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ORIGINAL ARTICLE

# Behavioural and emotional problems, intellectual impairment and health-related quality of life in patients with organic acidurias and urea cycle disorders

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**Abstract**
*Background* Organic acidurias (OADs) and urea cycle disorders (UCDs) are inborn metabolic disorders with a risk for acute and chronic metabolic decompensation resulting in impairments of the central nervous system and other organ systems. So far, there is no systematic study of intellectual functioning, behavioural/emotional problems and health-related quality of life (HRQoL), and how these domains are connected.
*Methods* Data of 152 patients with OADs ($n$=100) and UCDs ($n$=52) from the European Registry and Network of intoxication type Metabolic Diseases (E-IMD) using standardized instruments were compared with normative data.
*Results* Behavioural/emotional problems are increased in OADs or UCDs patients by a factor of 2.5 (3.0), in female asymptomatic carriers of X-linked inherited UCD ornithine transcarbamylase deficiency (fasOTCD) by a factor of 1.5. All groups show similar patterns of behavioural/emotional problems, not different from epidemiological data. Mental disability (IQ≤70) was found in 31 % of OAD, 43 % of UCD, but not in fasOTCD subjects. HRQoL was decreased in the physical domain, but in the normal range. Behavioural/emotional problems were significantly associated with intellectual functioning (OR=6.24, 95 %CI: 1.39–27.99), but HRQoL was independent from both variables.
*Conclusions* Patients with OADs and UCDs show increased frequencies of mental disability and behavioural/emotional problems. Profiles of behavioural/emotional problems were similar to epidemiological data. Intellectual disability and behavioural/emotional problems were strongly associated. Patients' HRQoL was in the normal range, possibly compensated by coping strategies of their families. Diagnostics and clinical care of OAD/UCD patients should be improved regarding behavioural/emotional, intellectual and quality of life aspects.

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**Abbreviations**

| | |
|---|---|
| ARG1 | Arginase 1 |
| ASL | Argininosuccinate lyase |
| ASS | Argininosuccinate synthetase |
| CPS1 | Carbamylphosphate synthetase 1 |
| E-IMD | European registry and network for intoxication type metabolic diseases |
| fasOTCD | Female asymptomatic OTC deficiency carrier |
| fsOTCD | Female symptomatic OTC deficiency carrier |
| GA1 | Glutaric aciduria type 1 |
| HHH syndrome | Hyperammonemia-hyperornithinemia-homocitrullinuria syndrome |
| HRQoL | Health-related quality of life |
| IMD | Inherited metabolic disease |
| IVA | Isovaleric aciduria |
| MI | Mental illness |
| MMA | Methylmalonic aciduria |
| mOTCD | Male OTC deficiency |
| NAGS | N-acetylglutamate synthase |
| OAD | Organic aciduria |
| OTC | Ornithine transcarbamylase deficiency |
| PA | Propionic aciduria |
| UCD | Urea cycle disorder |

## Introduction

Organic acidurias (OADs) and urea cycle disorders (UCDs) are rare inherited metabolic diseases (IMDs). Estimated prevalences are one in 35,000 (UCD) and one in 30,000–14,000 (OAD) new-borns (Kolker et al 2015b). Disorders present with acute and/or chronic metabolic intoxication of the central nervous system, resulting in neurological and intellectual impairment, and behavioural/emotional problems. Intellectual disability was reported in 55–80 % of UCD patients (Gyato et al 2004; Krivitzky et al 2009; Msall et al 1988), with 16 % showing mild behavioural/emotional problems without clinical significance (Krivitzky et al 2009). Classic OADs showed developmental delay in 25–65 % of patients with methylmalonic aciduria (MMA), 59–100 % with propionic aciduria (PA) (Baumgartner et al 2014), and 15–55 % with isovaleric aciduria (IVA) (Grunert et al 2012). In glutaric aciduria type 1 (GA1), developmental delay depends on the manifestation of dystonic movement disorder during infancy. Untreated, up to 95 % show delayed achievement of gross motor milestones, whereas normal development can be significantly increased by newborn screening programmes (Heringer et al 2010; Kolker et al 2007). In contrast to the severe motor handicap, cognitive function is usually thought to be preserved in GA1 patients. Although psychosocial factors, emotional problems and health-related quality of life (HRQoL) are regarded to be meaningful outcome parameters for MMA and PA, systematic investigations are lacking (Baumgartner et al 2014). Neurological outcome and metabolic treatment can induce profound changes in biographies and daily life of patients and their families (de Ridder et al 2008). However, systematic data on HRQoL of patients with OADs or UCDs are sparse and inconsistent, showing either no difference to norms or worse adjustment (Zeltner et al 2014).

This study is an exploratory data analysis (Leek and Peng 2015) of OAD and UCD patients, and has four aims: (1) to describe behavioural/emotional problems, (2) to describe intellectual functioning, (3) to describe HRQoL and (4) to investigate how the three areas are interrelated. Instead of using the term psychiatric symptoms (Walterfang et al 2013), we prefer the concept of behavioural/emotional problems for three reasons. First, the chapter V "Mental and behavioural disorders" of the system of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) (World Health Organization 2004a) classifies mental disorders with an aetiology in cerebral disease, brain injury, or other insult leading to cerebral dysfunction separately. The multiaxial system of *Diagnostic and Statistical Manual of Mental Disorders* version IV (American Psychiatric Association 2000), coded medical or neurological problems relevant to mental problems separately on Axis III. However, the DSM-5 system has removed multiaxial coding to permit that in fact psychiatric disorders are medical disorders (Kupfer et al 2013). Second, many patients with OADs or UCDs are not developed according to age. In the same way as a child below chronological age 5 years will not get an ICD-10 diagnosis of enuresis (F98.0), the same will be true for an older person with a developmental age below five. Third, most psychological problems do not fulfil the criteria of a psychiatric diagnosis, either due to severity or frequency.

## Patients and methods

The European registry and network for intoxication type metabolic diseases (E-IMD, EAHC no. 2010 12 01) is a project, which has received funding from the European Union in the framework of the Health Programme. It has been executed without industrial sponsoring. Detailed descriptions of the registry and the phenotype of OAD and UCD patients — with the exception of an analysis of behavioural and emotional problems — have been published recently (Kolker et al 2015a, b, c). The present study was approved by the local ethic committee of the coordinating centre (i.e. University Hospital Heidelberg, application no. S-525/2010) and then by all clinical partners. The complete sample of the E-IMD database is described in Supplementary Table 1 of the Appendix reporting sample sizes for each of 11 disorders (four OADs, seven UCDs) (cut-off date 25th August, 2014) and the subsamples of patients equal or older than 5 years of age, and

the respective age distributions. Female OTCD carriers were divided into symptomatic (fsOTCD) and asymptomatic (fasOTCD) subjects, as they have definitely different natural histories, reflecting differences in individual X-inactivation and thus residual OTC activity.

## Instruments

For the three domains investigated in this study three different types of standardized instruments have been used.

### Emotional and behavioural problems

Patients or caregivers were interviewed about 33 items of possible behavioural and emotional problems. Items were selected from the symptom list of a standardized psychiatric instrument (Esser 1989) and covered extraversive, introversive, autistic, attention deficit hyperactivity disorder (ADHD), and psychosomatic spectra (aggressiveness, anorexia, anxiety, complaining pain, compulsive behaviour, difficulties falling asleep, distractibility, encopresis, enuresis, hyperactivity, impulsiveness, lying, mood swings, mutism, overeating, phobias, pica, problems communicating wishes, problems understanding other people's feelings, being sad or unhappy, self-endangering behaviour, self-mutilation, self-stimulation, inappropriate sexual behaviour, short attention, being shy or timid, social withdrawal, stealing, substance abuse, temper tantrums, tics, waking up at night, yelling). Patients (when≥13 years and competent to understand the procedure) or carers had to indicate whether or not a behavioural/emotional attribute (e.g. being anxious) was considered as characteristic or not for the patient during the period of the last six months. For answers in the affirmative, severity (mild to moderate vs. severe) and frequency (at times vs. frequently) of the attribute had to be indicated. Finally, the respondent had to judge whether or not a characteristic attribute interfered with family life. The interview approach (Rutter and Cox 1981) does not end up with a psychiatric diagnosis as a categorical judgment but with a dimensional description of traits persistent over time and across situations. Motor behaviour or movement disorders were not included in our definition of behaviour.

### Intellectual functioning

Intellectual functioning was classified to be normal vs. intellectually disabled, based on the assessment by standardized IQ tests [Wechsler Adult Intelligence Scale (WAIS-IV), Wechsler Intelligence Scale for Children (WISC-IV), and Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III); scores<70 were classified as intellectually disabled], developmental tests [Denver Developmental Screening Test (DDST-II); developmental age appropriate/not appropriate for chronological age] or expert rating (e.g. derived from normal vs. special school attendance or not being testable).

### Health-related quality of life (HRQoL)

HRQoL was measured with the Pediatric Quality of Life Inventory Version 4 (PedsQL) (Varni et al 1999, 2007) [self-report form if competent to understand the procedure or parent report forms for children 5–7 and 8–12 years respectively, and adolescents 13–18 years], and the WHOQOL-BREF-2004 [a 26 items instrument for adults (World Health Organization 2004a, b)]. The PedsQL questionnaire measures functioning and adaptation in physical, emotional, social, and academic domains during the last month. The WHOQOL-BREF-2004 covers the domains of physical functioning, emotional functioning, social relationships and environmental resources (including work satisfaction and financial resources), and asks for a retrospective evaluation of the last 2 weeks.

### Statistical analysis

For descriptive statistics, computation of Pearson correlation coefficients and odds ratios with confidence intervals, $Chi^2$ test, Fisher's Exact test, principal component analysis and ANOVA, SPSS (IBM SPSS Statistics 22.0) was used. To compare distributions with the Anderson-Darling k-sample test, R package "adk" was applied (Scholz F (2011) adk: Anderson-Darling K-Sample Test and Combinations of Such Tests. R package version 1.0-2. http://cran.r-project.org/src/contrib/Archive/adk/). For computation of average odds ratios and confidence intervals the R function "metagen" in R package "meta" (Schwarzer G (2015) meta: General Package for Meta-Analysis. R package version 4.1-0. http://CRAN.R-project.org/package=meta) was used.

## Results

### Emotional and behavioural problems

Data were available for 100 OAD and 52 UCD patients (Supplementary Table 2). Compared with the total E-IMD sample this subsample contained relatively more patients with OADs and less patients with UCDs [$Chi^2$ (df=2, $N$=152)=7.86, p(2-sided)=0.020]. Disparity between the total sample distribution and the data sample distribution could not be explained. However, the distributions of diagnoses within the two groups of disorders were not significantly different from the total sample [OADs: $Chi^2$ (df=3, $N$=385)=4.96, p(2-sided)=0.17; UCDs: [$Chi^2$ (df=6, $N$=255)=3.53, p(2-sided)=0.74]. Distributions for sex [Anderson-Darling k-sample test adjusted for ties: T.AD=0.66, p(2-sided)=0.179] and age [Anderson-Darling k-sample test adjusted for ties:

T.AD=−0.42, p(2-sided)=0.453] were comparable to the whole sample. The OAD (UCD) data sets contained 75 (32) parent reports and 25 (12) self-reports.

As sample sizes were too small to compare the results of single items, the set of 33 items was reduced by principal component analysis, after varimax rotation resulting in ten different components (dissocial behaviour, dysphoria, attention problems, elimination problems, autistic behaviour, self-damaging behaviour, self-regulating problems, tics, anxious and withdrawing behaviour). Four symptoms were excluded from the analysis due to too low frequencies (inappropriate sexual behaviour and substance abuse were never reported, stealing was stated in only two and pica in four cases). Supplementary Table 3 shows the rotated principle component matrix and the items loading on the different components. Components were judged to be characteristic or interfering if at least one of the items loading on the respective component had been reported to inferfere with family life. As sample sizes for single disorders also were small, in all further analyses patients with an OAD or a UCD were merged into one group respectively. Subjects with fasOTCD were analysed separately.

Supplementary Fig. 1 shows percentages of characteristic components for subjects with a UCD, an OAD, or fasOTCD and data from an epidemiological study using a similar symptom list in a group of 191 physically healthy adolescents at the age of 13 years (Esser 1989), comparable to the age characteristics of the E-IMD sample (median=12.6 years; IQR 8–18 years). These data originate from parallel interviews of children and parents combined by a clinical conference of both interviewers resulting in a consensus judgment to determine the final assessment. Distributions of characteristic components reported by parent and self-reports were highly correlated (OAD: $r$=0.893, $p$>0.001; UCD: $r$=0.732, $p$=0.016), and therefore combined to a single data set to increase sample size.

Figure 1 shows distributions of components interfering with family life. Not all components reported as characteristic were interfering with family life, and again patients with UCDs and OADs showed a rather similar pattern. The probability that characteristic components were reported to be interfering increased from mild presentation at times to frequent and severe presentation (data not shown). The sample of fasOTCD was too small to draw any meaningful conclusion.

Distributions of interfering components in proxy- and self-reports showed lower and non-significant correlations (OAD: $r$=0.513, $p$=0.129; UCD: $r$=0.305, $p$=0.391). This result was not unexpected, as patients able to give self-reports are better functioning than patients unable to give self-reports. However, to increase sample size proxy- and self-reports were also combined. Except from interfering components of asymptomatic female OTC carriers, percentage distributions of all other groups were highly and significantly correlated (Table 1).

One-way ANOVA of average percentages across all characteristic components by group (OAD, UCD, fasOTC) was significant [F(3, 36)=3.38; $p$=0.028]. Compared with the epidemiological data (9.9 %), asymptomatic female OTC carriers (16.3 %), OAD (25.3 %), and UCD (29.8 %) showed increased prevalences of components.

Numbers of characteristic and interfering components per patient were discretized as 0, 1, 2–4 and ≥5. Number of characteristic components was not related to group of disorder [Fisher's Exact test p(2-sided)=0.288], sex [Fisher's Exact test p(2-sided)=0.530], but significantly associated with intellectual function [Fisher's Exact test p(2-sided)=0.001]. Intellectually disabled patients showed more components than normal ones [Fisher's Exact test p(2-sided)=0.001], and parents reported more components than patients themselves [Fisher's Exact test p(2-sided)=0.026]. Number of interfering components was associated with group of disorder [Fisher's Exact test p(2-sided)=0.054; UCD patients showing more components], with intellectual functioning [Fisher's Exact test p(2-sided)=0.006; intellectually disabled patients showing more components], but not with sex [Fisher's Exact test p(2-sided)=0.694]. A trend was observed for type of respondent [Fisher's Exact test p(2-sided)=0.083], with parents reporting more interfering components than patients.

## Comparison of characteristic and interfering components

Comparing the data from Supplementary Fig. 1 and Fig. 1, distributions of characteristic and interfering components were correlated for all patients ($r$=0.839, $p$=0.002, $n$=152), as well as for OAD ($r$=0.802, $p$=0.005, $n$=44) and UCD patients ($r$=0.802, $p$=0.005, $n$=44), but not for fasOTCD ($r$=0.067, $p$=0.854, $n$=8). Females ($n$=82) and males ($n$=70) showed similar distributions for characteristic ($r$=0.957, $p$<0.0001) and interfering ($r$=0.932, $p$<0.0001) components.

Repeated ANOVA of number of characteristic and interfering components by group of disorder (Fig. 2) revealed significant effects for disease group [F(2149)=3.12, $p$=0.047] and for characteristic vs. interfering components [F(1149)=80.21, $p$<0.0001; Greenhouse-Geisser], but no significant interaction of number of characteristic vs. interfering components by disease group [F(2149)=1.21, $p$=0.303; Greenhouse-Geisser].

On average in UCD patients characteristic components were interfering 1.48 times more frequently than in OAD patients [95%CI (1.0694; 2.0416), $p$=0.018].

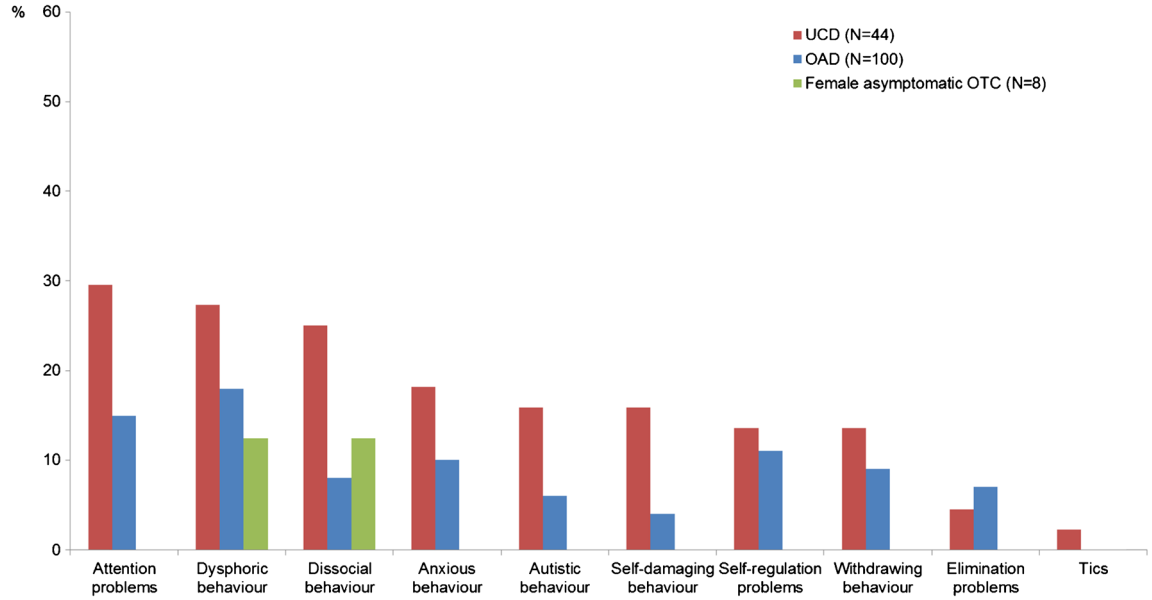


**Fig. 1** Distributions of components interfering with family life by group of disorder

## Attributes of characteristic components: severity and frequency

Each component characterizing a patient had to be classified as mild to moderate vs. severe and occurring at times vs. frequently. Odds for severe vs. mild/moderate characteristic components were similar for UCD vs. OAD patients [OR=1.19, 95%CI (0.806–1.7645), $p$=0.378]. The same was found for characteristic components appearing frequently vs. at times in UCDs vs. OADs [OR=0.91, 95%CI (0.6271–1.3342), $p$=0.643]. Data were in the same direction for parent reports and self-reports.

## Intellectual functioning

For 133 of the 152 patients who have been investigated for behavioural/emotional problems, evaluations of intellectual functioning were available (79 Wechsler IQ tests: WPPSI, WISC, or WAIS; 12 standardized developmental investigations using the Denver scales, and 42 expert ratings by health care professionals in charge of the patient). Based on this information, each patient was classified as normally developed or as intellectually disabled when IQ was less than 70, the patient was untestable, or developmental age was markedly below chronological age. Ninety patients were classified to be normally developed and 43 as intellectually disabled. Mean IQ was 96 (SD=14) for 57 normally developed patients, and 58 (SD=9) for 16 intellectually disabled patients; for six patients information regarding IQ results was only available as intellectually disabled ($n$=3) or normally developed ($n$=3).

Of 88 OAD patients 31 %, and of 37 UCD patients 43 % were intellectually disabled. None of the fasOTCD subjects was intellectually disabled. For 83 patients data regarding intellectual functioning and type of schooling (regular vs. special school) were available. Association between both variables was significant [Fisher's Exact test p(2-sided)<0.001]. Cross-tabulation of classification of intellectual functioning by three groups of patients (UCDs, OADs and fasOTCD) was marginally significant [Fisher's Exact test p(2-sided)=0.051] which can be explained by the fact that asymptomatic female OTC carriers ($n$=8) all had normal IQ test results. Degree of intellectual functioning was not associated with OAD or UCD alone [Fisher's Exact test p(2-sided)=0.217].

Having ≥1 characteristic component was significantly associated with intellectual functioning [$Chi^2$(df=1, $N$=133)=7.10, p(2-sided)=0.013; OR=6.24, 95%CI (1.39; 27.99)]. The same was found for interfering components [$Chi^2$(df=1,

**Table 1** Correlations of percentage distributions for characteristic (C) and interfering (I) components

| | OADs ($n$=100) | UCDs ($n$=44) | fasOTC carriers ($n$=8) |
|---|---|---|---|
| UCDs ($n$=44) | C: 0.914 ($p$<0.001)<br>I: 0.545 ($p$=0.002) | –/– | –/– |
| fasOTCDs ($n$=8) | C: 0.567 ($p$=0.001)<br>I: 0.144 ($p$=0.456) | C: 0.546 ($p$=0.002)<br>I: 0.255 ($p$=0.182) | –/– |
| Epidemiological sample ($n$=191) | C: 0.453 ($p$=0.051) | C: 0.507 ($p$=0.027) | C: 0.429 ($p$=0.067) |

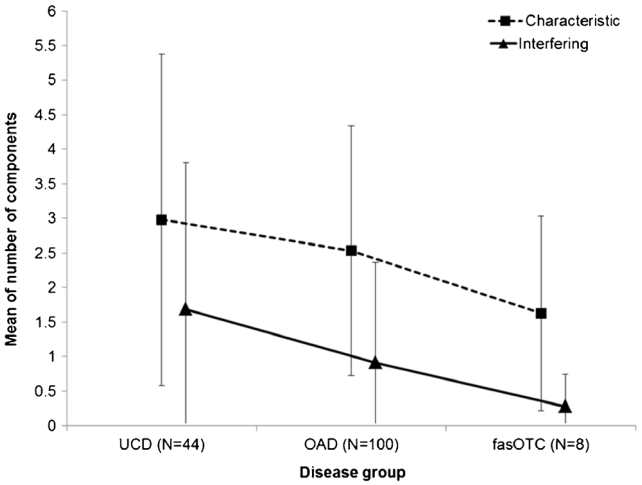


**Fig. 2** Mean number of characteristic and interfering components by group of disorder

*N*=133)=8.02, p(2-sided)=0.005); OR=2.92, 95%CI (1.37; 6.19)] (Table 2).

## Health-related quality of life

Data about HRQoL were available for 124 patients (Supplementary Table 3). The sample is representative for the total E-IMD sample with regard to the distribution of patients with OADs and UCDs, as well as fasOTCD [$Chi^2$(df=2, *N*=124)=4.94, p(2-sided)=0.082], sex [Anderson-Darling k-sample test adjusted for ties: T.AD=−0.56, p(2-sided)=0.497) and age [Anderson-Darling k-sample test adjusted for ties: T.AD=1.17, p(2-sided)=0.108]. For statistical analysis of the association with behavioural/emotional problems we used the variable "characteristic" as sample sizes for "interfering" components were too small. Self-report vs. proxy-report was associated with intellectual functioning and age [$Chi^2$ (df=3, *N*=91)=23.47, p(2-sided)<0.0001]; (Fisher's Exact test p(2-sided)<0.0001]. There was only one data set from an intellectually normal child alone, 83 % of data sets with only parents' reports were about intellectually disabled patients, 80 % of data sets with reports from both patients and parents were about normally developed patients, and 85 % of adults responding were normally developed.

Scores of the four domains of the PedsQL (physical, emotional, social, school functioning), and the four domains of the WHOQOL-BREF (physical functioning, emotional functioning, social relationships and environmental resources) were z-standardized using published normative data (Angermeyer et al 2000; Varni et al 2007). As the two instruments are not based on identical theoretical concepts and items we did separate analyses.

ANOVA of the four domains of the PedsQL by disease group (UCD, OAD), respondent (patient, proxy), intellectual functioning (normal, intellectually disabled), and≥1 characteristic component (yes, no) revealed only a significant main effect for domain [F(3187)=3.60, $p$=0.018, Greenhouse-Geisser]. Respondent [F(1,70)=1.29, $p$=0.261], disease group [F(1,70)=0.02, $p$=0.896], and≥1 characteristic component [F(1,70)=1.29, $p$=0.261] were not significant (Fig. 3). Social and emotional domains were rated highest, and scholastic and physical functioning were at the nadir. The factor intellectual functioning was not significant (F(1,70)=2.17, $p$=0.145). Data for fasOTCD could not be included into the analysis due to small sample size (*N*=2).

Due to missing values for one or more independent variables (IV) of the ANOVA, the sample size was reduced also by non-significant IVs. Therefore, we repeated an ANOVA of the four domains of the PedsQL instrument by disease group (UCD, OAD). Again main effect for domain [F(3378)=5.67; $p$=0.002, Greenhouse-Geisser] was significant. Post hoc tests showed significant mean differences between the social and physical (1.02; $p$<0.001), and the social and emotions domains (0.85; $p$<0.001) with physical functioning being at the nadir. Main effect for disease group was not significant [F(1149)=0.73; $p$=0.395], neither was the interaction with domain [F(3378)=2.48; $p$=0.071].

Back-transformation of z-scores to 0–100 problem scores of the PedsQL (0–24=problem is present almost always; 25–49=often, 50–74=sometimes, 75–100=almost never to never) showed that on the average parents scored a category lower (sometimes) than children (almost never to never), although in absolute terms ratings represented low problem rates (Supplementary Fig. 2 in the Appendix).

ANOVA of the four domains of the WHOQOL instrument by disease group (UCDs, OADs), intellectual functioning (normal, intellectually disabled), and≥1 characteristic component (yes, no) revealed a significant main effect for domain [F(3,39)=5.83; $p$=0.002] (Fig. 4). Post hoc tests showed significant mean differences between the environmental and

**Table 2** Cross tabulation of behavioural/emotional problems and intellectual functioning (for statistical results see text)

| | | Intellectual functioning | | |
|---|---|---|---|---|
| | | Intellectually disabled | Normal | Σ |
| ≥1 component characteristic (interfering) | Yes | 41 (27) | 69 (33) | 110 (60) |
| | No | 2 (16) | 21 (57) | 23 (73) |
| | Σ | 43 | 90 | 133 |

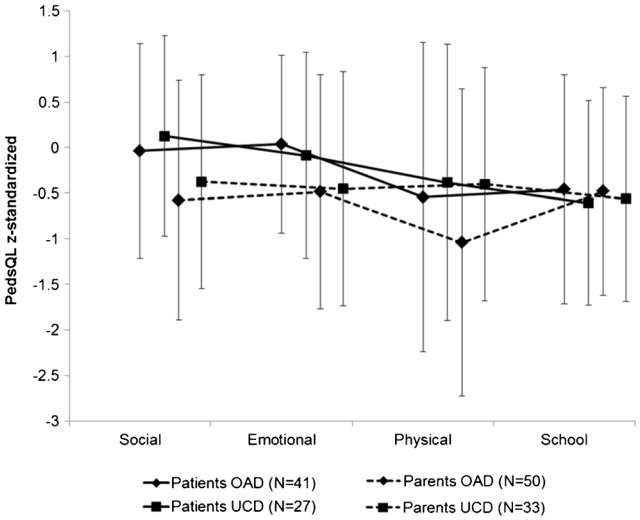


**Fig. 3** Mean z-scores for four domains of HRQoL measured with the PedsQL

physical domain [Mean diff.=1.21; $p$=0.002], with physical functioning being at the nadir. Main effect for disease group was not significant [F(2,13)=0.07; $p$=0.932], neither were any of the interactions. Also intellectual function was not significant [F(1,13)<0.01; $p$=0.962]. In a subsequent ANOVA of the four domains by disease group (UCDs, OADs), main effect for domain was significant [F(3,81)=9.28; $p$<0.001], with post hoc tests showing significant mean differences between the environmental and physical [1.02; $p$<0.001], and the environmental and emotions domains [0.85; $p$<0.001], with physical functioning being at the nadir. Neither main effect for disease group [F(2,27)=1.50; $p$=0.242], nor the interaction with domain [F(2,27)=1.50; $p$=0.242] were significant.

Back-transformation of z-scores to 0–100 satisfaction scores (0–24=not at all satisfied, 25–49=predominantly not, 50–74=halfway, 75–100=predominantly to completely) showed that UCD and OAD patients perceived themselves as predominantly to completely satisfied, whereas the four fasOTC subjects rated themselves as halfway satisfied in the emotional domain. (Supplementary Fig. 3 in the Appendix).

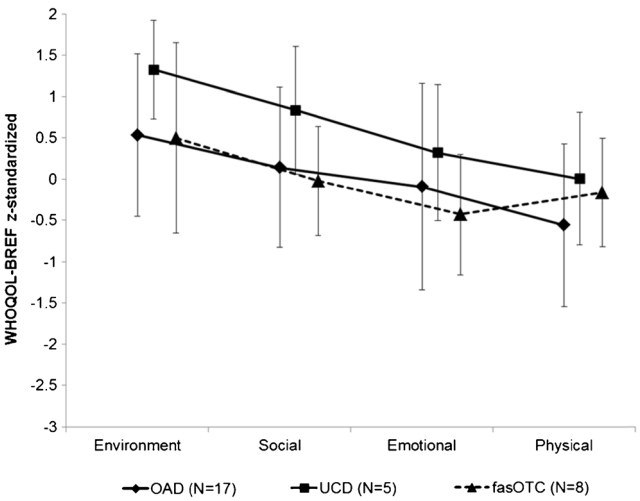


**Fig. 4** Mean z-scores for four domains of HRQoL measured with the WHOQOL-BREF

## Discussion

The present study is an exploratory data analysis searching for trends and relationships between three domains of measurements in two groups of IMDs. The type of analysis is also inferential quantifying whether data sets will hold beyond our own study. Overall, our results are in line with previous research, and without being redundant, add an original contribution on the possible relationship between the behavioural/emotional, intellectual, and HRQoL domains. Although our study has no randomized design, we can hypothesise about possible reasons underlying the pattern we have found (Leek and Peng 2015).

Even though the samples investigated were smaller than the total samples of the E-IMD register, except from the preponderance of OAD patients in the behaviour/emotion analysis, all samples analysed were representative for age, sex and group of disorder. Regarding the four aims of our study we come to the following conclusions.

### Patients with UCDs, OADs and fasOTCD carriers show similar distributions of characteristic and interfering behavioural and emotional problems

Distributions of problems being characteristic for patients as well as those interfering with family life showed similar patterns. The most frequent components interfering with family life were attention problems, and dysphoric emotionality, followed by dissocial behaviour and problems of regulation of self or social relationships. Elimination problems and tics were at the lower end of the distribution. The association of interfering components with frequency of occurrence and severity is in favour of the internal validity of the data. The same data patterns were observed for female and male patients. Proxy and self-ratings showed the same pattern for characteristic but not for interfering problems, which can be explained by two reasons. First, a common dissimulation trend in self-ratings (Canning 1994), and second, patients unable to give a self-report might be more handicapped than those who are able. Distributions of characteristic components for all three patients groups were also similar to those of an epidemiological sample, however showing increased prevalence by factors of about 1.5 for fasOTCD, 2.5 for OADs and 3.0 for UCDs.

These results are only partly in line with other studies. Much lower rates for externalizing and internalizing behaviour in UCD patients have been reported from the Urea Cycle

Disorders Consortium (Krivitzky et al 2009). No particular behavioural/emotional outcomes were found for fasOTCD (Gyato et al 2004). Further and more detailed investigation of fasOTCD subjects seems to be indicated. In a case series of nine patients with UCDs (three OTCD, two CPSD and two ASSD and ASLD each) (Serrano et al 2010) all patients underwent exhaustive psychiatric evaluation and assigning DSM-IV diagnoses. Patients showed confusion, anxiety, aggressiveness, speech and language problems, depression, impulsiveness, ADHD, autism, eating disorders and pica. The behavioural/emotional phenotype was nonspecific, and comorbidity with mental disability was constant. The whole spectrum of behavioural/emotional problems has also been reported in review papers (Gropman et al 2007).

## Intellectual disability is more prevalent in UCDs than in OADs

Intellectual disability defined as IQ≤70 was found in 31 % of OAD and 43 % of UCD patients, but never in fasOTC. These results are in line with other studies regarding intellectual functioning (Krivitzky et al 2009; Msall et al 1988). In a larger study of fasOTCD subjects, intellectual functioning was in the normal range, although the authors reported a specific neurocognitive phenotype (Gyato et al 2004).

## Health related quality of life was found to be normal but generic instruments may have poor sensitivity

HRQoL measured with the PedsQL or the WHOQOL was not associated with disease group, but showed a consistent pattern with social and emotional domains rated better than physical and academic functioning. Overall patterns of parents' and self-reports were congruent, particularly regarding the sequence of the subdomains of the PedsQL, rating emotional and social satisfaction higher than physical and scholastic satisfaction. Compared with published normative data (Varni et al 2007) the domain effect was in the same direction as for oncology patients, but different from healthy children who rated physical and social domains higher than school and emotional domains. However, although not significant but also in line with oncology data, parent ratings were slightly lower than childrens' self-ratings, a characteristic finding for children with health conditions but not for healthy children (Upton et al 2008). HRQoL of patients was in the normal range. Systematic reviews on psychological wellbeing and QoL in patients with chronic disease in general and intoxication type IMD in particular reported inconsistent results (Barlow and Ellard 2006; Zeltner et al 2014), finding patients' QoL to be better, equal or worse compared to population norms. Several factors might contribute to this result. According to the disability paradox, i.e. the fact that the majority of individuals with moderate to serious disabilities report having an excellent or good quality of life (Albrecht and Devlieger 1999), respondents focus on their coping facilities, strengths, or positive experiences in daily routine activities, and not on their weaknesses, failures, or unpleasant experiences (Ubel et al 2005). We also used generic instruments measuring HRQoL, with possibly low or no sensitivity to detect disease-related limitations (Zeltner et al 2014). Our finding, that self-reported HRQoL was consistently better than proxy-reports, might be due to the fact, that parents unburden their children by coping with the whole situation (Miller 1993), however, on the cost of their own QoL. A survey conducted together with the National Urea Cycle Disorder Foundation, a parents and patients organization, revealed the life changing nature of having a child with a metabolic disorder resulting in significant emotional and financial stress for parents (Cederbaum et al 2001). Fifty per cent of parents thought daily of the death of their child, 75 % at least weekly, and reported living in uncertainty about the child's life from one lab to the next. It is important to note that the professionals on the panel would have been less likely to have predicted this frequency than the representatives of the foundation, a discrepancy in perspectives not limited to OAD and UCD patients (Gramer et al 2014).

Our last aim was to investigate how the behavioural/emotional, intellectual and HRQoL areas are interrelated. Behavioural and emotional problems of patients with OADs and UCDs were significantly associated with intellectual functioning. This may indicate that intellectual impairment, i.e. decrease of vigilance as well as mental and global developmental disability, caused by acute and/or chronic metabolic decompensation, will secondarily cause behavioural/emotional problems. However, the underlying metabolic disturbance could also be a common cause resulting in two parallel effects.

No statistical effects of behavioural problems or intellectual functioning on HRQoL were found. The association between intellectual functioning and type of schooling may have boosted, and thereby levelled, the ratings of the academic QoL, as the items measure the adaptation to school requirements. Our finding that HRQoL appears to be an independent area of the patients' lives can be explained by the disability paradox, and parental unburdening by vicarious coping.

Our data corroborate the general finding that chronic illness significantly increases the risk for psychiatric disorders in children and young adults with a chronic disease (Bennett et al 2015), but also that chronic illness, notably when involving the central nervous system, is not associated with particular diagnoses (Cottrell 2015), as similarities of experience for children with chronic illness outweigh the differences due to particular diagnoses (Pless and Nolan 1991). UCDs and OADs are literally chronic conditions, they persist lifelong.

Are psychiatric concepts appropriate for metabolic patients? So far we have avoided calling behavioural/emotional problems psychiatric symptoms or psychiatric diseases. It has been repeatedly argued that individuals with intellectual/developmental disabilities (IDD) and mental illness (MI) are at risk to be inappropriately diagnosed (Fletcher et al 2009), as the diagnosis of IDD may overshadow the presence of psychopathology (Dykens 1998). However, the situation of patients with IMDs is even much more complicated, possibly making this issue easier to be tackled. Although not completely understood, acute and chronic metabolic imbalance in OADs and UCDs result in specific organic impairments. Therefore, these patients deserve a triple diagnosis, i.e. a chronic metabolic disorder leading to neurological impairment of the CNS, resulting in IDD and MI. Our results show that patients with OADS and UCDs did not show different profiles of problem areas, also similar to those of physically healthy controls. This is well in line with the so-called "non-categorical approach" suggesting, that similarities of experiences of chronic illness outweigh differences due to particular diagnoses (Cottrell 2015). In the present context the most salient similarity of all patients is the organic experience of a deranged metabolism leading to neurological damage. This is not to say that the behavioural/emotional problems of patients and families are nothing but intellectual problems. However, metabolic disorders may mimic psychiatric symptoms, and it has been shown that psychiatric pharmacotherapy is not, but metabolic treatment is effective (Serrano et al 2010). In the same way, it would be ill-advised to treat MI with OAD or UCD regimen. It might be more promising to interpret behavioural/emotional problems in a developmental perspective as it has been shown for the effective behavioural training approach. Feeding problems in OADs and UCDs may be caused by alterations in serotonin or other neurotransmitter imbalance, but may also be due to a conditioned response after a history of aversive feeling of nausea after ingestion of protein. In a positive reinforcement and parental guidance approach, food refusal could be successfully and persistently treated in five out of six patients in the age range of 14 months to 8 years (Hyman et al 1987).

What do our results teach us about quality of life? The use of generic QoL instruments may have been incommensurate, but it might also be inadequate to develop instruments for each rare disorder, particularly if it would be true, that "The administration of the instruments for individual patients will be most useful if the completion of the questionnaire is used as a discussion point between the patient and family (as appropriate) in the context of a consultation p.80" (Waters 2000). However, the fact that good quality of life has also been observed in other diseases (Albrecht and Devlieger 1999; Kunz et al 2011) should not result in an overestimation of patients' capacities and responsibilities (Holman and Lorig 2000). The personal and economic burden on families and children is immense (Cederbaum et al 2001; Cottrell 2015; Gramer et al 2014).

What can be concluded from the present result regarding possible interventions? OADs and UCDs are not only difficult to diagnose, but also treatment requires a deep understanding of metabolic medicine, drug and dietary measures, monitoring of maintenance and emergency treatment and skills of the necessary adaption in daily life. Therefore, it is not surprising, that child psychiatrists are reluctant because they feel insecure in the face of medical problems (Pless and Nolan 1991). Therapeutic and preventive interventions are not primarily psychiatric, but require behavioural and psychological medicine, i.e. behaviour change in managing chronic illness, adherence, restrictions and adaptation of activity, and regular monitoring, including family and community integrated care. The field needs clinicians who are strong in biomedical care of sick children (Stein 2015).

## Limitations

The main limitation of this study is the small sample size for fasOTCD and that no differentiation for single UCDs and OADs, neither for subtypes of single disorders with known associations to phenotypes, like $B_{12}$-responsive MMA (Horster et al 2007), or severe vs. mild forms (Grunert et al 2012) was possible. Furthermore, we did not distinguish early from late onset patients, for whom different results in cognitive outcome but not for behavioural/emotional domains have been reported (Krivitzky et al 2009). Last but not least, our data are outcome but not process-oriented, i.e. they do not allow to understand how different medical aspects of the disorders have contributed to the psychological facets. We also have not investigated coping styles possibly leading to normal QoL (de Ridder et al 2008) nor the price of coping strategies like recalibration, reprioritization and reconceptualization leading to better adjustment (Sprangers and Schwartz 1999).

## Conclusions

Patients with OADs and UCDs are at a threefold risk for metabolic chronic and acute decompensation resulting in organic, intellectual as well as behavioural/emotional problems. Both groups of disorders show significant and substantial increases of intellectual disability and behavioural/emotional problems. Patients with OADs or UCDs and also subjects with fasOTCD show similar profiles of behavioural and emotional problems comparable to the one of epidemiological data. Intellectual disability and behavioural/emotional problems are strongly associated with intellectual functioning. HRQoL of the patients was independent from the other variables and in the normal range; however, the "price" is

probably paid by coping and compensation strategies of the families. Behavioural health has historically been addressed at the level of speciality service clinics, but this separation between mental health care and medical health care is no longer feasible, the field of metabolic medicine needs clinicians who are strong in biomedical care of sick children (Kupfer et al 2013; Stein 2015), i.e. diagnostics and clinical care of OAD/UCD patients should also be improved with respect to behavioural/emotional, intellectual and quality of life aspects.

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**Compliance with ethics guidelines**

**Conflict of interest** None.

**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. Informed consent was obtained from all patients or their legal guardians prior to being included in the study in countries where this was needed by law.

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