

Newborn Screening Programmes in Europe, Arguments and Efforts Regarding Harmonisation: Focus on Organic Acidurias

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Abstract Background: The state of newborn screening (NBS) programmes for organic acidurias in Europe was assessed by a web-based questionnaire in the EU programme of Community Action in Public Health 2010/2011 among the – at that time – 27 EU member states, candidate countries, potential candidates and three EFTA countries.

Results: Thirty-seven data sets from 39 target countries were analysed. Newborn screening for glutaric aciduria type I (GA-I) was performed in ten, for isovaleric aciduria (IVA) in nine and for methylmalonic aciduria including cblA, cblB, cblC and cblD (MMACBL) as well as for propionic aciduria (PA) in seven countries. Samples were obtained at a median age of 2.5 days and laboratory analysis began at median age of 4.5 days. Positive screening results were mostly confirmed in specialised centres by analysis of organic acids in urine. Confirmation of a positive screening result usually did not start before the second week of life (median ages: 9.5 days [IVA], 9 days [GA-I], 8.5 days [PA, MMACBL]) and was completed

early in the third week of life (median ages: 15 days [IVA, PA, MMA], 14.5 days [GA-I]). Treatment was initiated in GA-I and IVA at a median age of 14 days and in MMACBL and PA at a median age of 15 days.

Conclusion: NBS for organic acidurias in Europe is variable and less often established than for amino acid disorders. While for GA-I its benefit has already been demonstrated, there is room for debate of NBS for IVA and especially PA and MMACBL.

Abbreviations

EFTA	European Free Trade Association
ESPE	European Society for Paediatric Endocrinology
FYROM	Former Yugoslav Republic of Macedonia
GA-I	Glutaric aciduria type I, OMIM 231670 deficiency of glutaryl-CoA dehydrogenase
GP	General practitioner
IVA	Isovaleric aciduria, OMIM 243500 deficiency of isovaleryl-CoA dehydrogenase
ISNS	International Society for Neonatal Screening
MMACBL	Methylmalonic aciduria including cblA, cblB, cblC and cblD defects OMIM 251000 methylmalonic aciduria, methylmalonyl-CoA mutase deficiency OMIM 251100 methylmalonic aciduria, cblA type OMIM 251110 methylmalonic aciduria, cblB type OMIM 277400 methylmalonic aciduria and homocystinuria, cblC type OMIM 277410 methylmalonic aciduria and homocystinuria, cblD type
NBS	Newborn screening

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PA	Propionic aciduria OMIM 232050 deficiency of propionyl-CoA carboxylase subunit β OMIM 232000 deficiency of propionyl-CoA carboxylase subunit α
SSIEM	Society for the Study of Inborn Errors of Metabolism

Introduction

In 2010/2011 regulation and practice of population newborn screening (NBS) for rare disorders were surveyed among – at that time – 27 EU member states (NBS in Belgium is different in the Flemish and in the French part, therefore contributed two data sets), five candidate countries (Croatia, Former Yugoslav Republic of Macedonia, Iceland, Montenegro, Turkey), four potential candidates (Albania, Bosnia Herzegovina, Kosovo, Serbia) and three EFTA countries (Norway, Switzerland and Liechtenstein) through a tender of the European Commission within the EU programme of Community Action in Public Health (Burgard et al. 2012; Loeber et al. 2012).

Data collection covered five domains of an NBS programme, and results have been reported previously (Burgard et al. 2012; Loeber et al. 2012; Cornel et al. 2011).

This article specifies the state of NBS programmes for organic acidurias in Europe in 2010, regarding four organic acidurias: glutaric aciduria type I (GA-I), isovaleric aciduria (IVA), propionic aciduria (PA) and methylmalonic acidurias including inherited deficiencies of methylmalonyl-CoA mutase as well as of cblA, cblB, cblC and cblD deficiency (MMACBL).

NBS for these disorders aims to detect elevations of characteristic acylcarnitines by tandem mass spectrometry and subsequent calculation of acylcarnitine ratios (Lindner et al. 2006, 2008; Ensenauer et al. 2011; Chace et al. 2001).

In IVA, MMACBL and PA patients may already develop life-threatening metabolic decompensation during the first days of life (Deodato et al. 2006; Vockley and Ensenauer 2006; Kölker et al. 2015a, b). Therefore, NBS process times are key performance indicators.

Methods

A web-based questionnaire asked for current practice of NBS and its possible regulation by directives and/or by guidelines (Burgard et al. 2012; Loeber et al. 2012).

In each country respondents nominated by European professional societies (ISNS; SSIEM; ESPE) reported data

for all disorders screened for according to the national NBS panel (Loeber et al. 2012). The survey started in August 2010 and was closed on January 14, 2011; reference date for all data is September 1, 2010. Values given for time points of obtaining NBS samples, conforming diagnosis and start of treatment are mostly experts' estimates for single disorders or groups of disorders, but not calculated measures based on individual measurements. Therefore standard deviations cannot be communicated. Process times were not differentiated by different methods to confirm a diagnosis.

Results

Description of the Data Set

From 39 target countries, 37 data sets were available for analysis (response rate 92.5%). Data sets were not available for Albania (NBS was not established), Liechtenstein (NBS is performed in Switzerland and data are included in the Swiss data set) and Kosovo (the questionnaire was not returned), but it was known by personal communication that newborn screening, if functional, does not include organic acidurias. Newborn screening for GA-I was performed in ten countries and for IVA in nine countries; MMACBL and PA were screened for in seven countries (Table 1).

Confirmation of Screening Results

Nine of ten countries answered that positive screening results for GA-I were confirmed by specialised centres but rarely also by local hospitals or by general practitioners/paediatricians in practice (2/10) (Table 1). Similar results were obtained for IVA: in 9/9 countries positive screening results are confirmed by specialised centres (Table 1). MMACBL and PA screening results are confirmed by specialised centres (7/7 countries), but rarely also in local hospitals (1/7 countries) or by general practitioners or paediatricians in private practice (1/7 countries) (Table 1). Screening results are confirmed most frequently by analyses of organic acids in urine. However, in the majority of countries, additionally mutation analysis and/or enzyme analysis is performed for the confirmation of diagnosis (Table 1).

Process Times

In most countries there is (written) information for prospective parents and informed consent is asked at the time of blood sampling (Burgard et al. 2012). Blood spots are taken at a median age of 2.5 days and analysis in the screening laboratory starts at median age of 4.5 days (Table 2).

Table 1 Confirmation of newborn screening and feedback of screening results

Countries	Point of confirmation		Method of confirmation			Feedback of screening results				
	Specialised centre	Local hospital	GP/ Paed.	Enzyme Metabolites activity	Mutation analysis	To screening lab	To registry	Only diagnosis	Detailed results	
Disorder: GA-I										
Austria	50%	50%	X	X	X	X			X	
Belgium (Flemish part)	X		X			X		X		
Czech Republic	X		X	X	X	X		X		
Denmark	X		X	X	X	X		X		
Germany	X		X	X	X	X			X	
Hungary	50%		50%	X		X	X		X	
Netherlands	na		X	X	X	na	na	na	na	
Portugal	X		X	X	X	X			X	
Spain	X			X	X	X		X		
Iceland	X		na	na	na	X			X	
Disorder: IVA										
Austria	50%	50%	X	X	X	X			X	
Belgium (Flemish part)	X		X			X		X		
Czech Republic	X		X	X	X	X		X		
Germany	X		X		X	X			X	
Hungary	50%		50%	X		X	X		X	
Netherlands	50%	50%	X	X	X	na	na	na	na	
Portugal	X		X	X	X	X			X	
Spain	X			X	X	X		X		
Iceland	X		na	na	na	X			X	
Disorder: MMACBLC										
Austria	50%	50%	X	X	X	X			X	
Belgium (Flemish part)	X		X			X		X		
Denmark	X		X	X	X	X		X		
Hungary	50%		50%	X		X	X		X	
Portugal	X		X	X	X	X			X	
Spain	X			X	X	X		X		
Iceland	X		na	na	na	X			X	
Disorder: PA										
Austria	50%	50%	X	X	X					
Belgium (Flemish part)	X		X			X		X		
Denmark	X		X	X	X	X		X		
Hungary	50%		50%	X		X	X		X	
Portugal	X		X	X	X	X			X	
Spain	X			X	X	X		X		
Iceland	X		na	na	na	X			X	

na data not available, GP general practitioner, Paed. paediatrician

Confirmation of a positive screening result usually does not start before the second week of life and is completed early in the third week of life (Table 2). Treatment starts in GA-I and IVA at a median age of 14 days (range 8–23 days) and in MMACBL and PA at a median age of 15 days (range 14–23 days) (Table 2).

Information Flow Between NBS Domains

In all countries with NBS for organic acidurias, results of the diagnostic confirmatory process are reported back to NBS laboratories (Table 1), following local guidelines (Table 3 Part II). Type and extent of transmitted data are varied, ranging from communication of only the confirmed diagnosis to reporting detailed results (Table 1).

Regulations

A guideline on how to confirm the diagnosis is usually available mostly on a national level, but usually written by local heads/directors of the institution executing the confirmation test – in contrast a national directive concerning the same topic is rarely available (Table 3 Part I). Where to confirm a diagnosis is also predominantly regulated by guidelines, mostly on a national level and less frequently by a directive (Table 3 Part I). The same holds true for the time needed to confirm a diagnosis (Table 3 Part II). Reporting positive results is also more often regulated by guidelines than by directives; few countries have guidelines as well as directives (Table 3 Part II). In Germany, for example, there is a national directive concerning NBS for GA-I, but a guideline endorsed by a national professional society is also in place (Kölker et al. 2011).

Discussion

The major aim of this study was to describe the concepts and state of established NBS programmes for organic acidurias in Europe. In contrast to amino acid disorders, organic acidurias are less often included in European NBS disease panels (Burgard et al. 2012). Therefore experience about the impact of different logistics on outcome of these disorders is scarce.

Our study reveals that performance and, confirmation of positive NBS results, and start of treatment for organic acidurias in Europe is variable. This may result in inappropriate interventions, delayed treatment, increased disease burden and finally health inequities and increased costs. Further studies shall provide systematic evaluation of existing NBS programmes for their impact on patients' outcomes and also costs and health equity. Particular

attention should be paid to the time schedule of the NBS process for these conditions (Kelm and Tanksley 2015).

Since patients with a classical organic aciduria such as IVA, MMACBL and PA are at risk to already present early in the neonatal period with a putatively life-threatening metabolic decompensation, it is important to accomplish NBS as early as possible in order to start treatment and care ideally in the still asymptomatic patient. In our survey, treatment in these disorders was reported to start after 15 days of life. This is clearly too late for most patients with a neonatal metabolic decompensation. Furthermore the confirmatory diagnostic process needs to be tailored to avoid therapy in patients with mild phenotypes which is especially recognised in IVA (Ensenauer et al. 2004).

The European Network of Experts on Newborn Screening (EUNENBS) delivered a consensus document with recommendations how to develop NBS in the European Union based on the results of the survey (Cornel et al. 2014). Within these recommendations GA-I is considered as a disorder with lower prevalence, not too difficult to test and prove health gain, IVA is a candidate disorder where NBS is more challenging according to the criteria by Wilson and Jungner (1968), and NBS for MMACBL or PA is not recommended at all.

NBS and subsequent treatment of GA-I according to an international guideline have significantly improved the neurological outcome of affected individuals (Heringer et al. 2010; Kölker et al. 2006, 2007, 2011), and NBS is considered a cost-effective diagnostic strategy for countries with healthcare systems comparable to Germany (Pfeil et al. 2013). According to this international guideline, it is crucial to start treatment early before the manifestation of irreversible neurologic damage (Kölker et al. 2011). Treatment has to be started early in the diagnostic process, i.e. immediately after demonstration of elevated concentrations of 3-hydroxyglutaric acid and already in advance of the final confirmation of the diagnosis by demonstration of two disease-causing mutations or impaired enzyme activity (Kölker et al. 2011). In our survey only in the Netherlands and in Germany, pre-emptive treatment of GA-I patients starts before the end of the confirmation process as recommended (Kölker et al. 2011). In Fig. 1a we illustrate the current practice mostly employed and show our proposed model (Fig. 1b). In concordance with an international guideline (Kölker et al. 2011), we strongly advocate starting pre-emptive treatment in the setting of a metabolic centre as soon as the suspicion of an organic aciduria arises from newborn screening and before the diagnosis is finally confirmed. This is important in GA-I, but may even be more crucial in MMACBL, PA and IVA, where neonatal decompensation is more frequent.

For IVA, successful experience with NBS programmes has been published (Ensenauer et al. 2011; Grünert et al.

Table 2 Process times of newborn screening

Countries	DBS sampling Mean age (days)	NBS lab analysis Age at start (days)	Confirmation		Treatment Mean start (days)
			Mean start (days)	Mean end (days)	
Disorder: GA-I					
Austria	2.3	3.8	11	14	14
Belgium (Flemish part)	2.2	4.2	10	12	14
Czech Republic	2.5	4.5	6	8	8
Denmark	2.5	4.5	5	12	na
Germany	2.2	3.2	11	16	14
Hungary	2.5	5.5	na	na	na
Netherlands	3.8	4.8	10	21	10
Portugal	2.2	4.2	8	na	na
Spain	3.8	7.8	8	15	15
Iceland	3	6	9	23	23
Median	2.5	4.5	9	14.5	14
Disorder: IVA					
Austria	2.3	3.8	11	14	14
Belgium (Flemish part)	2.2	4.2	10	12	14
Czech Republic	2.5	4.5	6	8	8
Germany	2.2	3.2	11	16	14
Hungary	2.5	5.5	na	na	na
Netherlands	3.8	4.8	10	21	10
Portugal	2.2	4.2	8	na	na
Spain	3.8	7.8	8	15	15
Iceland	3	6	9	23	23
Median	2.5	4.5	9.5	15	14
Disorder: MMACBL					
Austria	2.3	3.8	11	14	14
Belgium (Flemish part)	2.2	4.2	10	14	14
Denmark	2.5	4.5	5	15	15
Hungary	2.5	5.5	na	na	na
Portugal	2.2	4.2	8	na	na
Spain	3.8	7.8	8	15	15
Iceland	3	6	9	23	23
Median	2.5	4.5	8.5	15	15
Disorder: PA					
Austria	2.3	3.8	11	14	14
Belgium (Flemish part)	2.2	4.2	10	12	14
Denmark	2.5	4.5	5	15	15
Hungary	2.5	5.5	na	na	na
Portugal	2.2	4.2	8	na	na
Spain	3.8	7.8	8	15	15
Iceland	3	6	9	23	23
Median	2.5	4.5	8.5	15	15

na data not available, DBS dried blood spot

Table 3 Regulation of the confirmation process

Countries	How to confirm NBS				Where to confirm diagnosis?				Authors	
	Guideline	Application	Directive	Application	Guideline	Application	Directive	Application		
Disorder: GA-I PART I										
Austria	X	National			X	National			PS	PS
Belgium (Flemish part)	na				X	National			PS	PS
Czech Republic	X	Regional			X	National	X	National	HA	HA
Denmark	X	National	X	National	X	National	X	National	HA, LH	HA, LH
Germany	X	National			X	National	X	National	PS	HA, PS
Hungary	X	National			X	Regional			LH	LH
Netherlands	na			na	na		na			
Portugal	X	National			X	Regional				
Spain	na		na		na		na			
Iceland	X	Regional	X	Regional	X		X	National	LH	LH
Disorder: IVA PART I										
Austria	X				X	National			PS	PS
Belgium (Flemish part)	na		na		X	National			PS	PS
Czech Republic	X	Regional			X	National	X	National	HA	HA
Germany	X	National			X	National	X	National	HA, PS	HA, PS
Hungary	X	National			X	Regional			LH	LH
Netherlands	X				X		X		HA,PS	HA,PS
Portugal	X	National			X	Regional				
Spain	na		na		na		na			
Iceland	X	Regional	X	Regional	X		X	National	LH	LH
Disorder: MMACBL PART I										
Austria	X	National			X	National			PS	PS
Belgium (Flemish part)	na		na		X	National			PS	PS
Denmark	X	National	X	National	X	National	X	National	HA, LH	HA, LH
Hungary	X	National			X	Regional			LH	LH
Portugal	X	National			X	Regional				
Spain	na		na		na		na			
Iceland	X	Regional	X	Regional	X		X	National	LH	LH

Disorder: PA PART I

Austria	X	National				PS	X	National			PS
Belgium (Flemish part)	na		na				X	National			PS
Denmark	X	National	X			HA, LH	X	National	X		HA, LH
Hungary	X	National				LH	X	Regional			LH
Portugal	X	National					X	Regional			
Spain	na		na								
Iceland	X	Regional	X			LH	X	Regional	X		LH

Recommended age to confirm a suspicious NBS result

Countries	Guideline	Minimum age (days)	Maximum age (days)	Application	Authors	Feedback of final diagnosis					
						Guideline	Application	Directive	Application	Authors	
Disorder: GA-I PART II											
Austria	na						X	National			PS
Belgium (Flemish part)	X	1		National	LH		X	Regional	X		HA, PS
Czech Republic	na						X	Regional			LH
Denmark	na						X	National	X		HA, LH
Germany	X			National	HA,PS		X	National	X		HA
Hungary	na						X	National			LH
Netherlands	na						na				
Portugal	na						X	National			
Spain	X	3	20	National	PS		X	Regional	X		LH
Iceland	X			National	LH		X	National			LH
Disorder: IVA PART II											
Austria	na						X	National			PS
Belgium (Flemish part)	X	1		National	LH		X	Regional	X		HA, PS, LH
Czech Republic	na						X	Regional			LH
Germany	X			National	HA, PS		X	National	X		HA
Hungary	na						X	National			LH
Netherlands	X		14	National	PS		X				PS
Portugal	na						X	National			
Spain	X	3	20	National	PS		X	Regional	X		LH
Iceland	X			National	LH		X	National			LH
Disorder: MMACBL PART II											
Austria	na						X	National			PS
Belgium (Flemish Part)	X	1		National	LH		X	Regional	X		HA, PS, LH

(continued)

Table 3 (continued)

Countries	Recommended age to confirm a suspicious NBS result				Feedback of final diagnosis					
	Guideline	Minimum age (days)	Maximum age (days)	Application	Authors	Guideline	Application	Directive	Application	Authors
Denmark	na					X	National	X	National	HA, LH
Hungary	na					X	National			LH
Portugal	na					X	National			
Spain	X	3	20	National	PS	X	Regional	X	Regional	LH
Iceland	X			National	LH	X	National			LH
Disorder: PA PART II										
Austria	na					X	National			PS
Belgium (Flemish part)	X	1		National	LH	X	Regional	X	regional	HA, PS, LH
Denmark	na					X	National	X	National	HA, LH
Hungary	na					X	National			LH
Portugal	na					X	National			
Spain	X	3	20	National	PS	X	Regional	X	Regional	LH
Iceland	X			National	LH	X	National			LH

na data not available, LH local head of institution responsible for confirmation of NBS, PS professional society, HA health authority

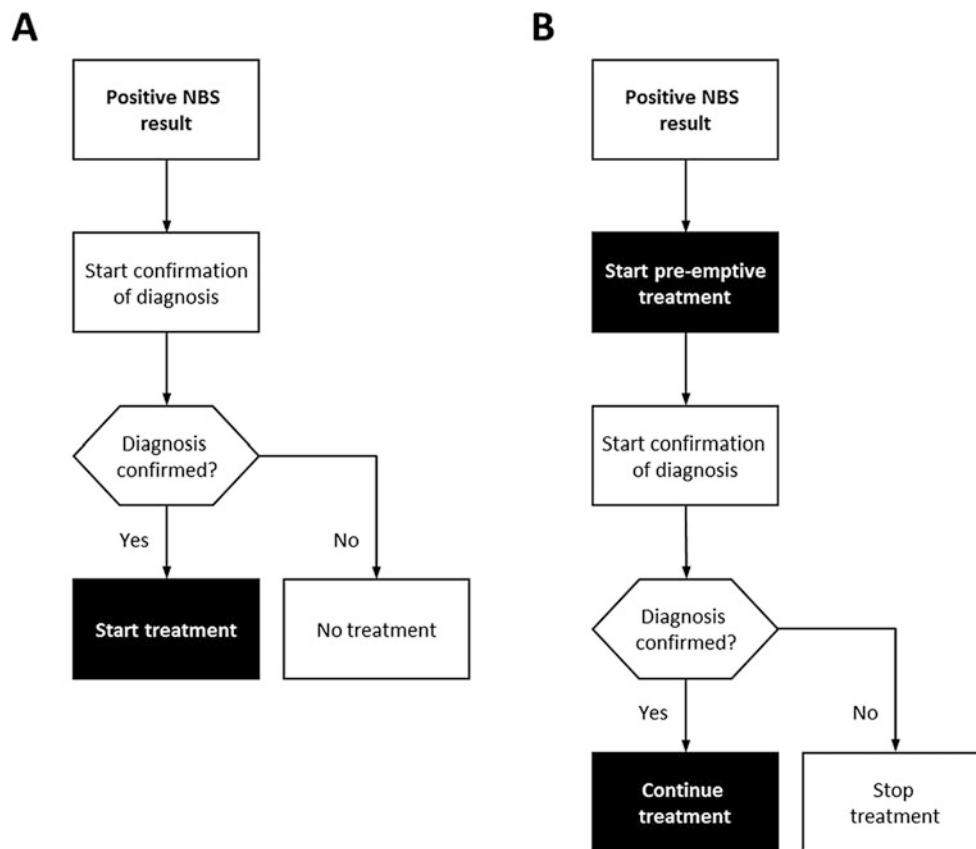


Fig. 1 Current practice after positive NBS result (a) versus a proposed model recommending pre-emptive treatment after a positive NBS result is received (b). This should be initiated and supervised by

a metabolic centre with the major aim to minimise the risk of a neonatal metabolic decompensation in patients with organic acidurias during the confirmatory diagnostic process

2012a, b; Lindner et al. 2011), and the natural history is favourable as long as early neonatal brain damage can be prevented by adequate therapy (Grünert et al. 2012a, b). However, about half of the individuals with a positive screening result for IVA are homozygous for mutation c.932C>T in the *IVA* gene, presumably associated with a benign phenotype (Ensenauer et al. 2004), for whom the benefit of screening is questionable.

The impact of NBS on history and outcome of PA and MMACBL was thought to be low due to the fact that many patients will have already presented clinically before the results of NBS are available (Leonard et al. 2003). In line with this, a study demonstrated that NBS for PA did not affect the outcome of these patients (Grünert et al. 2012a, b). However, there still is controversy whether PA and MMACBL patients with a late disease onset, i.e. presenting with first symptoms after the newborn period, might benefit from NBS (Dionisi-Vici et al. 2006; Couce et al. 2011). Follow-up studies on a larger number of patients are required to address this question.

In 2011, E-IMD (EAHC no. 2010 12 01; www.eimd-registry.org), an observational patient registry including organic acidurias, has been initiated. It currently includes

detailed follow-up data of more than 1100 patients (Kölker et al. 2015a, b).

Taking the start of confirmation as a surrogate parameter for the time when an organic aciduria can be suspected from NBS, percentages of patients identified before onset of symptoms can be estimated. For example, in Denmark confirmation of NBS for MMACBL starts on day 5 after birth (Table 2), which is the earliest among all European countries performing NBS screening for MMACBL. At that time at least 25% of all MMACBL patients have already been diagnosed by clinical symptoms [total number of patients: 101; median age at diagnosis (interquartile range): 21 (3–210) days] in the E-IMD sample. Similar results were obtained for PA with at least 25% of all patients being diagnosed until day 5 [total number of patients: 78; median age at diagnosis (interquartile range): 14 (4–90) days].

For IVA, confirmation of NBS is at first initiated at day 6 in the Czech Republic (Table 2); at that time at least 25% of patients have been diagnosed [total number of patients, 29; median age at diagnosis (interquartile range), 8 (5–465) days]. In contrast, since GA-I patients rarely present with symptoms before age 3 months (Kölker et al. 2006), neonatal onset in GA-I has been rarely observed until day

5 in the E-IMD survey. On day 5 confirmation of positive NBS results for GA-I is first started in Denmark [total number of patients: 52; median age at diagnosis (interquartile range): 300 (145–428) days].

Although being preliminary, these data support the call for NBS to be fast in intoxication-type organic acidurias such as MMACBL, PA and IVA and to initiate treatment early before completing follow-up investigations. Patients with late-onset forms of these disorders will most likely benefit the most from NBS programmes. This notion is supported by a recently published E-IMD study demonstrating that (1) NBS significantly lowers the age of diagnosis in classic organic acidurias compared to patients with late onset of symptoms identified by selective metabolic testing, (2) improves the neurological outcome in patients with GA-I and cobalamin-nonresponsive MMA and (3) reduces the probability of cardiac manifestation with increasing age in PA patients (Heringer et al. 2015).

However, the decision whether or not to screen for these diseases must be based on many more criteria, including long-term follow-up studies and health economic evaluations.

Conclusion

NBS for organic acidurias in Europe is variable and less often established than for amino acid disorders. While for GA-I its benefit has already been demonstrated, there is room for debate of NBS for IVA and especially PA and MMACBL patients. NBS for intoxication-type organic acidurias has to be fast and treatment has to be started pre-emptively, i.e. even before the diagnosis is finally confirmed.

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Synopsis

NBS for organic acidurias in Europe is variable and less often established than for amino acid disorders. While for GA-I its benefit has already been demonstrated, there is room for debate of NBS for IVA and especially PA and MMACBL defects. For optimal benefit NBS for intoxication-type organic acidurias has to be fast and treatment has to be started pre-emptively, i.e. even before the diagnosis is confirmed.

Authors' Contributions

Designing, planning and conducting the study: All authors
Collection of data and statistical analysis: Peter Burgard
Manuscript writing: All authors

Guarantor

Peter Burgard

Conflict of Interest

Friederike Hörster, Stefan Kölker, J. Gerard Loeber, Martina C. Cornel, Georg F. Hoffmann and Peter Burgard declare that they have no conflict of interests.

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Ethics Approval

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. No data on individual patients are included in this study; therefore no informed consent had to be obtained.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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