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SHORT REPORT

Cognitive, behavioural and adaptive profiles of children with glutaric aciduria type I detected through newborn screening

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Summary *Background:* Glutaric aciduria type I (GA I) is an autosomal recessive disorder of lysine and tryptophan metabolism due to a deficiency in glutaryl-CoA dehydrogenase activity. Recent reports suggest that early diagnosis through newborn screening and initiation of preventive therapy result in improved functional outcome; however, detailed neuropsychological profiles of children with GA I are seldom reported and thus the impact of the disease on cognition, motor abilities and behaviour remains uncertain. *Method:* We present detailed neuropsychological profiles of three children who were diagnosed with GA I through newborn screening and treated from early age, and one asymptomatic patient diagnosed through cascade screening. A comprehensive battery of standardized tests was administered including measures of intellectual function, attention/memory, executive function, motor skills, speech/language, as well as behavioural and adaptive skills. *Results:* The results reveal overall average cognitive outcomes; however, subtle, but significant, fine motor and articulation deficits were observed. The results are discussed with regard to potential links between fine motor deficits and speech impairments in children with GA I. Such difficulties can impact on the child's ability to engage in academic, leisure and daily activities. *Conclusions:* These findings highlight the importance of in-depth assessments of all aspects of neuropsychological function in patients with GA I and provide a basis for future neuropsychological assessment in similar groups of children. In spite of relatively preserved overall functioning, using a broad range of sensitive cognitive and motor measures facilitates the detection of subtle deficits, and allows for planning of early and adequate therapeutic interventions.

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Abbreviations

ABAS-II	Adaptive Behaviour Assessment System
BRIEF-P/BRIEF	Behavior Rating Inventory of Executive Function
CBCL	Child Behaviour Checklist
GA I	glutaric aciduria type I
MABC-2	Movement Assessment Battery for Children
WPSSI-III	Wechsler Preschool and Primary Intelligence Scale

Introduction

Glutaric aciduria type I (GA I) is an autosomal recessive disorder with a reported incidence of ~1:106 000 (Lindner et al 2004). It results from a deficiency of glutaryl-CoA dehydrogenase activity, an enzyme required for the degradation of the amino acids lysine, hydroxylysine and tryptophan (Kölker et al 2006b; Sauer et al 2006).

GA I is associated with a severe dystonic dyskinetic movement disorder in most clinically affected patients (Hoffmann et al 1996; Kölker et al 2006a). Neuroimaging studies show that these clinical manifestations are associated with subcortical pathology, predominantly striatal degeneration (Hoffmann et al 1996; Strauss et al 2003, 2007). Strauss and colleagues (2003) distinguished between patients with GA I-related brain injury confined to the putamen and those with caudate degeneration, indicating that the former have preserved intelligence while the latter have cognitive dysfunction; however, no further details were provided. In fact, existing reports of cognitive function in GA I are often limited to tests of general intelligence, but do not address functioning in specific cognitive domains, such as attention, memory, executive functions or language, perhaps owing to the severe dystonia and dyskinesia of clinically affected patients. Kyllerman and colleagues (1994) reported results of three cognitive tests administered to a series of eight patients with GA I. The patients in their study were quite severely affected by verbal speech and motor dysfunction and reduced endurance, which prevented administration of a fully standardized test procedure (Kyllerman et al 1994). Despite this, the authors described impaired expression of language and motor function with intact receptive language skills. Indications that GA I may result in language difficulties also come from reports that some patients attend speech therapy sessions as a result of both expressive and receptive delays (Naughten et al 2004), and one case report describing a child with GA I with a learning disability characterized by dyslexia, dyscalculia and dysgraphia (Patil et al 2004).

Recent reports indicate that newborn screening and the implementation of early therapy, which includes the provision of carnitine, dietary manipulation particularly when the child is unwell, and aggressive treatment of fever and intercurrent infections has significantly improved the functional outcome of patients with GA I (Boneh et al 2008; Kölker et al 2004, 2006a; Strauss et al 2007). Yet the impact of early diagnosis and treatment on cognitive and behavioural function has not been studied. It should be noted that there are some differences in management regimens of patients with GA I between different centres, making studies on large homogeneous patient populations practically impossible at this stage. Newborn screening for GA I was introduced in Victoria, Australia in October 2001. Newborns with a diagnosis of GA I are treated from an early age and followed up at a single medical centre, according to a single protocol (Boneh et al 2008). Neuropsychological assessments are gradually being introduced as part of the follow-up of patients with several metabolic disorders diagnosed through newborn screening. We report the results of comprehensive neuropsychological assessments of four children with GA I, documenting their motor, cognitive, behavioural and adaptive functioning.

Method

Patient case studies

The clinical history of the four patients described in this paper has been documented in detail in a previous publication (patients 2, 3, 4, and 5, respectively) (Boneh et al 2008). Three were diagnosed through newborn screening and one was diagnosed through cascade screening (patient 3). Patient 3 has never had an acute decompensation and is considered 'asymptomatic'. Patient 4 was born prematurely and owing to significant social issues was removed into foster care for a lengthy period. He was reported to have two episodes of severe gastroenteritis and an episode of otitis media, which did not result in encephalopathic crises but may have added to the complexity of his clinical outcome. Neuroimaging was available for two patients, as previously reported (Boneh et al 2008). Herein, we provide a detailed neuropsychological report on these patients. Another patient refused any additional tests but is clinically well and of normal development.

Neuropsychological assessment

Participants were administered a battery of standardized cognitive and motor tests as part of their standard clinical management. Evaluation was conducted during a single testing session lasting approximately 2 hours.

Intelligence: Wechsler Preschool and Primary Intelligence Scale-III (WPSSI-III: Wechsler 2002): Verbal (VIQ), Performance (PIQ), Full Scale (FSIQ) and processing speed index (PSI) scores (M=100, SD=15).

Attention/memory: Narrative memory, Memory for Designs and Statue subtests from the NEPSY-II (Korkman et al 2007) (M=10, SD=3).

Executive function: A validated and standardized parental questionnaire was used to assess executive function. Depending on age, either the preschool or

school version of the Behavior Rating Inventory of Executive Function (BRIEF-P/BRIEF: Gioia et al 2000, 2004) was completed by each child's mother. On the school version, administered to children aged 2 to 5–11 years, the Behavior Regulation Index (BRI), Metacognition Index (MI), and Global Executive Composite (GEC) are reported. On the preschool version, administered to children over 6 years of age, the following index scales are reported: Inhibitory Self-Control (ISCI), Flexibility (FI), and Emergent Metacognition (EMI) (*T*-scores, *M*=50, SD=10).

Motor function: Movement Assessment Battery for Children (MABC-2: Henderson et al 2007): Manual Dexterity, Aiming and Catching and Balance Indices (*M*=10, SD=3).

Speech and language: The general language index (GL) was derived from the WPSSI-III (*M*=100, SD=15). Qualitative observations were made throughout the assessment and children with apparent speech or articulation difficulties were referred for further speech and language assessment. In addition, a full history of speech and language development was obtained and speech pathology reports were consulted.

Behaviour and adaptive function

The following measures were completed by each child's mother:

Adaptive functioning: Four summary scores from the Adaptive Behaviour Assessment System (ABAS-II: Harrison and Oakland 2003) were used: General Adaptive Composite (GAC), Conceptual (CON), Social (SOC), Practical (PRA) (*M*=100, SD=15).

Behaviour: Three summary scores from the Child Behaviour Checklist (CBCL: Achenbach et al 2001) were used: Internalizing (INT), Externalizing (EXT), Total (TOT) (*T*-scores, *M*=50, SD=10).

Results

Standardized scores for all four participants on the neuropsychological assessment are presented in Table 1. Scores on all tests were compared with standardized age norms and a standard deviation of two or more below average was considered to be a significant deficit; a score 1.0–2.0 standard deviations from the norm was considered to be a mild deficit and noted to be clinically significant. Patient 4 was unable to complete four sub-tests (processing speed, statue, aiming and catching, balance) from the assessment battery that involved the motor system because of severe fine and gross motor difficulties and was therefore awarded a score of more than 2.0 standard deviations below the mean. Patients 2, 3, and 5 obtained average to above average results on tests of intellectual function, attention and memory, while patient 4 showed significant deficits in all these cognitive areas. All patients displayed significant deficits on a test of fine motor skills. No significant concerns were reported by the parents of any of the patients in terms of executive functioning, behaviour, and adaptive functioning, though patient 4 was noted to have significant deficits in adaptive skills. Of note, the results obtained for patients 2, 3, and 5 on the CBCL parent report were well below the expected rate of behaviours reported for typically developing children (1.5–2.5 SD below the average range). This exceptionally low rate of reporting casts some doubt on the reliability of the responses provided on this particular questionnaire and suggests that further assessment of behaviour in the context of GA I may be necessary.

In addition to the quantitative findings, when speech was assessed through qualitative observation of expressive language, all patients were found to have speech/articulation difficulties. Patient 2's speech was at times difficult to understand; however, a firm argument for the presence of articulation difficulties was not possible because of his young age. Patient 3 had previous evidence of articulation difficulties as reported in a separate, formal assessment of speech and language. In patient 5, clear confusions were noted between 'k' and 't' sounds (for example 'montey' for *monkey*; 'tow' for *cow*; 'puntin' for *pumpkin*) as well as 'd' and 'g' sounds (for example 'dirl' for 'girl'). These observations were confirmed through a formal speech pathology assessment using the Fisher Atkin Test of Articulation (Atkin and Fisher 1996), which revealed further difficulties with consonant blends including, for example, 'br', 'kl', 'thr' (for example 'bwown' for 'brown', 'tlot' for 'clock', 'frow' for 'throw'), indicating a 1½-year developmental delay in this area. Patient 4 had very restricted expressive speech and was able to utter only a limited number of single words, the intelligibility of which was hampered by articulation difficulties. A severe expressive language impairment and articulation difficulties were previously well-documented by a speech pathologist.

Discussion

Clinically diagnosed patients with GA I may have severe motor and speech disabilities and a high mortality rate (Kölker et al 2006a, 2007; Kyllerman et al 2004;

Table 1 GA I patients' scores on neuropsychological tests and questionnaires

	Patient			
	2	3	4	5
Age at testing (years–months)	3-0	6-11	6-0	4-10
Intellectual function (WPPSI-III)				
FSIQ	109	124	**62**	106
VIQ	111	118	**57**	93
PIQ	106	128	**70**	114
GL	119	110	**70**	105
PSI	n/a	106	**<70**	126
Attention and memory (NEPSY)				
Narrative memory	10	15	**1**	9
Memory designs	12	11	8	14
Statue	14	11	**<4**	13
Executive function (BRIEF/BRIEF-P)				
GEC	42	55	43	35
BRI	n/a	52	41	n/a
MI	n/a	57	45	n/a
ISCI	44	n/a	n/a	37
FI	40	n/a	n/a	38
EMI	46	n/a	n/a	36
Motor function (MABC)				
Manual dexterity	**5**	**4**	**1**	**6**
Aiming and catching	8	9	**<4**	*7*
Balance	10	10	**<4**	14
Behaviour (CBCL)				
Total	30	39	49	33
Internal	33	48	57	49
External	47	40	48	42
Adaptive function (ABAS)				
GAC	95	103	*73*	114
CON	95	96	*77*	99
SOC	113	112	96	124
PRA	99	99	**70**	102

Values in *italic* type signify clinically significant deficit (1.0–2.0 SD); values in **bold** type signify significant deficit (≥2 SD). n/a, not applicable (i.e. not a component of particular version of the measure). BRI, behaviour regulation index; CON, conceptual composite; EMI, emergent metacognition index; FI, flexibility index; FSIQ, full-scale intellectual quotient; GAC, global adaptive composite; GEC, global executive composite; GL, general language index; ISCI, inhibitory self-control index; MI, metacognition index; PIQ, performance intellectual quotient; PRA, practical composite; PSI, processing speed index; SOC, social composite; VIQ, verbal intellectual quotient.

Naughten et al 2004). Cognitive outcomes have been difficult to quantify in this group of patients, but neuroimaging showing brain atrophy suggests possible perturbation of cognition at least in some patients (Kölker et al 2006a, 2007; Kyllerman et al 2004; Naughten et al 2004). To the best of our knowledge, this is the first detailed neuropsychological report on patients with GA I treated 'prophylactically' from the neonatal period and an 'asymptomatic' patient.

Intellectual ability, attention, executive function

Patients 2, 3 and 5 had intellectual, attention, memory and executive skills in the average to above average range, indicating preservation of these abilities. Patient 4, however, was found to have an intellectual impairment and a severe language delay, which affected his scores on the neuropsychological evaluation in general. Executive functions include self-regulation, inhibition, cognitive flexibility, and goal setting (planning, organization, problem solving, etc.) and begin to emerge in childhood, but are generally not fully developed or consolidated until late adolescence (Anderson 2002; Anderson et al 2001). In this study, parental report revealed no significant concerns in any areas executive functioning, suggesting that at the time of assessment, the patients had intact executive skills according to parental opinion. However, given the

protracted development of these functions and the relatively young age of the participants, it may be important to further assess the impact of GA I on these complex functions as they evolve throughout childhood and adolescence using multiple direct measures of executive skills (Anderson 2001).

Behavioural and adaptive functioning

Behaviour and adaptive skills are seldom reported in studies of individuals with GA I. A study by Simons and colleagues investigated behavioural outcomes in a group of patients with seven different 'intoxication type' metabolic diseases including glutaric aciduria (Simons et al 2006). The authors found an increased rate of externalizing behaviours in these patients; however, given the heterogeneity of the group, it is difficult to conclude whether the findings are typical of patients with GA I. The patients in this study had overall age-appropriate behaviour and adaptive functions, as rated by parental report. Only patient 4 was found to have an impairment in adaptive skills, clearly due to the fact that his motor and speech impairments impact on his ability to engage in activities such as self-care and household chores. Given the potential bias of evaluating behaviour on the basis of parental report only, it may be useful in future studies to use multiple sources of information (e.g. teacher report, self-report, structured interviews) to assess the full range of behavioural and adaptive skills in patients with GA I.

Fine motor skills

All patients demonstrated significant fine motor impairments. As mentioned above, deficits in motor function are common in clinically affected children with GA I and can be characterized by dystonia and dyskinesia (Burlina et al 2004). In the present cases (2, 3, 5), however, gross motor function was spared in comparison to fine motor skills requiring precision and manual dexterity, suggesting that these may need to be considered separately when determining intactness of the motor system. These findings may characterize relatively well-functioning patients in whom difficulties are apparent only for subtle skills requiring fine motor precision. Such difficulties have an important functional impact as these children begin the school curriculum, when fine motor skills are an important part of daily tasks. It is likely that these difficulties will impact on their writing, cutting, and drawing abilities, as well as day-to-day activities such as getting dressed and leisure and sporting activities.

Verbal skills, speech and language

Speech and language difficulties in the context of GA I have previously been alluded to by Naughten and colleagues (2004) and Kyllerman and colleagues (1994), who reported poor expressive language function in their patients. Assessment of speech in our early-diagnosed and early-treated patients revealed expressive and articulation difficulties in all patients. These results suggest that speech and language skills may be affected in GA I, even in early-treated patients or 'asymptomatic' patients who do not have the 'classical post-encephalopathic' syndrome.

Expressive problems were mostly related to problems with articulation, suggesting that there may be a motor component underlying these speech production impairments, particularly given the concomitant observation of fine motor difficulties in all patients. In support of this, a review of the literature indicates substantial co-morbidity between language impairments and poor motor skills (Hill 2001). Such a link has also been investigated in children with abnormal oral-motor skills (including articulation problems), which were found to be associated with below-average fine motor performance (Newmeyer et al 2007). The potential link between these two functions further suggests the possible presence of an underlying motor cause, for instance a more global problem in planning and processing of fine motor movements (Dewey 1993; Newmeyer et al 2007). In this regard, a study of the association between speech production and motor maturity in twins found that the same genes that are risk factors for speech production also affect motor skills (Bishop 2002). Our findings of combined articulation and fine motor deficits in the four patients are also consistent with the nature of GA I cerebral pathology, which affects the striatal neural system known to underlie the production and coordination of motor movements (Groenewegen 2003; Strauss and Morton 2003).

Intellectual disability

Although there is evidence for intellectual disability in some GA I patients (Hoffmann et al 1996), it must be noted that patient 4's social and familial history is complex and includes prematurity and a period of reported neglect during early childhood for which he was placed in foster care, where his motor and language skills improved considerably. This suggests that his lower baseline functioning may not be directly explained by GA I; rather, environmental deprivation may have been an added risk factor. In support of this,

Breslau (1990) has demonstrated a *double-hazard effect* whereby the combination of brain pathology and environmental disadvantage result in poor outcomes in children. Further to this, Dennis (2000) suggested that neurobehavioural outcome is not merely a reflection of the risk associated with a particular medical condition, but rather may be thought of cumulatively as an algorithm expressed by the biological risk associated with the medical condition, moderated by environmental factors such as development and reserve available within the child, family, school and community environments. In this sense, the cognitive and behavioural outcome observed in GA I is likely to reflect a certain amount of variability in accordance with the environment and resources available to each child during development. The observation of average outcomes in terms of intellectual, attentional, mnesic, executive, adaptive and behavioural functions in three of our patients but not in the fourth underscores the fact that cognitive outcome may be vulnerable to extreme environmental factors, such as neglect or deprivation. On the other hand, we cannot exclude the possibility that patient 4 belongs to a small class of patients with GA I whose clinical presentation is insidious and whose overall clinical disability evolves over time and includes intellectual disability (Hoffmann et al 1996). Alternatively, it may also suggest a prenatal effect of the disorder on the developing brain, as has been suggested (Superti-Furga and Hoffmann 1997).

In summary, the case reports presented here provide a firm argument for an early neuropsychological assessment in patients with GA I, diagnosed through newborn screening. This assessment can reveal subtle symptoms such as reduced fine motor function, as well as articulation problems, even in the context of a generally age-appropriate cognitive profile. These findings indicate that despite appropriate treatment since birth patients with GA I may have mild fine motor and articulation problems, and raise the question of prenatal damage or subtle postnatal on-going neurotoxic effects of glutaric and hydroxyglutaric acids, or both. Documenting such difficulties early in development can provide a basis for timely referral to appropriate intervention programmes, thus maximizing the potential for better neurobehavioural outcomes in children with GA I. Further follow-up of these young patients at later stages of neurological and cognitive maturity, as well as neuropsychological assessments in larger cohorts of patients with GA I identified through newborn screening, possibly treated according to other treatment regimens, will be helpful in determining the long-term profile and outcomes of these children.

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