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ORIGINAL ARTICLE

Living with an inborn error of metabolism detected by newborn screening—Parents' perspectives on child development and impact on family life

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Abstract
Background Newborn screening for inborn errors of metabolism is regarded as highly successful by health professionals. Little is known about parents' perspectives on child development and social impact on families.
Methods Parents of 187 patients with metabolic disorders detected by newborn screening rated child development, perceived burdens on child and family, and future expectations on a questionnaire with standardized answers. Parental ratings were compared with standardized psychometric test results. Regression analysis was performed to identify factors associated with extent of perceived burden.
Results In 26.2 % of patients, parents perceived delays in global development and/or specific developmental domains (physical, social, intellectual, language). Parents expected normal future development in 95.7 %, and an independent adult life for their child in 94.6 %. Comparison with psychometric test results showed that parents of children with cognitive impairments tended to overrate their child's abilities. Mild/medium burden posed on the family (child) by the metabolic disorder was stated by 56.1 % (48.9 %) of parents, severe/very severe burden by 19.3 % (8.6 %). One third of families reported financial burden due to the metabolic disorder. Dietary treatment and diagnoses with risk for metabolic decompensation despite treatment were associated with higher perceived burden for the family. Disorders rated as potentially very burdensome by experts were not rated accordingly by parents, demonstrating different perspectives of professionals and parents.
Conclusion Although newborn screening leads to favourable physical and cognitive outcome, living with a metabolic disorder may cause considerable stress on patients and families, emphasizing the need for comprehensive multidisciplinary care including psychological and social support.

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Background

Newborn screening for inborn errors of metabolism, performed in many countries worldwide, is highly successful in prevention of health impairments. Outcome studies for single disorders (Nennstiel-Ratzel et al 2005; Kölker et al 2007; Wilcken et al 2007), and for comprehensive screening panels (Wilcken et al 2009; Lindner et al 2011), have shown that it allows for presymptomatic diagnosis and early treatment, resulting in mostly normal physical and intellectual development.

Quality of life and stress are important outcome parameters for health programmes concerning inborn errors of metabolism (World Health Organization 1997; Dellve et al 2006; Biesecker and Erby 2008; Sinha et al 2008). Systematic information about

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parents' perspectives on child development, expectations for the future and burdens on family life in inborn errors of metabolism detected by newborn screening will help to further improve care and support for patients and their families.

Patients and methods

In 360 of 1.349.603 newborns screened from 1999 until 2011 at the University of Heidelberg newborn screening centre, a metabolic disorder was confirmed. Parents of 220 patients gave written informed consent to participate in a study on long-term outcome. Patients who did not participate in this part of the study (n=140) either were not yet invited, lost to follow-up, or declined to participate. Data on physical and intellectual outcome have been previously reported (Lindner et al 2011). Here we report parental ratings of child development for 187 patients.

In April 2005 the German Federal Joint Committee enacted a screening panel including 12 metabolic disorders. During a pilot period from January 1999 until April 2005 the German screening panel was not regulated, and all metabolic disorders detectable by tandem-mass spectrometry recommended in the US panel (National Newborn Screening & Genetics Resource Center Austin Texas http://genes-r-us.uthscsa.edu/) were screened for in our centre. This study includes 161 patients with disorders of the "panel 2005", and 26 patients with disorders of the "additional panel" (Table 1). Both panels were analysed separately, in order to gain information on the disorders detected by current newborn screening practice in Germany, and to learn whether disorders currently excluded from screening in Germany are perceived differently by families than disorders from the "panel 2005".

Questionnaire

Parents rated their child's global and domain specific development as either accelerated, normal, or delayed in comparison to children of the same age without a metabolic disorder. Developmental domains were physical growth, social behaviour (interactions with peers and adults), intellectual functioning and language. For further analysis the rating scale was dichotomized to: normal/accelerated versus delayed development.

Regarding future expectations, parents could choose between four alternatives: development will continue to be normal, become normal, developmental problems will persist, or increase. Concerning future adult life, parents were asked if they expect that their child will live independently (like people without a metabolic disorder, e.g. go to work, live on their own, etc.), with some support (e.g. assisted living), or will always depend on help and care.

Perceived burdens due to the metabolic disorder for the family and child should be rated on a five point Likert scale as none, mild, medium, severe or very severe. For analysis the scale was reduced to three categories: none, mild/medium; severe/very severe burden. Parents were asked to indicate whether monthly net family income was <1500€, 1500–3000€, or >3000€ (representing crude averages for unskilled, skilled, and managerial positions (Statista 2013)), the

Table 1 Patients included in the screening panel 2005 and the additional panel

Group of disorders	Disorders	*N*
Amino acid disorders 2005	PKU	64
	MHP (not included in this study)	0
	MSUD	8
Additional	ASLD	1
	CIT I classic	2
	CIT I mild	1
	TYR I	3
	TYR III	1
Fatty acid oxidation disorders 2005	CPT ID	1
	CPT IID	0
	CACTD	0
	MCADD	46
	LCHADD/mTFP	5
	VLCADD	5
Additional	CTD	2
	SCADD	2
	MADD	1
Organic acidurias 2005	GA I	5
	IVA classic	6
	IVA mild	7
	BIOD	3
Additional	3-MCCD	4
	Cbl C/D	4
	PA	4
	HMG-CoA LD	1
Others 2005	Galactosaemia	11
	Total 2005	161
	Total additional	26
	Grand total	187

ASLD argininosuccinate lyase deficiency; *BIOD* biotinidase deficiency; *CACTD* carnitine acylcarnitine translocase deficiency; *Cbl C/D* cobalamin C/D defect; *CPT ID* carnitine palmitoyltransferase I deficiency; *CIT I* citrullinaemia type I; *CPT IID* carnitine palmitoyltransferase II deficiency; *CTD* carnitine transporter deficiency; *GA I* glutaric aciduria type I; *HMG-CoA LD* 3-hydroxy-3-methylglutaryl-CoA lyase deficiency; *IVA* isovaleric aciduria; *LCHADD* long-chain 3-hydroxy-acyl-CoA dehydrogenase deficiency; *MADD* multiple acyl-CoA dehydrogenase deficiency; 3-*MCCD* 3-methylcrotonyl-CoA carboxylase deficiency; *mTFP* mitochondrial tri-functional protein deficiency; *MCADD* medium-chain acyl-CoA dehydrogenase deficiency; *MHP* mild hyperphenylalaninaemia; *MSUD* maple syrup urine disease; *PA* propionic aciduria; *PKU* phenylketonuria; *SCADD* short-chain acyl-CoA dehydrogenase deficiency; *TYR* I/III tyrosinaemia type I/III; *VLCADD* very long-chain acyl-CoA dehydrogenase deficiency

metabolic disorder was a financial burden for the family, if the family had to cope with additional burdens (e.g. further family members with metabolic disorder or requiring care), and which family members were involved in care for the affected child (mother, father, grandparents, siblings). Questionnaires were completed on routine visits to the metabolic outpatient clinic before communication of psychological test results.

Standardized psychometric tests

Intellectual development was evaluated by standardized psychometric instruments appropriate for age: 1.5 years Denver test or Bayley Scales of Infant Development (BSID-II), 3.5 years K-ABC or WPPSI-III, 6–9 years SON-R-2.5-7, WISC-IV. IQ of at least 85 was considered as normal, results <85, and Denver results not appropriate for age were scored as subnormal.

Statistical methods

For correlations Pearson's r, and for associations between categorical variables chi square tests were used. Differences between ratings for child and family were tested with Wilcoxon signed-rank test (IBM SPSS Statistics 20.0). Perceived stress for the family as a function of type of treatment (dietary vs. medication), risk for decompensation despite treatment, family income, additional burdens, and number of family members taking care of the patient (one vs. several) was analysed using ordinal logistic regression analysis and a partial proportional odds model with SAS procedure NLMIXED (SAS 9.2). Disorders were clustered using SAS procedure FASTCLUS following classification of each disorder by a medical expert regarding a set of five burdensome factors: dietary treatment, medication, risk for metabolic decompensations despite treatment, risk for death, risk for disability. Short-chain Acyl-CoA dehydrogenase deficiency (SCADD) was rated as a non-disease and not included in this analysis. *P*-values≤0.05 were considered statistically significant, values>0.05 and <0.1 reported as trends.

Results

Patients

For patients from the "panel 2005" mean age at evaluation was 3.5 years (SD 2.5; median 2.6; range 0.6–12.5), 45.3 % were male, 54.7 % female. Patients from the "additional panel" had a mean age at evaluation of 4.7 years (SD 2.4; median 5.2; range 1.4–9.7), 50 % were male, 50 % female. 60.4 % of patients were of German, 12.3 % of Turkish origin. All other ethnic backgrounds (n=20) accounted for less than 5 % of patients individually.

Developmental ratings by parents

Panel 2005

For 21.1 % of patients development was rated as delayed by their parents—either globally plus in one or more specific developmental domains (n=6), or just in one or more specific domains (n=28). Development was rated as normal/accelerated in all domains for 78.9 % of patients. The domain most frequently reported as delayed was language (25 of 161; 15.5 %). Intellectual (3 of 160; 2 %) and social behavioural (4 of 160; 3 %) problems were rarely reported. Isolated language delay with normal development in all other areas was reported for 10.7 % of patients (17 of 161). Percentage of reported developmental delay did not differ between patients born before April 2005 or born afterwards (χ^2(df=1, n=161)=0.32; p=0.700, two-sided).

Additional panel

For 57.7 % of patients, parents reported delayed development - in global development only (n=1), global development plus one or more specific domains (n=6), or just in one or more of the specific domains (n=8). Normal/accelerated development in all aspects was reported by 42.3 % of parents. Language was most frequently reported as delayed (9 of 25; 36 %). Isolated language delay with normal development in all other areas was observed by 11.5 % of parents. Percentage of reported developmental delay was significantly higher in the "additional panel" than in patients with "panel 2005" disorders born before April 2005 (χ^2(df=1, n=187)=15.49; p=0.001, two-sided).

Parental perceptions versus standardized psychometric test results

Results of standardized psychometric tests (available for 167 patients) were within normal range for 150 patients (89.8 %). Subnormal results were found in 7.6 % of patients from the "2005 panel" (11 of 145), and 27.3 % from the "additional panel" (6 of 22). Parents' evaluations of cognitive development and test results were discrepant for 13 patients (7.8 %). One patient with normal IQ result was perceived as delayed by the parents. In 12 of 17 patients (70 %) with IQ<85 parents rated cognitive development as normal. Mean IQ of these patients was 70 (SD 12.6).

Parental expectations for future development

For the "panel 2005" normal future development was expected by 89.3 % of parents (142 of 159), 8.8 % expected developmental delay to be caught up. Two families expected developmental delay to persist, one family assumed that developmental problems will increase.

All parents who rated their child's current development as normal on all aspects also expected a normal future development (n=126). Of parents reporting a global developmental delay 83.3 % (5 of 6) expected that development will become normal in the future, one family of a child with glutaric adicuria type I (GA I) expected that developmental delay will persist.

The majority of parents reporting developmental delay in one or more specific domain, but normal global development, had positive expectations for their child's future development (92.6 %). They either anticipated that development will continue to be normal (16 of 27; 59.3 %), or that the child will catch up his/her developmental delay (9 of 27, 33.3 %). One family of a child with classical galactosaemia expected persistence of developmental delay, the family of one patient with maple sirup urine disease (MSUD) anticipated developmental problems to increase.

For disorders of the "additional panel" normal development was expected by 61.5 % of parents, 19.2 % anticipated developmental delay to be caught up. For 15.4 % of patients parents expected developmental delay to persist, for one patient developmental problems were anticipated to increase.

Also in this group all parents who rated their child's current development as normal expected normal future development (n=11). In contrast to the "panel 2005 group" only 28.6 % of parents (2 of 7) reporting global developmental delay expected the development to become normal in the future. All parents who observed developmental delay in one or more specific domains, but normal global development, had positive expectations for their child's future development: 62.5 % (5 of 8) believed that development will continue to be normal, 37.5 % (3 of 8) expected that developmental delay will be caught up.

Parental expectations for the child's future

In the "panel 2005" group 98.7 % (157 of 159) of parents expected an independent life for their child. One patient with carnitine palmitoyltransferase I deficiency was expected to require some support, one patient with GA I to always depend on help. In the "additional panel" 69.2 % of parents anticipated an independent life for their child, 23.1 % expected their child to require some support. The expectation that their child will always depend on help was expressed by 7.7 %.

Burdens resulting from the metabolic disorder

Mild/medium burden resulting from the metabolic disorder for the family was stated by 56 % of all parents (n=187), 19 % perceived severe/very severe burden. Concerning impact on their child's life, parents stated mild/medium burden in 49 % (91 of 186), and severe/very severe burden in 9 % (Fig. 1). For the "panel 2005" (n=161) mild/medium burden was stated for the child by 48.4 % of parents, and for the family by 60.2 %. Severe/very severe burden was reported for the child in 7.5 %, for the family in 16.1 %. For the "additional panel" (n=26) a mild/medium burden for the child was reported by 50 % of parents, for the family by 30.7 %. A severe/very severe burden was stated for the child by 15.4 %, for the family by 38.5 % of parents. For the whole group perceived burdens for child and family were significantly correlated (r=0.642; p<0.01; n=186), with burden judged to be higher for the family than for the child (Wilcoxon signed-rank test: Z=−5.67; p<0.001).

Financial and additional burdens

Financial burden due to the metabolic disorder was reported by 31.7 % of parents (58 of 183), and was associated with family income: 56.3 % (18 of 32), 33.6 % (36 of 107), and 10.8 % (4 of 37) of families with a monthly income of <1500€, 1500–3000€, and >3000€. Financial burden was significantly more frequent in families of patients with dietary treatment, than without dietary treatment (contingency coefficient=0.428, p<0.001). Additional burdens on the family were reported in 21 % (39 of 183).

Explanatory approach to perceived stress

Ordinal logistic regression analysis including only children with dietary or medical treatment revealed that dietary treatment was associated with higher odds for an at least medium burden for the family compared to medical treatment (OR 4.43 [95 % CI, 1.93–10.15]; p=0.0006). There were higher odds for severe/very severe burden for the family for diagnoses with risk for metabolic decompensation despite treatment compared to diagnoses without such risk (OR 2.5 [95 % CI, 1.1–5.6]; p=0.028). No significant associations were found between burden attributed to the disease and "additional burdens" (OR=1.0 [95 % CI, 0.5–2.2]; p=0.958), "patient care by only one family member" (OR=1.3 [95 % CI, 0.7–2.5]; p=0.367), or "family income" (ORs for all income categories ≤1.5 [maximal 95 % CI, 0.2–4.8]; all p-values >0.350).

Cluster analysis of disorders based on expert ratings resulted in three clusters with high, intermediate or low number of burdensome factors. Cross-tabulation of the expert clusters with the frequencies of parental ratings given in each cluster revealed a significant pattern (χ^2(df=2, n=187)=9.73; p=0.045, two-sided) (see Table 2). Patient judgment and expert cluster were convergent in 29.7 % of the cases. In 10 % of the cases parents rated disorders in the clusters high or low not to present a severe burden. On the other side 60.5 % of the parental ratings of disorders in the intermediate and low clusters were medium or high.

Discussion

Our study revealed three important results for the evaluation of newborn screening programmes. First, despite good

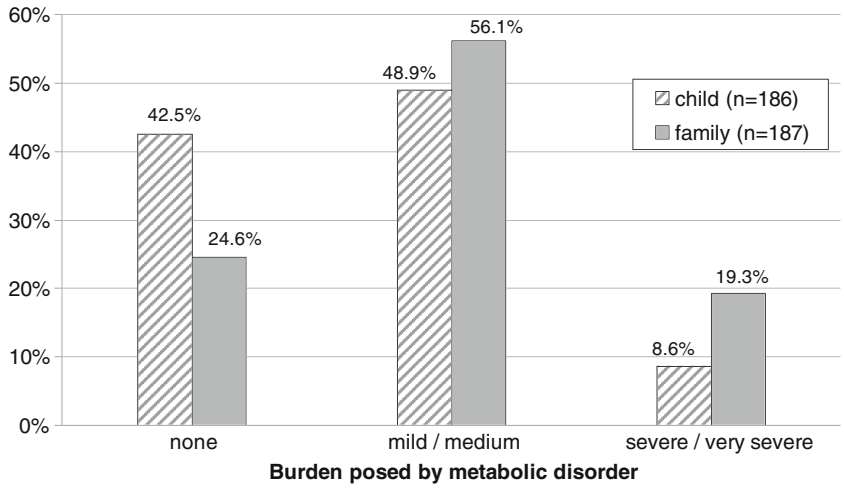

Fig. 1 Parental assessment of burden posed by the metabolic disorder on the child and family

outcome of children identified by newborn screening, a considerable proportion of parents report substantial burden from the disorder and its preventive treatment. Second, parents do not seem to perceive disorders in the same way as suggested by objective features of treatment, risk for metabolic decompensation, and outcome. Third, parental evaluation of cognitive development and standardized test results were discrepant in 8 % of patients, mostly due to parental overestimation of the child's development.

Studies on impact of chronic childhood diseases on families revealed divergent results, reporting high parental stress (Dellve et al 2006), and impaired quality of life for children (Bosch et al 2004), but also lack of differences to families of healthy children (Kazak et al 1988). In our study 75 % of all parents reported the metabolic disorder to pose a burden on their family. In the "panel 2005", where physical and cognitive outcome was predominantly normal (Lindner et al 2011), still 60 % of parents reported mild/medium, and 16 % severe burden. Despite prevention of physical, intellectual, and behavioural impairments by newborn screening, the metabolic disorder can have a substantial impact on life of affected families. However, detection of a metabolic disorder through newborn screening seems to cause less parental stress than clinical diagnosis (Waisbren et al 2003).

Adaptation to a chronic disease is a multidimensional process (Wallander and Varni 1998). Disorders without perceived burden by the family were conditions treated with medication only, like biotinidase deficiency, or potential non-diseases like SCADD. Burden for the child was correlated with burden for the family. In accordance with a study on galactosaemia (Bosch et al 2004), the extent was higher for the family than for the child. The lower burden stated for children could be a result of families' coping strategies. Accuracy of parental proxy-reports on children's lives may be limited (Theunissen et al 1998), but most patients in our study were too young to state their own point of view on burdens posed by the disorder.

Table 2 Crosstabulation of expert clusters by parental rating of burden for the family

		Frequency of parent's rating of burden for the family		
Expert cluster	Diagnosis	Severe/very severe	Mild/ medium	None
High	ASLD[a]	0	1	0
	Cbl C/D[a]	2	0	2
	CIT I classic[a]	2	0	0
	CIT I mild[a]	0	1	0
	GA I[a]	1	2	2
	HMG-CoA LD[a]	1	0	0
	IVA classic[a]	1	4	1
	MADD[a]	1	0	0
	PA[a]	1	2	1
	SUM	9	10	6
Intermediate	MSUD[a]	6	2	0
	VLCADD[a]	0	4	1
	LCHADD[a]	0	4	1
	SUM	6	10	2
Low	3-MCCD[a]	0	1	3
	BIOD	0	1	2
	CPT ID	0	1	0
	CTD	2	0	0
	Galactosaemia	2	5	4
	IVA mild	1	1	5
	MCADD	2	28	16
	PKU	13	45	6
	TYR I	1	2	0
	TYR III	0	1	0
	SUM	21	85	36

[a] Disorders with potential risk of decompensation despite treatment

For cross-tabulation of the sum rows for the three clusters two-sided χ^2 (df=2, n=187)=9.73; p=0.045

Report of financial burden was associated with family income but also with dietary treatment. This can be explained by the fact that in Germany dietary treatment (apart from special formulae and amino acid mixtures) is not covered by health insurance, and low protein food is much more expensive than a regular diet (Arbeitsgemeinschaft für Pädiatrische Diätetik 2007).

Disorders with a high number of objective stress factors were rated by parents as severe/very severe burden in only 35 %. Disorders with a low number of stress factors according to expert rating were judged by only 25 % of the parents not to be a burden. Both findings demonstrate that modifying factors unrelated to the type of metabolic disorder are of relevance for families' perception of the disorder. These could be psychological coping strategies or efficacy in following treatment recommendations (Wallander and Varni 1998). This is in agreement with previously published studies, that the severity of a disorder does not predict adaptation (Loonen et al 2002; Biesecker and Erby 2008), and that psychosocial factors may be more important for health related quality of life than medical variables (Hatzmann et al 2009).

Parental evaluation of cognitive development and standardized test results were discrepant in 8 % of all patients, mostly due to parental overestimation of their child's development. In 70 % of patients with subnormal IQ results parents rated intellectual development as normal. Parental evaluation of child development has been investigated in multiple studies (Rennen-Allhoff 1991; Glascoe and Dworkin 1995; Glascoe and Sandler 1995; Ireton and Glascoe 1995; Deimann et al 2005). Some authors found significant agreement between parental estimations and standardized measures (Sonnander 1987; Glascoe and Dworkin 1995; Johnson et al 2008), others reported highly variable correlations (Buch et al 2006). Glascoe and colleagues demonstrated that parents are able to accurately assess global development when comparing their child to other children (Glascoe and Sandler 1995), without influence of parental levels of education (Glascoe and Dworkin 1995). However, parents' ratings were shown to be more accurate in children with normal, than with abnormal social behaviour and development (Deimann et al 2005).

In our study, child development was perceived as delayed in comparison to children without a metabolic disorder by 21 % of parents in the "2005 panel" and 58 % of parents in the "additional panel". Language development was the domain most frequently reported as delayed. For classical galactosaemia this is a common finding despite early and continuous treatment (Sarafoglou et al 2009). Some of the other patients with language delay might be "late talkers", and catch up to normal language development later on (Dale et al 2003).

The percentage of children whose parents perceive developmental delay in the "panel 2005" group was similar to that reported for children at school enrolment in a German federal state (Gottschling et al 2012). The difference between "panel 2005" and "additional panel" is not confounded by patients' age, as it was consistent when comparing both panels only for children born before April 2005. This is in line with our previous publication, where the majority of patients from the "2005 panel" showed normal physical and intellectual development on standardized examinations, whereas patients from the "additional panel" showed subnormal physical and intellectual development in 78.6 % and 45.5 %, respectively (Lindner et al 2011). In some of these "additional" disorders, severe neonatal metabolic decompensation can occur before the result of newborn screening is available, or optimal outcome cannot be achieved despite early treatment.

Parental overestimation of their child's functioning has been previously reported (Rennen-Allhoff 1991), especially for children with abnormal social behaviour (Deimann et al 2005). This could be explained as a parental coping strategy reducing stress, and may also promote the child's future development (Deimann et al 2005). Parental reports may provide additional information on aspects not covered by psychometric tests, like every day functioning. However, the finding that parents overestimated abilities in most children with cognitive impairments highlights limitations of this method. Expectations for children's future development and independence were predominantly positive, also in parents who rated their child's current development as delayed. However, as long-term outcome studies of children detected by newborn screening are still missing, future research has to show if these expectations will be fulfilled.

Conclusion

The positive effect of newborn screening for physical and cognitive outcome of patients with disorders from the current German screening panel is undoubted, and the majority of these patients show normal physical and intellectual development (Lindner et al 2011). However, despite this positive outcome, coping with a metabolic disorder poses a considerable burden on everyday life of patients and their families. Of all parents 75 % reported that the metabolic disorder poses a burden on their family—the extent being mild or medium in 56 %, severe or very severe in 19 %. One third of the families reported a financial burden. Although a considerable number of parents perceived some aspects of their child's development as delayed, expectations for future development and autonomy were predominantly positive. In comparison to results of psychometric tests parents of children with cognitive impairments tended to overrate their child's abilities. This highlights the importance of standardized tests in long-term follow-up of newborn screening programmes to reliably identify developmental impairments and allow for timely interventions. This should be considered in routine care for patients with metabolic disorders, and underlines the need for comprehensive

multidisciplinary care including psychological, social, and financial support.

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Compliance with Ethics Guidelines

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Conflict of interest None.

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