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Clinical outcome and long-term management of 17 patients with propionic acidaemia

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Abstract A retrospective study was performed on the clinical outcome and long-term treatment of 17 patients with propionic acidaemia diagnosed during the last 20 years in our hospital. The study group consisted of 12 patients with early onset type of disease and 5 patients with late onset. Seven (41%) patients died, five with early onset and two with late onset. The deceased early onset patients had a median survival of 0.4 years while the deceased late onset patients died at the age of 2.8 and 4 years respectively. Median age of the living early onset patients was 5.2 (1–9.25) years, the late onset patients were 4, 7 and 23 years old. Patients were all treated with natural protein restriction and in most cases carnitine and metronidazole were added. The early onset patients were almost all treated with daily home tube feeding. The mean natural protein intake of early onset patients (6.3 ± 1.5 g/day) was significantly lower than the natural protein intake of late onset patients (17.6 ± 5.3 g/day). Supplemental protein intake was higher in early onset patients.The general neurological outcome of our study group was satisfactory with a better outcome for early onset patients. As to growth, many patients showed a failure to thrive, this was particularly for height. The strong protein restriction during the first years of life probably contributed to this.

Conclusion The prognosis for patients with propionic acidaemia appeared to be satisfactory in terms of survival and outcome characteristics such as neurological and mental development. Despite these results the authors feel that the prognosis and quality of life of these patients might be improved with liver transplantation or possibly somatic gene therapy in the future.

Key word Propionic acidaemia

Abbreviations *MMA* methylmalonic acidaemia · *PA* propionic acidaemia · *PCC* propionyl CoA carboxylase · *SDS* standard deviation score

Introduction

Propionic acidaemia (PA) was first described in 1968 by Hommes and co-workers [6]. Initially known as ketotic hyperglycinaemia [3] the name was changed to the major metabolite found in plasma [1, 8]. The defective propionate carboxylation in leucocytes was clarified by Hsia et al. [7] and is caused by the enzymatic deficiency of propionyl CoA carboxylase (PCC) as described by Gompertz and his co-workers [5]. The clinical aspects of the disease were summarized by Wolf et al. [21] presenting data from 65 patients. Clinical symptoms are nonspecific such as feeding difficulties, lethargy and vomiting. The biochem-

ical findings are raised 3-hydroxypropionate, methylcitrate and propionate in body fluids and, frequently, hyperglycinaemia while hyperammonaemia is almost always present. The enzyme consists of two polypeptides: an α chain with a biotin prosthetic group and a β chain, arranged as an $\alpha_4\beta_4$ octomer. Two distinct complementation groups pccA and pccBC code for the genes PCCA and PCCB that account for the α and β chain respectively [12]. Recently, the cloning of functional PCC and the correction of the enzyme deficiency in fibroblasts has been demonstrated [15]. Little is known concerning the prognosis of PA. Surtees et al. [15] published a paper focusing on the neurological outcome of patients with PA and another on the cardiomyopathy in some of these patients [10]. Recently, comprehensive clinical, biochemical and treatment data on 30 patients with PA, diagnosed by selective screening were presented by Lehnert et al. [9]. However, they did not present detailed information with regard to the prognosis and outcome. Moreover, their data were a compilation from different centres. We here present the results of a retrospective study on all patients with PA diagnosed and treated at our hospital. The most important clinical data as well as aspects of treatment and outcome will be presented.

Patients

Seventeen patients were included in this study. All were diagnosed since the early 1970s at the Hôpital Necker Enfants Malades in Paris. In most of them the diagnosis was confirmed with enzymatic assay of PCC. Biotin responsiveness was checked in all patients but none responded neither clinically nor biochemically. Twelve patients presented within 3 weeks after birth (early onset group), whereas 5 of them were diagnosed later in life: from 3.5 months to 3 years of age (late onset group).

Clinical presentation

Early onset

The most prominent symptoms in this group were feeding difficulties, vomiting, hyperventilation, dehydration and hypothermia. The neurological picture was characterized by slow reactivity, pedalling movements, axial hypotonia and limb hypertonia with large amplitude tremors and myoclonic jerks. A profound coma was present in 6 patients, whereas 2 suffered from convulsions. In most cases emergency treatment measures such as assisted ventilation, exchange transfusions, peritoneal dialysis were undertaken while in later years biotin and carnitine were added. Subsequently, a dietary treatment of low-protein intake was begun. Recently, two of our patients with PA underwent orthotopic liver transplantation. At present, their clinical situation is reasonable and stable; however, despite liver transplantation the urinary organic acid profile showed elevated levels of methylcitrate and 3-OH propionate. Moreover, protein restriction remains necessary. A detailed description of these two patients will be presented in a separate report.

The cause of death was irreversible metabolic decompensation complicated by infections such as septicaemia and meningitis.

Late onset

The clinical picture of these patients differed in many aspects from the early onset patients. Three patients had a mainly gastro-enterological presentation, consisting of vomiting and feeding difficulties with concomitant failure to thrive and malnutrition. One patient was thought to have food intolerance. These symptoms became obvious after 3–6 months of life. Another patient presented with a predominantly neurological picture. She was hypotonic, had apyretic convulsions and ultimately became somnolent and comatose. Failure to thrive and a slight psychomotor retardation with hypotonia were the presenting symptoms of a boy at the age of 3 years. The late onset patients that died suffered from repeated and ultimately irreversible metabolic decompensations.

Methods

To study different aspects of outcome we used the same methods as in our patients with methylmalonic acidaemia (MMA) [18]. A "disability scale" was applied which contained seven subscales subdivided into four grades: normal, minor, intermediate and major abnormalities.

Neuromotor outcome – expresses the presence or absence of neurological abnormalities and the degree of motor development. Mental outcome – reflects the intellectual development of the child, as measured by psychological testing [2, 21] and the degree of schooling. Normal: developmental quotient (DQ) between 90 and 110; minor deficiency: DQ between 75 and 90; intermediate deficiency: DQ between 50 and 75; and major deficiency: DQ less than 50. Psychological outcome – considers the behavioural status of the child. Visceral outcome – points to the involvement of heart, liver, kidney or pancreas. Sensory outcome – reflects the presence or absence of visual or hearing problems. Social outcome – describes the presence of social and familial problems, such as problems in socio-cultural adaptation, parental difficulties in coping with the disease, marriage disturbances, poor family circumstances and/or the need for placing the child in a centre for special care. Nutritional outcome – the nutritional status as reflected by weight and height and, to a lesser degree, head circumference.

Dietary treatment

The basic principles of the dietary treatment of patients with PA do not really differ from those of patients with MMA [18]. From the early 1970s the dietary treatment was based upon restriction of natural protein. The amount of natural protein given to the patients was comparable to that given to patients with phenylketonuria. An amino acid mixture free of precursor amino acids (threonine, methionine, valine, isoleucine and leucine) was prescribed to meet the recommended daily allowance. After 1980 treatment principles changed. Home tube feeding became a virtually indispensable part of the patient's routine daily treatment. Furthermore, based on reports in the literature and own research, carnitine (100 mg/kg/day) and a few years later metronidazole (20 mg/kg/day) were added to the therapy [13, 19]. Parental co-operation was recognized as an important issue in the treatment. All parents were informed and trained in how to manage under circumstances such as fever, vomiting and food refusal and were capable of placing a nasogastric tube in case of urgent or semi-urgent treatment at home. Parents and children had easy access to the dietary department, in most cases by telephone and patient contacts at the outpatient clinic with one of the dieticians. Changes in regimen were kept under strict surveillance and noted. All children were seen at the outpatient clinics at regular intervals by a team consisting of a clinician (J.M.S.), a dietician (E.D.) and a child psychologist (D.R.) who have been working as a team for over 20 years now. Plasma amino acids and urinary organic acids were regularly monitored.

Table 1 Clinical and treatment data of the patients (values represent mean and range)

	Early onset	Late onset
Number of patients	12	5
Age at diagnosis	9.3 days (3–19)	16.3 months (3.5–3 6)
Total time in hospital	4.1 months (2–12)	2.9 months (1–7)
Number deceased	5	2
Age of death	3, 3.6, 5, 6 months and 9.5 years	2.8 and 4 years
Present age	5.6 years (1–9.3)	11.4 years (4–23)
Patients treated with		
Tube feeding	9	1
Carnitine	11	3
Metronidazole	6	2

Statistical analysis

For comparison of mean natural and supplemental protein intake and standard deviation scores (SDS) of height, weight and head circumference of the patients, an unpaired, two-sided *t*-test was performed with a significance level of $P<0.05$.

Results

Clinical and treatment data of all patients are presented in Table 1. Of the 12 early onset patients, 5 were non-European immigrants, while all the late onset patients originated from France. Five (42%) of the early onset and 2 (40%) of the late onset patients died. The median survival time of the deceased early onset patients was 0.4 years. Median age of the living early onset patients at the time when this study was concluded was 5.2 years (range 1–9.3 years). The late onset patients were 4, 7 and 23 years of

Table 2 Mean (and standard deviation) of natural and supplemental protein intake per day of all patients according to age

	Early onset		Late onset	
	Natural protein	Supplemented protein	Natural protein	Supplemented protein
0–6 months	5.0 ± 1.1	4.2 ± 2.6	7.3 ± 3.3	3.5 ± 3.3
6–12 months	5.6 ± 0.9	6.0 ± 4.6	9.0 ± 3.5	5.8 ± 4.5
1–2 year	5.7 ± 0.9	8.3 ± 4.3	13.9 ± 5.0	6.2 ± 6.1
2–3 year	6.5 ± 2.1	7.9 ± 4.6	18.4 ± 2.7	9.4 ± 9.7
3–4 year	6.8 ± 1.2	10.8 ± 5.4	18.4 ± 4.5	1.3 ± 2.8
4–5 year	7.7 ± 1.1	12.4 ± 3.4	23.2 ± 9.4	0
5–6 year	9.1 ± 1.1	15.6 ± 1.7	28.2 ± 10.1	0
from 6 year	10.7 ± 2. 2	11.9 ± 5.6	27.6 ± 7.3	0

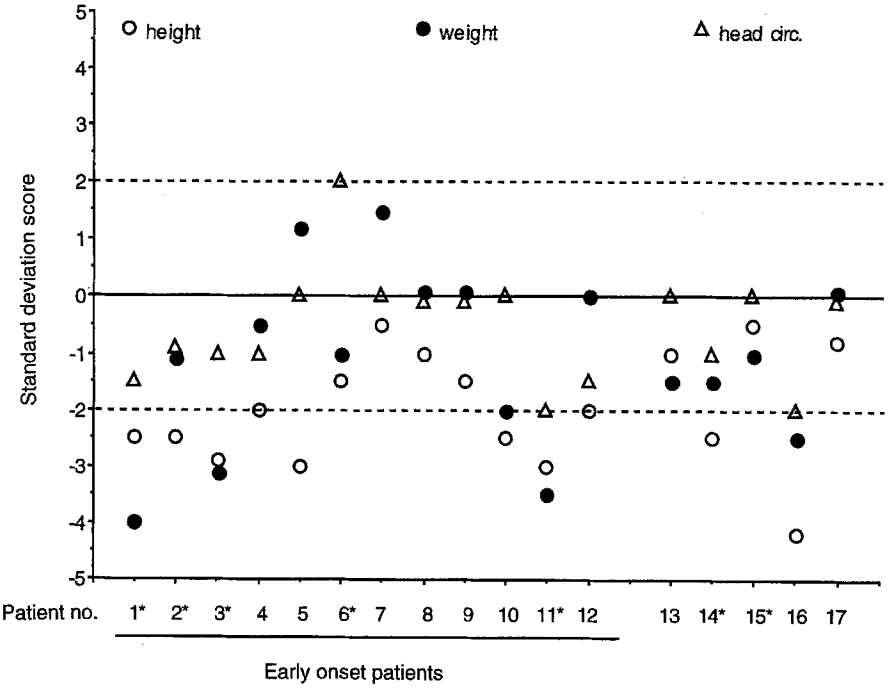

Fig. 1 Height, weight and head circumference with SDS of all patients; early onset: *1–12*, late onset: *13–17* (* deceased)

Table 3 Outcome of patients by means of the disability scale. For further details see text under methods

	Time of onset							
	Early (n = 12)	Late (n = 5)	Early	Late	Early	Late	Early	Late
Type/degree of handicap	Normal		Minor		Intermediate		Severe	
Nutritional	3	2	4	1	2	1	3	1
Neuromotor	4	0	8	3	0	2	0	0
Mental	3	0	9	4	0	1	0	0
Psychological	5	0	7	5	0	0	0	0
Sensorial	0	0	0	0	0	0	0	0
Social	7	2	1	3	4	0	0	0
Visceral	0	0	0	0	0	0	0	0

age respectively. Table 2 represents the mean natural and supplemental protein intake per day of all our patients in relation to age. The natural protein intake per day remained fairly stable during the first 3–4 years of life in the early onset patients. After the 6th year of life the total natural protein intake hardly changed and seldom reached values higher than 13 g/day. The supplemental protein intake showed a steady but strong increase and leveled off from the age of 6 years. The natural protein intake of late onset patients was higher and rose more rapidly to an almost normal protein intake after 3–4 years of life. The differences between the mean natural protein intake of early and late onset patients were significant in all age groups ($P < 0.0001$, t-test). Table 3 outlines the results of the disability scale. Late onset patients suffered more frequently from minor to intermediate neuromotor, mental and psychological disabilities than the early onset patients. The visceral scale, pointing to involvement of other organ systems, showed no abnormalities in particular with regard to the heart and pancreas. An echocardiography was performed in six of the ten living patients: no convincing signs of cardiomyopathy were found. Almost all patients showed some degree of delay whether in height, weight or head circumference (Fig. 1). Out of 17 patients, 10 were at or beneath the –2 SDS for one of the parameters. The mean SDS for height of all patients was –2, almost twice the SDS for weight which was –1.1. There was no relationship between time of onset and either one of the forementioned parameters, although the early onset patients did show a tendency towards a more severe score with regard to the nutritional scale.

All figures were the result of measurements taken or scoring performed shortly before death or, in case of the living patients, at the time of the last evaluation shortly before this study was concluded.

Discussion

From a clinical point of view there was a clear distinction between patients with early onset and patients with late onset PA. The early onset patients presented the classical clinical picture of vomiting, lethargy and typical neurological symptoms with a keto-acidotic coma. The late onset patients had a more diverse presentation; a symptomatology that could be misleading and cause a delay in diagnosis with consequently a higher morbidity and possibly mortality rate. However, the mortality in our early onset patients was comparable to that of the late onset patients, 42% and 40% respectively. Although the number of patients is limited, the mortality in the early onset group is low when compared to the mortality of early onset PA patients in the London study [16]. Whether this was related to the composition of their early onset patient group, which consisted predominantly of non-Europeans and the fact that they had three patients with lethal cardiomyopathy, remained uncertain. With respect to morbidity however, our results show that late onset patients more frequently suffered from neuromotor, mental and psychological disabilities than did early onset patients. Delay in diagnosis might be an important cause for these differences. Clinical symptoms in late onset patients were frequently more obscure, consequently they might have been exposed to several metabolic "strokes" before the correct diagnosis was established. Interestingly, the neurological outcome of the early onset patients in the London study [16] was very poor, while their late onset patients had a better outcome. In our study on patients with MMA, it became clear that the early onset MMA patients had a worse neurological and mental outcome than our late onset patients. Furthermore, the mortality in our early onset MMA patients was twice that of the late onset patients [18]. Possibly, the PA patients, of which the majority was born in later years, profited from our experience with treating MMA patients.

The type of treatment did show some important changes during the years. With the introduction of nasogastric tube feeding, we observed less frequent metabolic decompensations and hospitalisations. In later years the explanation for this phenomenon was found in the fact that catabolism and thus lipolysis, causes an increased production of odd-numbered long chain fatty acids finally

leading to propionate production [14, 20]. Furthermore, in 1983 Roe and co-workers [13] described the efficacy of carnitine in removing propionyl groups by enhancing the urinary excretion of these compounds and restoring the metabolic balance. The discovery of the gut flora as an important non-protein source of propionate and the subsequent introduction of metronidazole in the treatment, decreased the number of unnecessary dietary adjustments and temporarily lowering of natural protein intake [19]. The basic treatment of our patients, however, consisted of natural protein restriction with or without added supplemental protein mixtures. We prescribe the protein intake in gramme per day unlike others who prefer gramme per kilogram body weight. The difficulty with this manner of prescribing is that body weight and protein tolerance do not exhibit a linear correlation. Therefore, the most important risk threatening patients with inborn errors of protein metabolism is that the protein intake steadily increases with body weight and ultimately overcomes protein tolerance. Moreover, because the daily minimal essential protein requirement remains almost stable during the first 3–4 years of life, prescribing protein intake in grammes per day has the advantage of being more practical for parents, patient, dietician and doctors.

The final aspect of outcome as depicted in Fig. 1 focused on aspects of growth. Our patients showed a tendency of failure to thrive. This was particularly reflected in their mean SDS for height: –2 and to a lesser extent in the mean SDS for weight: –1.1. In this context, the short stature of our patients was probably caused by the iatrogenic protein restriction, particularly in the first years of life. A daily natural protein intake of 5–7 g is significantly lower than the calculated recommended daily amount of protein [4]. Consequently, these patients were not able to meet their growth potential. This was also reflected in the growth curves of most of our patients: height velocity had a tendency to decrease in the first years of life, while weight gain was frequently better. Due to the protein restriction, the daily caloric intake was composed of a relatively high proportion of fat and carbohydrates. Moreover, the patients older than 5 years had a mean SDS for height of –2.2, while their SDS for weight was –0.6. This pointed out that short stature remained present while weight gain in PA patients was normal.

An important aspect of the cause of death in our PA patients needs to be accentuated. Patients 2, 3 and 11 all died quite unexpectedly because of an overwhelming infectious disease: varicella, septicaemia and meningitis respectively. Intercurrent infections are an important risk factor in aggravating metabolic decompensations. Pancytopenia is a well-known presenting feature in PA [17], and cellular and humoral immunological disturbances in these patients have been described [11, 12]. These aspects stress the importance of an attentive and experienced follow up of these patients.

The prognosis for patients with PA appeared to be satisfactory in terms of survival and outcome characteristics such as neurological and mental development. However, the price that parents, patients and the medical profession have to pay for this accomplishment might not be in the proper range. Recent developments in medical techniques such as liver transplantation might add to a better outcome and quality of life for patients with this kind of inborn errors of metabolism. However, the metabolic block in tissues other than liver such as muscle and skin might cause unforeseen complications. On the other hand, the developments in the field of somatic gene therapy are very promising. Recently the enzyme deficiency was corrected in fibroblasts by cloning functional alpha PCC [15]. Possibly somatic gene therapy for patients with PA is not too far away.

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