1	1	8	1	1
<i>Memory</i>												
Visual memory	Dot Locations learning	–	9	14	5	10	11	4	2	7	–	–
	Dot Locations delay	–	9	12	–	–	12	5	7	11	–	–
Narrative memory	Stories learning	–	9	8	6	5	4	–	6	7	–	–
	Stories delayed	–	10	8	4	–	3	–	6	7	–	–
	Narrative memory	7	11	–	–	–	–	–	–	–	5	9
Verbal memory	Word Pairs learning	–	6	10	1	6	7	–	–	–	–	–
	Word Pairs delayed	–	6	12	1	2	10	–	–	–	–	–
	List Memory	–	–	–	–	–	–	11	6	9	5	4

Attention and memory scores are scaled scores, $M = 10$, $SD = 3$. Bold text signifies >2 standard deviations below the mean

Table 4 Behaviour scores pre- and post-liver transplantation

Measure	Patient 1			Patient 2			Patient 3			Patient 4			
Age (years–months)	3–7	7–3	9–0	3–11	6–2	7–2	10–3	7–5	9–4	11–3	4–8	7–6	9–9
Transplant status	<i>Pre</i>	<i>Post</i>	<i>Post</i>	<i>Pre</i>	<i>Pre</i>	<i>Post</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Post</i>	<i>Pre</i>	<i>Post</i>	<i>Post</i>
Months post	–33	17	38	–29	–2	11	48	–11	12	35	–13	21	48
<i>BASC-2</i>													
Internalizing Problems Composite	72	85	71	<i>60</i>	48	43	<i>67</i>	57	52	52	<i>63</i>	57	56
Externalizing Problems Composite	<i>69</i>	74	74	<i>63</i>	<i>65</i>	50	59	104	<i>66</i>	<i>67</i>	80	58	<i>62</i>
Behavior Symptoms Index	<i>65</i>	74	76	<i>65</i>	58	52	<i>69</i>	96	<i>61</i>	59	83	74	74
Adaptive Skills Composite	47	45	43	37	25	28	29	23	35	41	25	26	26
<i>BRIEF-P/BRIEF</i>													
General Executive Composite	–	68	70	81	78	55	66	86	53	64	–	–	–

BASC-2: presentation in italics: T-Score 60–69 at-risk; presentation in bold: >70 impaired range

Presentation in italics: Adaptive Skills Composite 31–39 at-risk. Presentation in bold: <30 impaired range

BRIEF and BRIEF-P: presentation in bold type represents score at impaired level, T Score >65

in all areas of behaviour including adaptive skills, her externalising behaviours were still in the at-risk range at the most recent assessment. Patient 4 was in the impaired range for all behaviour at all assessments except internalizing behaviours at the last assessment.

Parent Rated Behaviour Executive Function A parent of patients 1, 2 and 3 completed this scale and all had executive function difficulties prior to LTx. Problems remained for patients 1 and 2 following LTx. Patients 3's

skills improved and she was no longer in the impaired range.

Discussion

Brain damage in urea cycle disorders has been attributed to the toxic effect of ammonia and the deficiency of arginine, and hence deficiency of NO and Creatine (Braissant 2010). The level of hyperammonaemia and its duration have been considered pivotal in the pathogenesis of CNS damage

(Bachmann et al. 2004; Braissant 2010). Genetic (i.e., the severity of the mutation, and the degree of X-inactivation in female patients) and ‘medical’ (i.e., age at diagnosis and initiation of treatment and compliance with treatment) factors are the main determinants of outcome. The neuro-cognitive impairments found in patients with OTC deficiency are thought to be associated with damage to white matter (Gyato et al. 2004). In children, where the brain is continually developing, the impact of white matter damage is difficult to clarify and is likely to be associated with impairments across multiple functional neural areas disrupting ongoing skill acquisition and maturation (Fouladi et al. 2004; Scantlebury et al. 2011).

Theories of early vulnerability imply that a diffuse insult to the brain early in life is detrimental to both ongoing brain development and future skill acquisition, leaving little healthy tissue available to compensate. The result is typically global cognitive and functional impairments (Ewing-Cobbs et al. 2003). Indeed, pre-LTx impairments were seen in all children except for patient 1. Patient 3, who was diagnosed at an older age compared with the others, had the lowest IQ of all three girls prior to LTx. Given that all patients were school age at the time of LTx, it is difficult to speculate about what might have been the outcome of the procedure if they had been transplanted earlier, and future case reports will be needed to clarify this point.

There is very little detailed information on the long-term neurocognitive effect(s) of LTx in children with OTC. Research available on post-transplantation outcomes has focused heavily on IQ outcomes or developmental scales with little information provided on specific cognitive domains such as attention, memory and academic skills (Kim et al. 2013; Stevenson et al. 2009). The current study provides detailed information on the effect of LTx on cognitive and behavioural function of children with OTC deficiency up to 4 years post-LTx. The final assessment completed 3–4 years after LTx shows the ongoing deficits associated with OTC deficiency when the impacts of missing school, feeling unwell, etc., have stabilised. The immediate effect of LTx may not appear beneficial in terms of cognition, but seems to enable stabilisation to premorbid function longer term. Post-transplantation assessments of our patients suggest an improvement in memory skills. It may be that memory skills are dampened by the presence of toxicity, or more resilient to the effect of hyperammonaemia/arginine deficiency or are impacted by medication prescribed to correct the deficiency. It seems that memory deficits are somewhat reversible following correction of the metabolic defect. Memory improvement may aid learning skills over time and lead to IQ gains. The improvement in academic skills in patients 2 and 3 at the final assessment may be related to gains made in memory skills, translating to improved learning in the classroom.

Behavioural problems were highly prevalent in our patients, mainly prior to LTx. However, at 3–4 years post-LTx, some behavioural problems remained. Behavioural problems are likely due to both impacts on the brain in terms of emotional regulation and attention, as well as environmental stressors of regular hospitalisations, medication regimes, school absenteeism, and parental worries and strains (Compas et al. 2012).

There are several limitations to this study. The group is small and heterogeneous and there is no control group to compare to who have received conventional treatment. All children were school-age at LTx, therefore we cannot comment on the outcomes of a LTx at a younger age.

Conclusion

Children with OTC deficiency have impairments in both general cognition as measured by IQ tests and more specific difficulties in areas such as attention and executive function. In our small and heterogeneous group of patients, LTx appears to be associated with improvements in memory and likely as a consequence, in academic skills. Ongoing impairments in attention and parent-rated executive function are still noted post-LTx. In theory, LTx earlier in life may be more beneficial, but more data are required to substantiate this hypothesis.

Take-Home Message

Liver transplantation for OTC deficiency may lead to improvement in memory and learning in some children, but the short-term effect of transplantation on cognition is limited.

Contributions of the Authors

Louise Crowe designed the study, conducted the assessments, carried out the analysis and wrote the paper. Vicki Anderson supervised assessments, provided neuropsychological input and assisted with writing and editing the paper. Winita Hardikar provided medical knowledge on the topic and assisted with writing and editing the paper. Avihu Boneh provided information on the disorder, clinical and medical information and wrote the paper with Louise Crowe.

Competing Interests

None declared.

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Ethics

This project was approved by the Royal Children's Hospital Ethics Committee, #34140. As the patients are children, their parent (mother in all cases) gave consent for their child to participate in this study.

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