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Original article

Impact of newborn screening for fatty acid oxidation disorders on neurological outcome: A Belgian retrospective and multicentric study

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ABSTRACT

Fatty acid oxidation (FAO) disorders are autosomal recessive genetic disorders affecting either the transport or the oxidation of fatty acids. Acute symptoms arise during prolonged fasting, intercurrent infections, or intense physical activity. Metabolic crises are characterized by alteration of consciousness, hypoglycemic coma, hepatomegaly, cardiomegaly, arrhythmias, rhabdomyolysis, and can lead to death. In this retrospective and multicentric study, the data of 54 patients with FAO disorders were collected. Overall, 35 patients (64.8%) were diagnosed after newborn screening (NBS), 17 patients on clinical presentation (31.5%), and two patients after family screening (3.7%). Deficiencies identified included medium-chain acyl-CoA dehydrogenase (MCAD) deficiency (75.9%), very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency (11.1%), long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency (3.7%), mitochondrial trifunctional protein (MTP) deficiency (1.8%), and carnitine palmitoyltransferase 2 (CPT 2) deficiency (7.4%). The NBS results of 25 patients were reviewed and the neurological outcome of this population was compared with that of the patients who were diagnosed on clinical presentation. This article sought to provide a comprehensive overview of how NBS implementation in Southern Belgium has dramatically improved the neurological outcome of patients with FAO disorders by preventing metabolic crises and death. Further investigations are needed to better understand the physiopathology of long-term complications in order to improve the quality of life of patients and to ensure optimal management.

1. Introduction

Mitochondrial β−oxidation of fatty acids (FAO) is a metabolic pathway producing a large amount of energy, which is critical in situations where glucose supplies are limited, like fasting, fever, and exercise. This complex catabolic pathway requires the participation of several enzymes, transporters, and facilitating proteins. About 20 genetic disorders have been identified until now, and their diagnosis is usually based on acylcarnitine profiles and genetic evaluations. Following the introduction of tandem mass spectrometry in dried blood spots, several disorders are part of the newborn screening (NBS) program in Southern Belgium [1–3].

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common FAO disorder, with a prevalence of 1/15.000 in the Caucasian population [4]. The classical presentation is usually seen in children aged from 3 to 24 months, and is characterized by seizures,

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hepatomegaly, cardiomegaly, and alteration of consciousness. These symptoms are associated with hypoketotic hypoglycemia, dicarboxylic aciduria, hyperammonemia, and increased transaminases [4]. Metabolic crises lead to a high mortality rate, and neurological complications involve intellectual deficiency, language disorders, behavioral disorders, seizures, and failure to thrive [4,5]. However, some patients remain asymptomatic [6].

Very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency has a prevalence of 1/30.000 births and is characterized by three different phenotypes [7]. The first phenotype has a severe presentation during the neonatal period, characterized by hypertrophic or dilated cardiomyopathy, pericardial effusion, and cardiac arrhythmias, associated with hypoketotic hypoglycemia, hypotonia, hepatomegaly, and hepatocellular dysfunction. Morbidity and mortality from cardiomyopathies and arrhythmias are high [8,9]. The second phenotype affects young children and is characterized by hepatomegaly and hypoketotic hypoglycemia. Episodes of metabolic crises are less frequent, and mortality is lower [7,10]. The third phenotype is the adolescent and adult myopathic phenotype, which is characterized by episodes of rhabdomyolysis during prolonged fasting or physical activity [7,8].

The clinical manifestations of mitochondrial trifunctional protein (MTP) and long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiencies are similar to those described for other FAO disorders, except that affected patients may develop peripheral neuropathy and progressive retinopathy as long-term complications [11].

Carnitine palmitoyltransferase 2 (CPT 2) deficiency has been divided into three phenotypes: a late-onset form, a severe infantile form, and a lethal neonatal form. The neonatal form is associated with dysorganogenesis of the brain and kidneys and is usually lethal. The infantile form is characterized by hypoketotic hypoglycemia associated with metabolic acidosis, hepatomegaly, and cardiac involvement. The late-onset form is characterized by rhabdomyolysis episodes, while the affected individuals are generally asymptomatic between decompensation episodes. CPT 2 deficiency is not currently part of the NBS program in Belgium [12–14].

2. Methods

This retrospective and multicentric study included 54 patients with FAO disorders followed at Cliniques Universitaires Saint-Luc (CUSL), Hôpital Universitaire des Enfants Reine Fabiola (HUDERF), Centre Hospitalier Universitaire de Liège (CHU de Liège), and Clinique du Mont-Légia (CHC Liège) between 1991 and 2017. The study was accepted by the ethical committee of each hospital. The selected patients were identified after NBS or on clinical presentation before NBS implementation in Belgium. 35 patients (64.8%) were diagnosed after newborn screening (NBS), 17 patients on clinical presentation (31.5%), and two patients after family screening (3.7%). The diagnosis was confirmed for 51 patients (94%) by molecular analysis or by measuring enzymatic activities on cultured fibroblasts for former patients. NBS results, corresponding to the acylcarnitine profiles in dried blood spots, from 25 patients with MCAD, VLCAD, or LCHAD deficiencies were reviewed. Each acylcarnitine was expressed as standard deviation (SD) of the mean.

3. Results

The data of 54 patients with FAO disorders were collected. A total of 35 patients were diagnosed following NBS (64.8%) and initial acylcarnitine profiles were reviewed for 25 of them. Out of these 35 patients, 17 were diagnosed following clinical presentation (31.5%) and two patients were diagnosed after family screening (3.7%). The latter included an antenatal screening and a diagnosis following the clinical presentation of a relative (Table 1).

Table 1
Characteristics of the studied population.
MCAD: Medium-chain acyl-coenzyme A dehydrogenase; VLCAD: very long-chain acyl-coenzyme A dehydrogenase; LCHAD: long-chain hydroxyacyl-coenzyme A dehydrogenase; MTP: mitochondrial trifunctional protein; CPT 2: carnitine palmitoyltransferase 2.

	Newborn screening	Clinical diagnosis	Family screening	Total
MCAD deficiency	31/41 (75.6%)	9/41 (22.0%)	1/41 (2.4%)	**41 (75.9%)**
VLCAD deficiency	3/6 (50%)	2/6 (33.3%)	1/6 (16.6%)	**6 (11.1%)**
LCHAD deficiency	1/2 (50%)	1/2 (50%)	0/2 (0%)	**2 (3.7%)**
MTP deficiency	0/1 (0%)	1/1 (100%)	0/1 (0%)	**1 (1.8%)**
CPT 2 deficiency	0/4 (0%)	4/4 (100%)	0/4 (0%)	**4 (7.4%)**

3.1. MCAD deficiency

A total of 41 patients were affected by MCAD deficiency (75.9%), with a male/female ratio of 1.15/1. Overall, 31 patients were diagnosed following NBS (75.6%). The NBS results of 22 patients were reviewed and acylcarnitines were expressed as SDs of the mean. C6 acylcarnitines were increased between +4.2 SD and +118 SD, C8 between + 26 SD and +293 SD, C10 between −0.5 SD and +15 SD, and C10:1 between −0.2 SD and +23 SD. Specific ratios C8/C2, C8/C10, and C8/C12 were also significantly increased between +17 SD and +332 SD, +0.7 SD and +50 SD, and +10 SD and +195 SD, respectively (Figs. 1 and 2).

Before NBS implementation, nine patients were diagnosed following clinical presentation with an average age at diagnosis of 22 months. During their first metabolic decompensation, acute symptoms were seizures (33%), alteration of consciousness (77%), coma (66%), arrhythmias (22%), hepatomegaly (22%), nausea (22%), vomiting (33%), and rhabdomyolyses (11%). Initial biological results showed hypoglycemia (77%), metabolic acidosis (44%), elevated transaminases (77%), hyperuricemia (66%), hyperammonemia (44%), elevated creatine kinase (CK, 55%), and myoglobinuria (11%) (Fig. 3).

Overall, 44% of the patients diagnosed after a clinical event had an intellectual deficiency and epilepsy, 33% had attention deficit disorders, speech disorders and behavioral disorders, and 11% of the patients showed muscular weakness and motor dysfunction. None of the 31 patients diagnosed following NBS had a metabolic crisis but it is important to point out that the follow-up period for clinically diagnosed patients is longer than the follow-up period for patients diagnosed after NBS. Nevertheless, when comparing the follow-up of the 2 cohorts over a 10-year period, we obtain the same results. Hospitalizations during fever and infections were frequent. The fasting periods were adapted to the children's ages. Carnitine supplementation was started in 37 patients (90.2%) with decreased free carnitine levels. All screened patients showed an optimal cognitive development, except for one patient with mild cognitive deficiency and behavioral disorders. Two patients had attention deficit disorders (Fig. 4).

Genetic testing of the *ACADM* gene revealed that 28 patients were homozygous for the Caucasian common variant c.985A > G p.(Lys304Glu) (68.3%), eight patients were compound heterozygous for the common variant (12.2%), and three patients had different genetic variants of the *ACADM* gene (7.32%). Genetic analyses were not available for two patients (4.88%).

3.2. VLCAD deficiency

Six patients had a VLCAD deficiency, with a male/female ratio of 1/1. Three patients were diagnosed following NBS, two patients following clinical presentation, and one through antenatal screening following the diagnosis of a relative. The NBS results of two patients with VLCAD

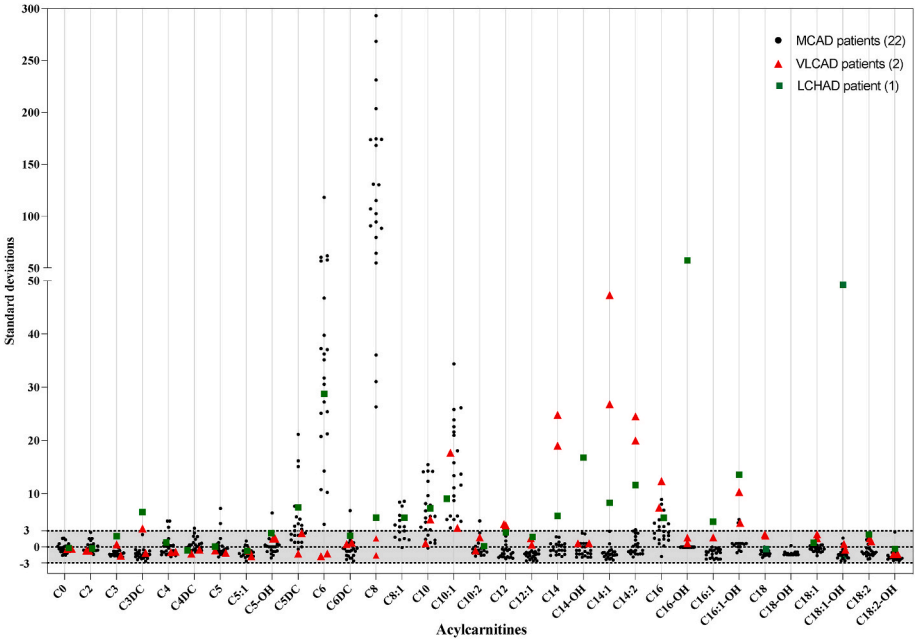

Fig. 1. Newborn screening results of 25 patients with MCAD deficiency (n = 22), VLCAD deficiency (n = 2), and LCHAD deficiency (n = 1). Acylcarnitines are expressed as standard deviations of the mean. The grey zone indicates normal values between +3 SD and −3 SD. MCAD: Medium-chain acyl-coenzyme A dehydrogenase; VLCAD: very long-chain acyl-coenzyme A dehydrogenase; LCHAD: long-chain hydroxyacyl-coenzyme A dehydrogenase.

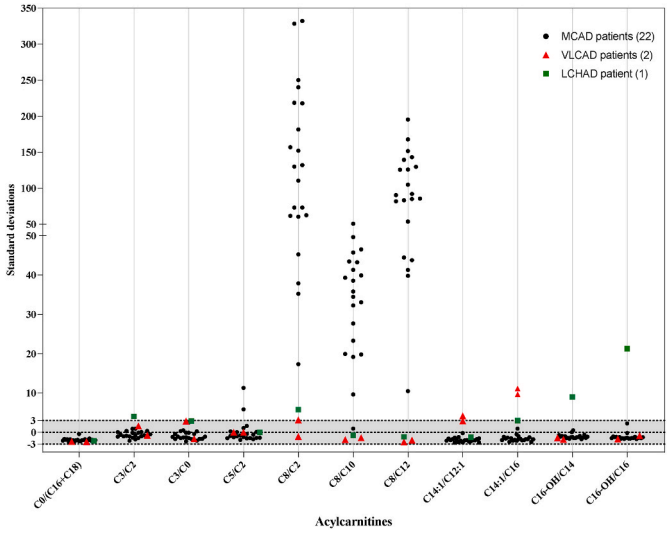

Fig. 2. Newborn screening ratios of 25 patients with MCAD deficiency (n = 22), VLCAD deficiency (n = 2), and LCHAD deficiency (n = 1). Acylcarnitines are expressed as standard deviations of the mean. The grey zone indicates normal values between +3 SD and −3 SD. MCAD: medium-chain acyl-coenzyme A dehydrogenase; VLCAD: very long-chain acyl-coenzyme A dehydrogenase; LCHAD: long-chain hydroxyacyl-coenzyme A dehydrogenase.

deficiency showed increased acylcarnitines C14 (+19 SD and +24 SD), C14:1 (+26 SD and +47 SD), C14:2 (+20 SD and +24 SD), C16 (+7 SD and +12 SD), and C16:1-OH (+4 SD and +10 SD). Specific ratios were also increased: C14:1/C12:1 (+2.9 SD and +4.2SD) and C14:1/C16 (+11.1 SD and +9.7 SD) (Figs. 1 and 2).

The first patient diagnosed after clinical presentation had an acute gastroenteritis at 18 months of age, followed by alteration of consciousness, seizures, and coma. Biological analyses highlighted hypoglycemia (0.6 mmol/l), metabolic acidosis, hyperuricemia, increased transaminases, and increased CK. The second patient had a cardiorespiratory arrest at the age of 10 months. Following this episode, a dilated cardiomyopathy with arrhythmias and a chronic hepatopathy were diagnosed (previously reported by Sluysmans et al., 1997) [15]. The two patients suffered from epilepsy and one patient had a mild cognitive impairment. None of the patients diagnosed after NBS or antenatal screening had neurological complications but one patient was lost to follow-up. All patients with VLCAD deficiency followed a diet with fasting periods adapted to their age and to the metabolic circumstances. They were all supplemented with medium-chain triglycerides (MCTs) and four patients received carnitine supplementation. Despite taking an appropriate diet and medical treatment, patients were frequently admitted with metabolic decompensation including muscular pain and increased CK, requiring hospitalization for intravenous glucose intake. During those episodes, specific acylcarnitines were generally increased in plasma and dried blood spots. At the molecular level, two siblings had the c.1097G > A p.(Arg366His) variant in exon 11 and the c.1269+1G > A variant in exon 12. A third patient had the c.1322G > A p.(Gly441Asp) variant in exon 13 and the p.(Lys238del) variant in exon 9 in the *ACADVL* gene. The last patient had a positive NBS but was lost to follow-up before a genetic study or measure of enzymatic activity could be performed.

3.3. LCHAD deficiency and MTP deficiency

Two male patients had an LCHAD deficiency, one was diagnosed following NBS and one was clinically diagnosed. In NBS results, an increase of many acylcarnitines were found with hydroxylated long-chain acylcarnitines such as C16–OH (+57 SD), C16:1-OH (+13 SD), C18:1-OH (+49 SD), and an increase of specific ratios such as C16–OH/C14 (+9 SD) and C16–OH/C16 (+23 SD). Medium- and long-chain acylcarnitines such as C6, C8, C10, C12, C14C14:1, C14:2, C16, and 16:1 were also mildly increased (Figs. 1 and 2). The patient who developed clinical symptoms was diagnosed at 9 months of age. He had digestive symptoms and hypotonia associated with hypoglycemia (3.2 mmol/l), elevated transaminases, lactate dehydrogenase (LDH), and increased CK levels. None of the patients showed cardiomegaly, hepatomegaly, cognitive impairment, or epilepsy. However, they both developed a peripheral retinal dystrophy around 6 and 14 years, respectively. The patient with a clinical diagnosis developed peripheral polyneuropathy

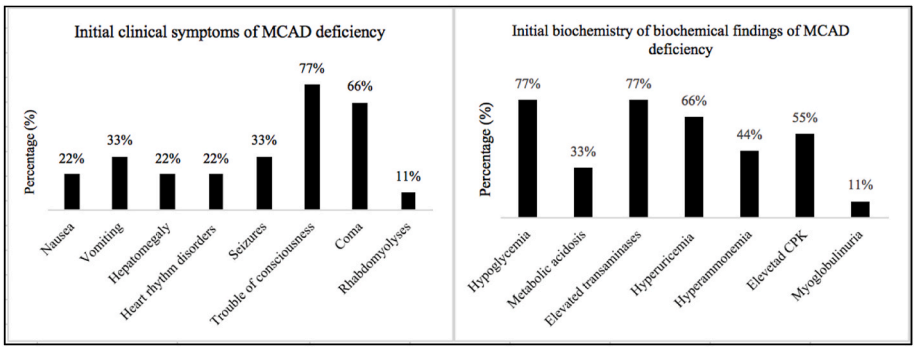

Fig. 3. Initial clinical symptoms and initial biochemistry of biochemical findings of patients with MCAD deficiency during their first metabolic decompensation. MCAD: medium-chain acyl-coenzyme A dehydrogenase.

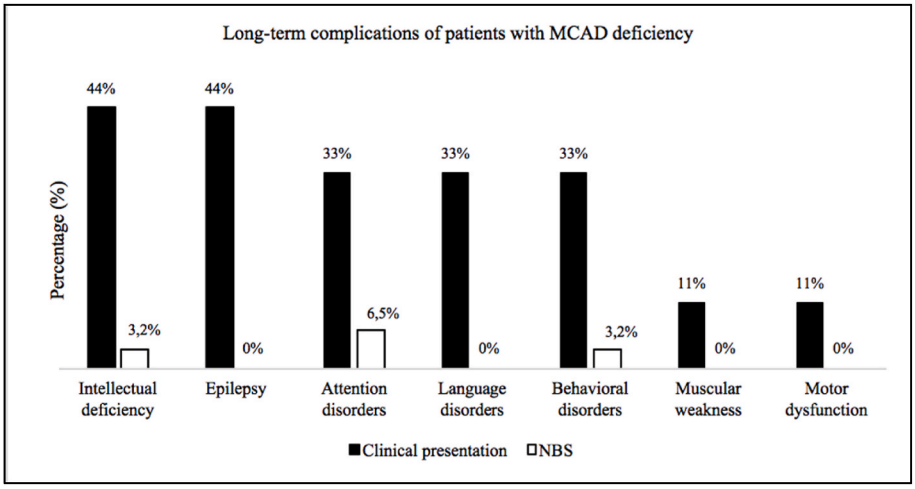

Fig. 4. Comparison of long-term complications in screened and clinically diagnosed patients with MCAD deficiency. MCAD: medium-chain acyl-coenzyme A dehydrogenase; NBS: newborn screening.

when he was 16 years old. The patient diagnosed following NBS did not develop peripheral polyneuropathy but the follow-up time is only 6 years. Fasting periods were adapted to the children's ages, and eviction of long chain triglycerides (LCTs) was recommended with an MCT-enriched diet. They experienced multiple episodes of metabolic decompensations during intercurrent infections, which required hospitalizations for intravenous glucose infusion. Both patients were homozygous for the Caucasian variant c.1528G > C p.(Glu510Gln) of the *HADHA* gene.

One patient had MTP deficiency. He was diagnosed at the age of 4 days after a severe life-threatening event following a 4-h fasting. He presented with hypotonia, apathy, hepatomegaly, and respiratory distress. No biological results were available. The diagnosis was confirmed by enzymatic activity measurement on cultured fibroblasts. The enzymatic activity of 3-hydroxyacyl-CoA dehydrogenase was 53.4 nmol/min.mg.protein (62.4–63.9) and the enzymatic activity of the 3-ketoacyl-CoA long chain thiolase was 0.7 nmol/min.mg.protein (17.8 ± 3.5). The patient had behavioral and attention deficit disorders. He presented with peripheral polyneuropathy causing amyotrophy and distal muscle weakness. He had to be hospitalized several times and had two episodes of seizures.

3.4. CPT 2 deficiency

The four patients with CPT 2 deficiency were all diagnosed following clinical presentation. The male/female ratio was 3/1. Two patients displayed the late-onset form of CPT 2 deficiency. They were diagnosed at 6 and 14 years, respectively, with muscle cramps, dark urines, and abdominal pain after physical activity. Biological analyses revealed elevated CK, LDH, transaminases, and myoglobinuria. These patients had multiple episodes of rhabdomyolysis following significant physical efforts or intercurrent infections, but neurological outcome was optimal according to their chronological age. The patients were compound heterozygous. The first one had the c.338C > T p.(Ser113Leu) variant in exon 3 and the c.1667del variant in exon 5. The second one had the c.149C > A p.(Pro50His) variant in exon 1 and the c.[1239_1240delGA; 1342T > C] variant in exon 4.

One patient had the infantile form of CPT 2 deficiency and was diagnosed following an arrhythmia at 2 days old, leading to hemodynamic instability and respiratory distress. The patient presented with alteration of consciousness, cardiomegaly, and hepatomegaly associated with hypoglycemia (1 mmol/l), metabolic acidosis, hyperuricemia, increased transaminases, and elevated CK. The patient died at 5 months of age after she was found in asystole. She was homozygous for the c.534_558 deletion in exon 4.

One patient presented the lethal neonatal form of CPT 2 deficiency, with macrocephaly secondary to hydrocephalus associated with polymicrogyria and vermian agenesis. The kidneys showed corticomedullary dedifferentiation with the presence of cortical cysts. Blood glucose was normal, but hyperammonemia (188 µmol/L) and dicarboxylic aciduria were detected. He quickly developed severe hypotonia with a brady-apneic syndrome, which led to his death on the second day of life. CPT 2 activity measured on cultured fibroblasts was only 0.6 nmol/min/mg (2.08 ± 0.41). He was homozygous for the c.680C > T p.

(Pro227Leu) variant [12].

4. Discussion

4.1. Impact of NBS on neurological outcome

NBS of FAO disorders was gradually introduced in Southern Belgium between 1999 and 2007. The aim of the screening program was to provide an early management of patients with FAO disorders, in order to avoid metabolic crises, irreversible neurological impairment, and death [3]. In our study, 44% of MCAD patients diagnosed on clinical manifestations had an intellectual deficiency and epilepsy, 33% had attention deficit disorders, language disorders and behavioral disorders, and 11% showed muscle weakness and motor dysfunction. Conversely, none of the 31 patients diagnosed by NBS had a metabolic crisis. Only 3.2% of the screened patients suffered from an intellectual deficiency and behavioral disorders, and 6.5% had attention deficit disorders. In addition, no missed cases of FAO disorders where reported after implementing of NBS, with exception of the patients with CPT2 deficiency. This highlights the drastic impact of NBS on the neurological outcome of patients with MCAD deficiency and goes hand in hand with several other studies [5,6,11]. The counterpart of an effective screening program is that NBS has been shown to result in the diagnosis of more patients, increasing the incidence of FAO disorders. Initially, the incidence of MCAD deficiency was 1/30.000 and 16–26% of the children died during a metabolic crisis [4]. Following the implementation of NBS, the incidence of MCAD deficiency increased and is estimated at 1/16.000 in Southern Belgium, according to the cumulated data from the NBS centers until 2022. The global incidence in Northern European populations is estimated at 1/15.000, with patients with milder phenotypes and a broader spectrum of genotypes [5,11]. Although early diagnosis is lifesaving for severe phenotypes, it is debated for milder phenotypes. Those patients have been identified through NBS after a slight increase of specific markers, leading to significant parental stress and many emergency room visits. This observation is also seen for the myopathic forms of VLCAD and CPT 2 deficiencies. These patients might experience episodes of rhabdomyolysis during important physical activity or episodes of increased metabolism, despite a well-controlled diet and medical treatment, thus highlighting the limits of a preventive treatment on metabolic decompensations [11,16]. There may be some possible limitations in our study as this is a retrospective study. Nevertheless, we believe that early diagnosis helps to raise awareness and educate patients and their families, resulting in proper management and interventions in emergency care units.

4.2. Newborn screening of patients with CPT 2 deficiency

CPT 2 deficiency is not currently part of the NBS program in Belgium. In addition, the four patients with CPT 2 deficiency were diagnosed following clinical presentation. The patient with the infantile form and the patient with the lethal neonatal form presented a metabolic decompensation in the first days of life, making newborn screening impossible. One patient with the late-onset form of CPT2 deficiency had a normal newborn screening and the other patient with the late-onset form was born before implementing of newborn screening in Belgium. This is consistent with the observations of de Sain-van der Velden et al., 2013, postulating that CPT2 deficiency can be missed in dried blood samples [17]. Although NBS of the adult benign form remains difficult, implementing new NBS ratios such as (C16 + 18:1)/C2 and C14/C3, as suggested by Tajima et al., 2019, could increase the sensitivity of NBS and prevent life-threatening events by allowing a quicker and more efficient management of metabolic crises in patients with the severe infantile form of CPT 2 [18].

5. Conclusion

FAO disorders are inherited metabolic diseases whose neurological outcome has significantly improved following their inclusions in the NBS program in Southern Belgium. The importance and impact of NBS has been shown to be effective in limiting most of the medium- and long-term complications of these diseases through an appropriate diet and medical treatment. Early management of acute metabolic crises in situations of limited glucose supply, such as fever and exercise, remains the cornerstone for these diseases and requires quick hospitalizations, as well as substantial intravenous glucose infusion. Further investigations are needed to better understand the physiopathology of long-term complications in order to improve the quality of life of patients and to ensure optimal management.

Statements and declarations

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Declarations of competing interest

None.

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