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'Classical' organic acidurias, propionic aciduria, methylmalonic aciduria and isovaleric aciduria: Long-term outcome and effects of expanded newborn screening using tandem mass spectrometry

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Summary 'Classical organic acidurias' comprise isovaleric aciduria, propionic aciduria and methylmalonic aciduria. Available data from the literature suggest that the use of 'new' therapeutic strategies has improved survival but has not modified neurodevelopment. Progressive neurocognitive deterioration is almost invariably present in propionic and methylmalonic acidurias, while large-scale studies on the long-term outcome of patients with isovaleric aciduria are still lacking. In order to answer to some of the questions suggested by Wilson and Jungner in 1968 about the criteria of disease screening, we compared the natural history of patients with 'classical' organic acidurias diagnosed on clinical bases to those diagnosed through neonatal mass screening using tandem mass spectrometry. Decreased early mortality, less severe symptoms at diagnosis, and more favourable short-term neurodevelopmental outcome were recorded in patients identified through expanded newborn screening. The short duration of follow-up so far does not allow us to draw final conclusions about the effects of newborn screening on long-term outcome. The evaluation of the effect of neonatal screening on the detection rate of these three diseases showed that the incidence of isovaleric aciduria was significantly higher in the screening population than in clinically detected cases, with no changes for propionic and methylmalonic acidurias. Further multicentre longitudinal studies are needed to assess the usefulness of expanded newborn screening for 'classical' organic acidurias and to better understand the clinical spectrum of these diseases. This paper describes the long-term outcome and the impact of expanded newborn screening on the so-called 'classical' organic acidurias (propionic aciduria, methylmalonic aciduria and isovaleric aciduria).

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Introduction

The term 'classical organic acidurias' conventionally defines three different types of inherited disorders of branched-chain amino acids: isovaleric aciduria (IVA, McKusick 243500), propionic aciduria (PA, McKusick 606054) and methylmalonic aciduria (MMA, McKusick 251000) (Ogier de Baulny and Saudubray 2000). IVA is caused by a deficiency of isovaleryl-CoA dehydrogenase (EC 1.3.99.10), which catalyses the third step in the catabolism of leucine. PA is caused by a deficiency of propionyl-CoA carboxylase (EC 6.4.1.3), which converts propionyl-CoA, derived from the catabolism of isoleucine, valine, methionine, threonine and odd-chain fatty acids, to methylmalonyl-CoA. MMA is caused by a defect in the conversion of methylmalonyl-CoA to succinyl-CoA, a reaction catalysed by methylmalonyl-CoA mutase (EC 5.4.99.2). Patients with isolated methylmalonic acidaemia may have a defect of the

apoenzyme (mut^0 and mut^-) or of the synthesis of its coenzyme adenosylcobalamin (cbl A, cbl B).

All these disorders are characterized by an acute or progressive neurological involvement caused by the accumulation of toxic compounds proximal to the metabolic block. In most cases the onset of the disease is in the neonatal period, but a later-onset presentation can occur with appearance of symptoms during the firsts years of life.

The neonates present acute neurological deterioration after an initial symptom-free period, ranging from hours to days from birth. Typically the progression of symptoms moves from feeding refusal, vomiting, progressive weight loss, generalized hypotonia, and abnormal posturing and movements, through lethargy, seizures and coma, leading to death within a few days or to severe brain damage, if not promptly treated.

In the later-onset form, the clinical picture is more variable, ranging from acute life-threatening encephalopathy to intermittent or chronic symptoms of various degrees. These include intermittent ataxia, abnormal behaviour, and poor feeding with selective refusal of protein-rich foods, recurrent vomiting, etc. Failure to thrive is often present as well as neurodevelopmental delay.

Acidosis, ketonuria, hyperammonaemia, leukothrombocytopenia, anaemia and hyperuricemia are the most common laboratory abnormalities. In IVA only, urine and sweat have a characteristic smell of 'sweaty feet'.

The diagnosis is based on urinary organic acid analysis and blood acylcarnitine profile, showing the characteristic metabolic compounds for each disorder. Further confirmation can be obtained by enzymatic and molecular studies.

Despite the improvement in our understanding of the biochemistry of these diseases, their management remains difficult. Treatment can be schematically divided into two main steps: emergency treatment and long-term management. The acute phase, either at the onset or during a relapse of metabolic decompensation, represents a true medical emergency and its management is usually performed in the intensive care units. Emergency treatment is based on exogenous protein restriction, inhibition of endogenous catabolism by adequate parenteral energy supply, high dose of carnitine, vitamin supplementation and, in patients unresponsive to medical therapy within the firsts few hours, on extracorporeal removal of toxic metabolites through dialysis (Picca et al 2001). The use of sodium benzoate to increase ammonia detoxification in organic acidurias is still controversial. More recently, carbamyl glutamate has been successfully used for this purpose in MMA and PA (Gebhardt et al 2003, 2005).

The mainstay of the long-term treatment is a low-protein and high-energy diet, supplemented with a specific amino acid mixture free of precursor amino acids. Nasogastric and gastrostomy feeds are often used to maintain a satisfactory nutritional status. Carnitine is supplemented to prevent deficiency, metronidazole is used to reduce gut propionate produced by intestinal bacteria, and vitamin B_{12} is used in the responsive forms of MMA. In IVA, peroral glycine supplementation increases the excretion of isovaleric acid.

The aim of treatment is to prevent brain damage and the selective organ involvement (i.e. kidney, heart, pancreas) while maintaining normal development and nutritional status. However, despite intense medical therapy most patients, especially those with the severe form with neonatal onset, have a high risk of relapsing episodes of acute metabolic decompensation triggered by intercurrent stressing events such as fever, gastroenteritis and vaccinations.

More recently, as an alternative therapy to conventional medical treatment, liver transplantation has been attempted to cure the underlying metabolic defect in PA and MMA. However, the few scattered experiences reported to date did not clearly demonstrate the effectiveness of this therapy either to prevent further deterioration or to improve survival and quality of life (Chakrapani et al 2002; Kayler et al 2002; Leonard et al 2001; Morioka et al 2005; Nyhan et al 2002; Saudubray et al 1999; van't Hoff et al 1999).

What we know from the literature about the long-term outcome of patients with 'classical' organic acidurias

There is great difficulty in establishing the natural history and predicting the prognosis and long-term outcome in patients with 'classical' organic acidurias. From a careful review studies reporting longitudinal evaluation on large series of patients as well as selective organ complications (Baumgartner and Viardot 1995; Burlina et al 1995; Deodato et al 2004; Lehnert et al 1994; Mardach et al 2005; Massoud and Leonard 1993; Nagarajan et al 2005; Nicolaides et al 1998; North et al 1995; Ogier de Baulny et al 2005; Rousson and Guibaud 1984; Sass et al 2004; Saudubray et al 1999; Surtees et al 1992; Van Calcar et al 1998; van der Meer et al 1994, 1996; van't Hoff et al 1999), we can at least conclude the following.

- The late-onset forms have a better prognosis compared to the neonatal/early onset ones.
- The progresses made in treatment with the use of the 'new' therapeutic strategies has improved survival but has not modified the neurodevelopmental outcome.
- Progressive neurocognitive deterioration is almost invariably present.
- Relapsing episodes of acute metabolic decompensation are associated with a high risk of basal ganglia stroke, responsible for severe motor disabilities.
- Long-term complications with selective organ impairment are frequent. In particular, cardiomyopathy and pancreatitis can represent severe life-threatening events, and

progressive renal failure is typically observed in vitamin B_{12}-unresponsive MMA.
- Failure to thrive and poor nutritional status are frequently observed.
- The most severe forms with neonatal onset are more frequently observed in patients with PA and IVA (75%) compared to those with MMA (56%).
- There are no uniform criteria with respect to the day of life for the definition of what is a neonatal/early-onset form.
- There are no standardized measures for evaluating the long-term cognitive outcome.

Surprisingly, a careful retrospective analysis of the literature revealed the complete lack of large-scale studies describing the long-term outcome of patients with IVA, with only one abstract reporting the follow-up of 22 patients (Ensenauer et al 2003).

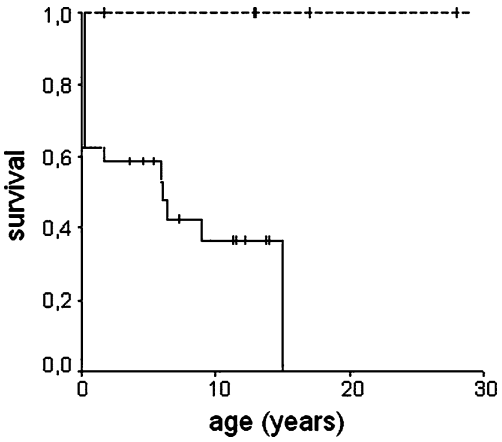

Fig. 1 Kaplan–Mayer actuarial survival curves comparing patients with neonatal onset (solid line) and those with late onset (dashed line); $p < 0.01$.

The impact of expanded newborn screening for 'classical' organic acidurias

In recent years, the application of electrospray tandem mass spectrometry (MS/MS) to newborn screening for inborn errors of metabolism has radically changed the scenario. In contrast t conventional programmes based on the use of a specific test for each disease, the simultaneous analysis of amino acids and acylcarnitines in blood by MS/MS allows the identification of more than 30 different diseases in the one test. However, the introduction of this new technology into routine clinical practice raises several questions about the real advantage that may be achieved by diagnosing newborns with 'classical' organic acidurias at a presymptomatic or early symptomatic stage. According to the criteria established more than 35 years ago (Wilson and Jungner 1968) and still valid, many issues remain to be clarified. To answer some of these questions, in this review we compared the natural history in two groups of patients with 'classical' organic acidurias: those diagnosed on clinical bases and those diagnosed through neonatal screening. The study evaluated mortality, neurocognitive development and organ complications in each group.

Patients identified by clinical symptoms

The group of symptomatic patients comprised 29 individuals diagnosed and followed at the Bambino Gesù Children's Hospital in Rome from 1983. Fifteen patients had MMA, 13 had PA and 1 had IVA. In 24 patients (82%) symptoms appeared within the first 28 days of life (neonatal-onset) and in the remaining 5 cases symptoms appeared later (late-onset). In the neonatal-onset group the mean age at diagnosis was 11 days. This value decreased to 7 days among patients diagnosed after 1995.

Overall, the mortality rate was 51%, with a significantly higher mortality ($p < 0.01$) in the neonatal-onset group compared to the later-onset cases, in which no deaths were recorded (Fig. 1). About 40% of patients died during the initial phase of the disease or before the second year of life, a finding very similar to the report by Surtees and colleagues in a series of patients with PA (Surtees et al 1992). The 'new' therapies developed throughout the years, based on the use of standardized emergency protocols combined with the improvement of dialysis techniques, influenced early survival of patients by reducing neonatal mortality.

In all patients, cognitive development was longitudinally assessed with conventional neuropsychological tests, and according to the IQ/DQ score patients were classified as normal (IQ > 79, DQ > 74), mildly retarded (IQ50–79/DQ60–74) or severely retarded (IQ < 49/DQ < 59). For patients with neonatal onset, the neurocognitive outcome was evaluated in two sequential periods, considering the psychomotor development in the firsts two years of life (short-term outcome) and the final long-term outcome.

At the first evaluation before the 2nd year of life, normal neurodevelopment was observed in 60% of surviving patients. As we previously reported in newborns affected both by branched-chain organic acidurias and by urea cycle defects (Picca et al 2001), the only parameter that significantly influenced early survival and the short-term outcome was the duration of coma, and in particular the duration of coma preceding the beginning of therapy. Through the following years, most of the affected children showed progressive cognitive deterioration or died. The mortality rate increased from 36% to 62%, and a normal neurocognitive outcome was recorded in only 27% of patients, with a complete reversal of the proportions observed at the early evaluation. As is evident

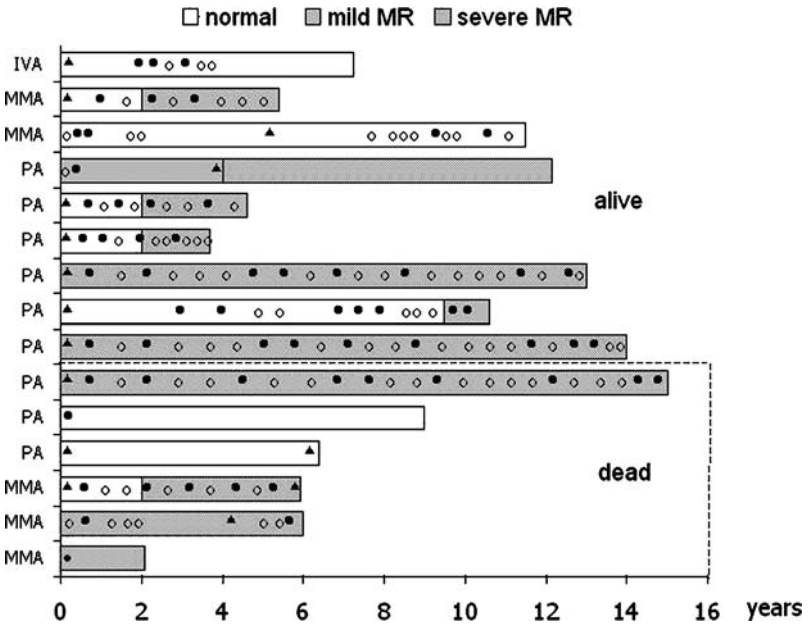

Fig. 2 Cognitive development of 15 patients with neonatal-onset 'classical' organic acidurias. Deceased patients are illustrated in the lower part, living patients in the upper part. Episodes of metabolic decompensation, mild (○) and severe (●), as well as episodes of coma (▲) are indicated for each patient. IVA, isovaleric aciduria; MMA, methylmalonic aciduria; PA, propionic aciduria; MR, mental retardation

from Fig. 2, the course of these diseases is characterized by frequent and severe relapses of metabolic decompensation, which undoubtedly influences the progression of neurological symptoms and the poor long-term prognosis. The findings of our study are very similar to the longitudinal evaluations previously reported in PA and MMA (Nicolaides et al 1998; North et al 1995).

As shown in Fig. 3, if we combine the risk of death with the risk of developing neurocognitive impairment we observe an event free 'window' corresponding to the first two years in which patients surviving the neonatal period show a relatively stable metabolic condition. This suggests that the option of liver transplantation as a potentially radical treatment should preferably be considered within this time period before the development of an irreversible neurological damage.

Unlike in neonatal-onset cases, the natural history in the late-onset cases clearly appears more favourable. Although our study was limited by the small number of patients, not only survival but also neurocognitive outcome was better, with 4 out 5 patients showing a normal/borderline development. Besides the absence of progressive cognitive deterioration, patients have a more stable clinical course with less frequent and less severe relapsing episodes of metabolic decompensation. One of our patients with mut^t MMA had two successful pregnancies with an uneventful postpartum period (Deodato et al 2002).

Regarding specific organ complications, we observed cardiomyopathy in 3 patients with PA, basal ganglia stroke in 2 patients with MMA, and acute pancreatitis in 1 patient with PA. One patient with neonatal-onset PA and normal cognitive level died suddenly at school from cardiomyopathy at the age

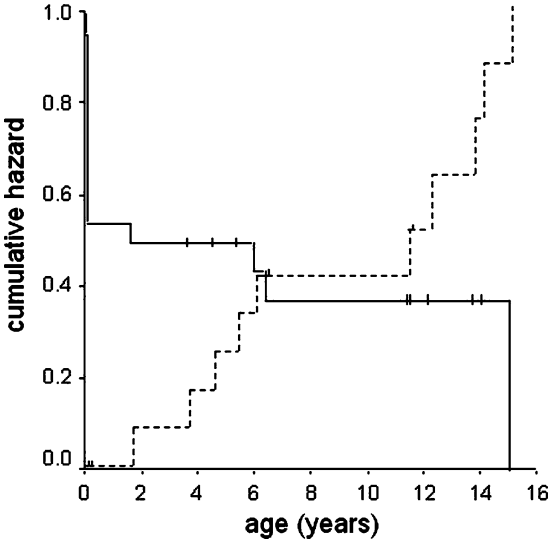

Fig. 3 Hazard plot showing the actuarial survival (solid line) and the developing of mental retardation (dashed line) in15 patients with neonatal-onset 'classical' organic acidurias surviving neonatal period

of 9 years. Signs of chronic renal failure were detectable in all MMA patients after the sixth year of life.

Patients identified by newborn screening

We evaluated the clinical characteristics at diagnosis, the neurocognitive outcome and the mortality rate in a series of 18 patients (7 IVA, 7 PA and 4 MMA) diagnosed by neonatal screening in Australia (11 patients) and in Munich, Germany (7 patients, 4 of whom were prospectively diagnosed because

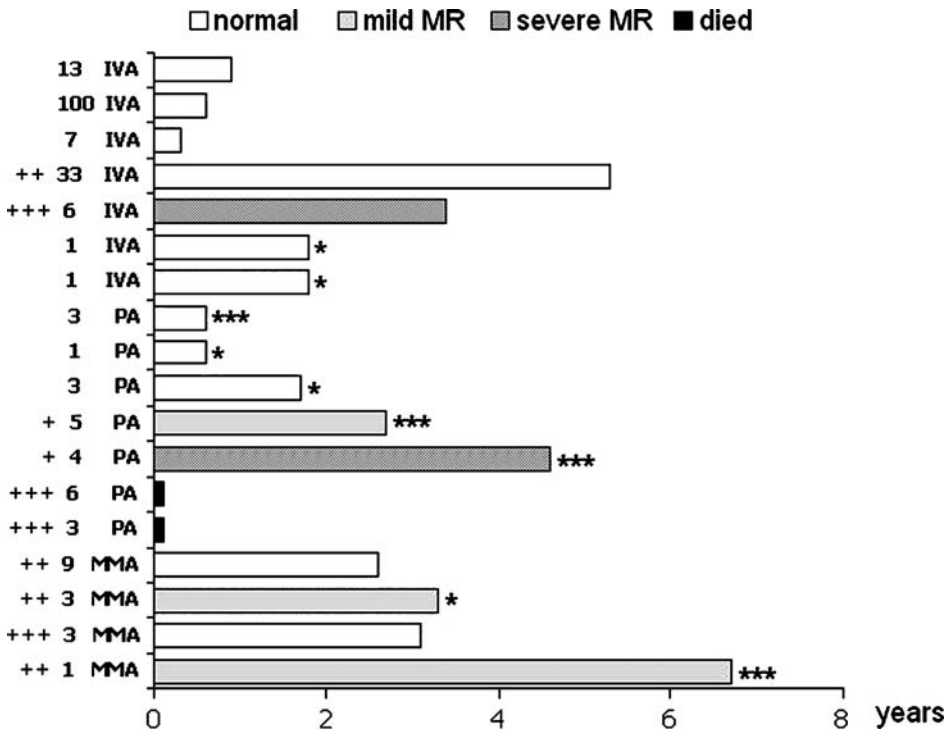

Fig. 4 Outcome of 18 patients with 'classical' organic acidurias detected by expanded newborn screening. The presence and severity of symptoms before the result of screening (+) as well as metabolic instability (*, mild; **, moderate; ***, severe) are indicated. IVA, isovaleric aciduria; MMA, methylmalonic aciduria; PA, propionic aciduria; MR, mental retardation.

of an affected elder sibling). The median age at diagnosis was 4 days (range 1–33 days) and more than 50% of patients were already symptomatic at the time of diagnosis. The clinical signs included tachypnoea in 3 patients, and metabolic decompensation with ketoacidosis and/or hyperammonaemia in 7 patients. Two of these 7 patients received treatment prior to the result of neonatal screening being available.

The neonatal mortality in this group of patients was significantly lower than in symptomatic patients ($p < 0.03$): only two patients with PA died, at the age of 5 and 13 days, respectively.

Early neurocognitive outcome was normal in 69% of cases, with a median age at follow-up in these patients of 1.7 years (range 0.3–5.3 years). The remaining 31% with neurocognitive impairment (severe in two patients,1 IVA and 1 PA; mild in three patients, 1 PA and 2 MMA) had a median age at follow-up of 3.4 years (range 2.7–6.7 years).

The clinical course was more stable than that observed in the series of symptomatic patients, with less-frequent relapsing episodes of metabolic decompensation; this was even more evident in IVA, in which metabolic crises never occurred in 5 out 7 cases (Fig. 4).

Only one patient with MMA, aged 40 months at last evaluation, shows mild renal dysfunction.

Impact of newborn screening on the detection rate

We analysed the effect of expanded neonatal screening by MS/MS on the frequency of these three diseases in the general population and compared the results with the available epidemiological studies based on clinical diagnosis. Combining the results of the different studies, the mean incidence of the three diseases in the symptomatic population is 1.19 ± 0.32 cases per 100 000 births (range 0.88–1.58) (Applegarth et al 2000; Dionisi-Vici et al 2002; Klose et al 2002; Wilcken et al 2003), compared to 1.94 ± 0.38 per 100 000 births in the neonatal screening group (range 1.58–2.4) (Hoffmann et al 2004; Rhead this study; Schulze et al 2003; Wilcken this study). Despite an apparent positive trend, these figures did not reach statistical significance ($p < 0.19$).

If we analyse the three diseases separately, figures for MMA and PA did not show significant differences between the two groups, with an overall incidence for these two diseases of 0.99 ± 0.35 per 100 000 births in the clinically diagnosed group compared to 1.04 ± 0.36 in the screening group. Remarkably, the incidence of IVA was significantly higher in the screened population, 0.89 ± 0.49 per 100 000 births versus 0.20 ± 0.13 ($p < 0.0001$) (Fig. 5).

Combining all cases reported in clinical studies ($n = 308$), the proportion of IVA in this group of patients is 10.4%, with an IVA/PA+MMA ratio of 1/9.6 (Applegarth et al 2000; Dionisi-Vici et al 2002; Hori et al 2005; Klose et al 2002; Rousson and Guibaud 1984; Waisbren et al 2003; Wilcken et al 2003). Whereas in the screened population ($n = 44$) this proportion increases to 40.9% of cases, with an IVA/PA+MMA ratio of 1/1.4 (Rhead this study; Röschinger this study; Schulze et al 2003; Wilcken this study).

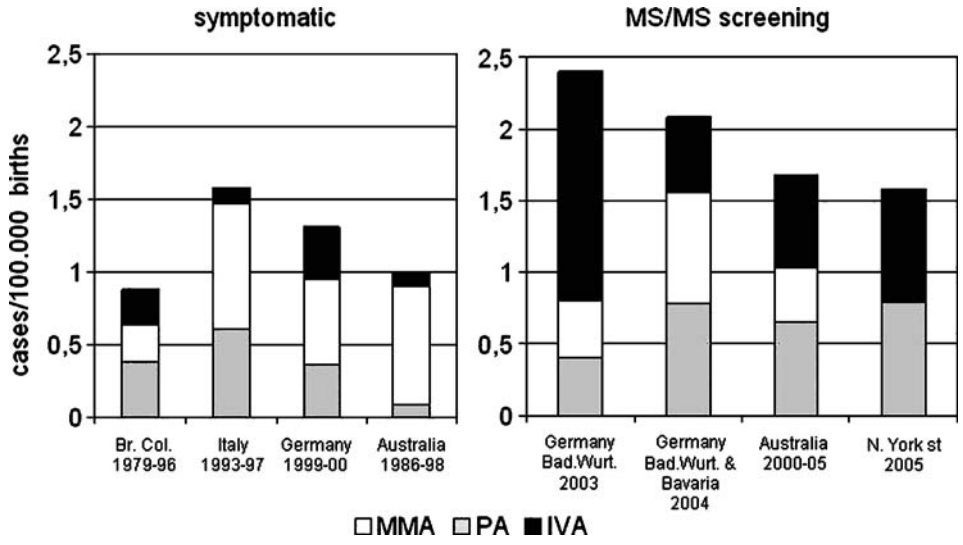

Fig. 5 Incidence (number of cases per 100 000 births) of 'classical' organic acidurias in symptomatic and neonatal mass screening populations. Different bars correspond to references (Applegarth et al 2000; Dionisi-Vici et al 2002; Hoffmann et al 2004; Klose et al 2002; Rhead this study; Schulze et al 2003; Wilcken et al 2003, this study)

Conclusions

Our study based on the comparison of the natural history of patients with 'classical' organic acidurias diagnosed on clinical bases with those diagnosed through expanded newborn screening may help to indicate whether these conditions fulfil the still valid principles of early disease detection established in 1968 (Wilson and Jungner 1968). In our series of cases, expanded newborn screening decreased early mortality and symptoms at diagnosis were less severe. Moreover, the short-term neurodevelopmental outcome seems to be more favourable in patients detected by newborn screening However, the duration of follow-up in these patients is too short and therefore the long-term outcome seems to be still unpredictable. A less compromised condition might be of further benefit when deciding the option of liver transplantation in selected cases.

Since neonatal screening could not discriminate the early-onset patients from those with a later onset, the major advantage from screening would probably be obtained in patients with milder phenotypes, facilitating appropriate treatment in a presymptomatic stage of the disease to prevent the appearance of severe clinical signs.

Regarding the potential psychological and social consequences of neonatal screening on patients and their families, the markedly increased detection rate of patients with IVA clearly requires a particular awareness. This increase would be the result either of underdetection by conventional diagnosis or of overdetection of mild cases by MS/MS screening. The recent identification of a common mutation of the isovaleryl-CoA dehydrogenase gene (932C > T) associated with a mild phenotype or even asymptomatic IVA (Ensenauer et al 2004), further supported by the observation of six cases of IVA diagnosed by neonatal screening with a fully normal phenotype (Knerr et al 2005), may explain this finding. Clinicians should as far as possible avoid inducing the so-called 'vulnerable' child syndrome by treating a benign condition as a serious disease (Waisbren et al 2003).

Neonatal screening does not modify the detection rate of MMA and PA, unlike for IVA, underlining the existence of a more severe phenotype in these two diseases, as confirmed by the unfavourable outcome at follow-up.

In conclusion, further multicentre longitudinal studies are needed to assess the usefulness of expanded newborn screening for 'classical' organic acidurias and to allow better understanding of the clinical spectrum of these diseases. In addition, the complete lack of large scale studies on the outcome of IVA should stimulate clinicians to collaborate in establishing the natural history of this disease. For all these reasons, the opportunity to include 'classical' organic acidurias in the expanded neonatal screening is still being debated.

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