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Original Article

Inborn errors of metabolism in a neonatology unit: Impact and long-term results

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Abstract ***Background***: Inborn errors of metabolism (IEM) have greater repercussions in neonatology units. The goal of our study was to evaluate the impact of IEM in a neonatology unit and the outcome of these neonates.
Methods: All patients with IEM admitted in our unit were evaluated during an 8-year period for specific diagnosis, clinical features, therapy and long-term neurodevelopment.
Results: The study group was comprised of 31 infants, 18 of which required admission to the neonatal intensive care unit (NICU) (1.63% of income) due to severe symptoms. Twenty-two of the 31 had an earlier diagnosis and treatment due to expanded newborn screening, made from the third day of life. The most frequent diagnosis in the NICU, representing 66.66% (12/18), was diseases that cause an endogenous intoxication. Despite the diagnosis by tandem mass spectrometry, many of these patients had severe clinical symptoms prior to the screening results. Aggressive support was often necessary (extracorporeal removal therapy, mechanical ventilation). Death occurred generally in the first year of life (5/6). The death rate in the NICU was 10.3%. The survivors presented higher scores on the Psychomotor Development Index if the diagnosis of the disease was either made or helped by screening. This also depends on the type of disease.
Conclusion: Earlier diagnosis by expanded newborn screening and earlier treatment is essential in order to be able to prevent neurological sequelae.

Key words expanded newborn screening, inborn errors of metabolism, neonatal intensive care, neonates.

Introduction

Individually inborn errors of metabolism (IEM) are rare. However, collectively, they represent an important area as they are increasingly being described. Over 25% of metabolic diseases are present in the neonatal period, and making an early diagnosis and treatment is essential to reduce morbidity and mortality.[1–3]

Recent advances, such as expanded newborn screening (NBS) programs by tandem mass spectrometry (MS/MS),[4–7] have allowed for diagnosing and treating metabolic diseases even when patients are asymptomatic. Early symptoms occasionally require immediate action, even before making tests or waiting for screening results, and sometimes the diagnosis is only possible to make through the clinical symptoms and biochemical, enzymatic and/or molecular genetic tests. Staff with specific experience in metabolism and advanced neonatology intensive care are required to care for these neonates.

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As yet, there are hardly any studies published reflecting the impact of IEM in neonatology services and the assessment of the factors involved in its early diagnosis and therapeutic intervention.[8] We conducted a retrospective analysis of patients admitted to our Neonatology Service from July 2000 (when NBS by MS/MS was introduced) to December 2008, and compared the neonatal screening and clinical diagnosis, as well as studied the long-term development.

Patients and methods

Infants admitted with an IEM in the Neonatology Unit of Clinical Universitary Hospital of Santiago de Compostela, Spain, were studied for an 8-year period (from July 2000 to December 2008). During this period, an average of 411 patients each year were admitted in our Neonatal Service, 130 of which were admitted to the Neonatal Intensive Care Unit (NICU). Our hospital works as referral center for metabolic diseases in Galicia (north west Spain). We evaluated the neonates that were admitted because of clinical symptoms as well as those diagnosed by metabolic screening for whom hospitalization was recommended (according to our protocol) even when they have no symptoms.

In Galicia, the commencement of NBS by MS/MS was in July 2000, and blood samples and urine-impregnated filter paper were collected for metabolic screening between the 5th and the 8th day

of life until 2001. This recommendation changed in 2002 to start the collection on the third day of life after 48 h of milk intake, highlighting the importance of early diagnosis and prompt intervention.

We evaluated the age and year of admission, family history (if there was consanguinity or not), obstetric history (abortions or other children affected), reason for admission (clinical symptoms, newborn screening, or both), biochemical markers suggesting diagnosis, if admission was in the NICU, and if mechanical ventilation and/or dialysis techniques were needed. The data collected included the specific diagnosis as well as the long-term development.

Each diagnosis was classified in one of the four major groups of IEM: Group I, including aminoacidopathies that do not lead to an acute intoxication; Group II, including disorders by endogenous intoxication; Group III, IEM due to an abnormal energy production and utilization; and Group IV, covering other disorders, in our case IEM caused by transport defects, according to a previously described pathophysiological classification.[1]

We reassessed the Psychomotor Development Index (PDI) or Intellectual Quotient (IQ) of survivors using the Brunet Lézine Scale in infants, the McCarthy Scales of Psychomotor Skills (MSCA) in preschool children and the Wechler Intelligence Scale for Children Revised (WISC-R) in children older than 7 years. The overall index score of cognitive and/or developmental quotient is considered in the normal range when it is above 85. The statistical study was performed by analysis of variance (ANOVA) with the average PDI/IQ related to the diagnostic method (screening and/or symptoms). Informed consent of their parents was obtained for all the patients. The study was made with the approval of our hospital ethics committee.

Results

There were 3496 infants admitted during the study period and 31 (0.89% of admissions) were diagnosed with an IEM. The number of diagnosed patients requiring admission to the NICU was 18 (1.63% of 1105 admitted to the NICU). Table 1 reflects the characteristics of neonates with IEM that were referred at diagnosis, the need for dialysis and mechanical ventilation, and changes that occurred in the neonatal period.

In general, the family history of consanguinity was not frequent. Except in two patients, we did not find any siblings or other relatives with similar pathology. The frequency of previous spontaneous abortions was higher in organic acidurias (4/9, including maple syrup urine disease (MSUD)), in the other diseases there was just one abortion in 22 cases. The average age at admission was 12.23 ± 8.78 days, and in all cases except for those with phenylketonuria (PKU) and homocystinuria (HCY), admission to the NICU for a period of 8.11 ± 7.07 days was required.

The most frequent diagnosis, representing 41.93% of the diagnosed patients (13/31) was Group I, aminoacidopathies that do not lead to an acute intoxication. The diagnosis was made by screening all patients of this group, and all of them were completely asymptomatic at diagnosis and remain asymptomatic with dietary treatment and/or drug.

In group II (12/31), intermediary metabolism diseases that cause an endogenous intoxication pattern, elevation of tyrosine in the screening of two patients alerted us to the diagnosis of tyrosinemia (TYR I). Both had abnormal clotting, elevated transaminases, and one of te had renal tubular dysfunction.

Screening for early diagnosis allowed a more rapid action in the five newborns diagnosed with organic aciduria, the four with MSUD and the one with citrullinemia I (CIT I); most of them were at home at the moment of screening, although clinical symptoms were detected at admission. Many patients (5/10) needed extracorporeal removal therapy and 30% (3/10) required respiratory support with mechanical ventilation. The patient diagnosed with CIT I had an excellent response to treatment with benzoate + sodium phenylacetate IV and dialysis was not necessary, even though venous access had been obtained.

The four patients belonging to Group III (abnormal energy production or utilization) and two patients in Group IV (transport defects) were diagnosed after severe clinical symptoms and needing NICU admission. The patients with lactic acidosis (LA) were admitted because encephalopathic symptoms, ventricular bleeding and coma. The patient with multiple Acyl CoA dehydrogenases deficiency (MADD) had a clinical diagnosis of acidosis, cardiomiopathy and coma. The reason for presentation of the patient with hemochromatosis (HE) was a hepatic failure and of the patient with Glut-1 deficit it was convulsions. The results of NBS in all these patients were normal. All of te except for one presented with respiratory failure, and support with mechanical ventilation was provided.

Veno-venous continuous eodiafiltration was performed as a dialysis technique in organic acidurias (except for with pyroglutamic aciduria (PGA), in which the patient received exchange transfusion), and maintained for an average time of 17 h (range 10–36 h). Peritoneal dialysis was performed in the two MSUD patients over a period of 24 h.

Two of the patients with IEM progressed badly, resulting in death a few days after admission (3 and 4 days) due to multiorgan failure and severe ventricular bleeding, respectively. They represent 11.11% (2/18) of admissions in the NICU. General neonatal mortality in our hospital NICU was 5.25% during that period. Another four patients died, as reflected in Table 2, after 60 days, 62 days, 4 months and $1^1/_2$ years due to acute metabolic decompensation in relation to sepsis. The PDI/IQ (Table 3) is above 85 in 84% of survivors (21/25). The four patients with values less than 85 already had symptoms at diagnosis. The average PDI/IQ was 106.84 ± 12.95 if the initial diagnosis was made by screening ($n = 13$); 73.6 ± 22.73 if it was made with clinical findings ($n = 5$) and 93.85 ± 12.87 ($n = 7$) if screening and clinical diagnosis was made. The differences were significant ($P < 0.002$), but also depending on the type of disease.

Discussion

The incidence of IEM in our NICU was 1.63% during the studied period, lower than the 2.2% reported by Jouvet *et al*.[8] in ICUs (pediatric and neonatal). We hypothesize that this finding is

Table 1 Characteristics of neonates admitted in the neonatology service for the suspicion of inborn errors of metabolism (IEM) for an 8-year period

Disease	Patients (*n*)	Consanguinity family history (*n*)	Obstetric history [Previous abortions (*n*)]	Reason for admission (NBS/CS)	Age at admission (days, mean [range])	Biochemical markers (mean [range])	NICU stay (days per patient)	Mechanical ventilation (*n*)	ECRT (*n*)	Early death (*n*)
Aminoacidopathies without acute intoxication										
PKU	12	0	1	NBS	10,7 [8–15]	Phe: 1382 µmol/L [624–2060]	0	0	0	0
HCY	1	0	0	NBS	27	Met: 1086 µmol/L tHcy: 148 µmol/L	0	0	0	0
Endogenous intoxication										
TYR I	2	0	0	NBS + CS	24,4 [19–30]	Tyr: 677, 543 µmol/L APTT 85 s; Phosphorus 2.8 mg/dL	2, 2	0	0	0
MSUD	4	1	1	NBS + CS (3); CS (1)	12 [7–19]	Leu:1608 µmol/L [263–2347] Ileu: 343 µmol/L [99.1–511]	14, 4, 10, 8	1	2	0
PGA	1	0	0	CS	1	Hb:7,9g/dL; pH:7.05 Bicarbonate 11mmol/L	3	0	1	0
PA	2	0	1	NBS + CS	9 [8–10]	NH3: 700 µmol/L APTT 66s	5, 7	1	1	1
MMA	1	0	1	NBS + CS	4	NH3: 868 µmol/L; coagulopathy	4	1	1	0
MVA	1	0	1	CS	30	Urine mevalonic acid: 11600 mmol/mol crea.	10	0	0	0
CIT I	1	1	0	NBS + CS	9	Cit: 2400 µmol/L; Gln: 2800 µmol/L; NH3: 680 µmol/L	15	1	0	0
Abnormal energy production or utilization										
LA	3	0	0	CS	19,3 [0–30]	Lactate: 20 mmol/L	4, 9, 3	2	0	1
MADD	1	0	0	CS	13	pH 6.75; Bicarbonate: 6 mmol/L	15	1	0	0
Transport defects										
HE	1	0	0	CS	1	Ferritin 7978 mg/mL Iron 239 mg/dL	5	1	0	1
Glut-1	1	0	0	CS	30	Glycorrhachia/ Glycemia <0.2	8	0	0	0

CIT I, type I citrullinemia; CS, clinical symptoms; ECRT, extracorporeal removal therapy; Glut-1, Glut-1 deficit; HCY, homocystinuria (CßS def.); HE, hemochromatosis; LA, congenital lactic acidosis; MADD, multiple acil-CoA dehydrogenase deficiency; MMA, methylmalonic acidemia; MSUD, maple syrup urine disease; MVA, mevalonic aciduria; NBS, newborn screening; PA, propionic acidemia; PGA, piroglutamic aciduria; PKU, phenylketonuria; TYR I, type 1 tyrosinemia.

Table 2 Age and cause of death in patients admitted for suspected IEM during the study period

Disease	Patients (*n*)	Age at death	Cause of death
Endogenous intoxication			
PA	2	18 m; 4 m	Cardiogenic shock; septic shock
MMA	1	2 m	Sepsis with multiorganic failure
Abnormal energy production or utilization			
LA	2	4 d; 2 m	Massive intracranial eorrhage; refractory metabolic acidosis
Transport defects			
HE	1	6 d	Fulminant hepatic failure

d, days; m, months.

probably related to the NBS on the 3rd day of life, which has been performed in Galicia since 2002. This early screening could allow for early diagnosis and treatment of a group of patients in an asymptomatic period, who otherwise would have needed admission. At the same period of time, many patients were diagnosed without clinical symptoms using the NBS. They were treated, no admission was needed and they were ambulatory controlled: two classical galactosemia, one defect of the long-chain 3-hydroxyacyl-coenzyme A dehydrogenase, one methylmalonic aciduria mut0, and one argininosuccinic aciduria. Also, we have other patients diagnosed by NBS who probably could have developed later clinical symptoms (medium-chain acyl-coenzyme A dehydrogenase deficiency, glutaric aciduria type I, . . .).

The IEM more frequently diagnosed were aminoacidopathies and organic acidurias, as expected and consistent with the literature.[9–11] The NBS contributed to a faster diagnosis in all cases except for three. One of these patients had MSUD, which was diagnosed prior to 2002, and was admitted at 7 days old without any screening sample. The other patients were affected with PGA and mevalonic aciduria (MVA), who were admitted with severe symptoms at 24 h and 30 days of life, respectively. Despite this prompt diagnosis, patients with classic organic aciduria, MSUD and CIT I displayed clinical signs prior to the screening results. This evidence supports the performance of a sample for extended tandem mass spectrometry screening 24 h after starting feeding, as suggested by some authors.[4,12]

It is assumed that elevation of tyrosine is not a good biochemical marker for the detection of TYR I because of the high incidence of transient neonatal tyrosinemia (ranging from 0.2 to 10% of newborns). Two patient with TYR I were receiving a diet of moderate protein restriction and ascorbic acid supplements, but

Table 3 Index score of psychomotor development index (PDI) or intellectual quotient (IQ) in survivors

Patient	Diagnosis	Reason for admission (NBS/CS)	Age at evaluation (years)	PDI/IQ (%)
1	Classic PKU	NBS	7	113
2	Classic PKU	NBS	7	127
3	Classic PKU	NBS	7	91
4	Classic PKU	NBS	5	110
5	Classic PKU	NBS	8	119
6	Classic PKU	NBS	5	86
7	Classic PKU	NBS	0.5	94
8	Classic PKU	NBS	0.5	101
9	Classic PKU	NBS	8	115
10	Classic PKU	NBS	3	126
11	Classic PKU	NBS	2	107
12	Mild PKU	NBS	3	100
13	HCY	NBS	4	100
14	TYR I	NBS + CS	6	88
15	TYR I	NBS + CS	6	80
16	MSUD, classic form	NBS + CS	4	94
17	MSUD, intermediate form	NBS + CS	1	105
18	MSUD, intermediate form	NBS + CS	7	117
19	MSUD, classic form	CS	6	87
20	PGA	CS	4	52
21	MVA	CS	0.5	48
22	CIT I	NBS + CS	0.5	86
23	LA	CS	0.5	88
24	MADD	CS	2	100
25	Glut-1	CS	2	80

CIT I, type I citrullinemia; CS, clinical symptoms; Glut-1, Glut-1 deficit; HCY, homocystinuria (CßS def.); LA, congenital lactic acidosis; MADD, multiple acil-CoA dehydrogenase deficiency; MSUD, maple syrup urine disease; MVA, mevalonic aciduria; NBS, newborn screening; PGA, piroglutamic aciduria; PKU, phenylketonuria; TYR I, type 1 tyrosinemia.

they both had coagulation disorders and one had renal tubular dysfunction at admission. In addition, we had a false negative for TYR I despite having the cut-off of tyrosine at 220 μmol/L. In Galicia, the urine succinilacetona screening was added to the tyrosine determination for diagnosis of TYR I in 2008.[13]

The clinical presentation as well as biochemical alterations were very important for diagnosis in all patients with energy deficit and transport defects (they presented with neurological, cardiac and hepatic symptoms depending on the type and respiratory failure in 66.6%). The screening of acylcarnitines was very useful in a patient diagnosed with MADD. This screening alerted us to a possible defect in the β-oxidation of fatty acids, although further studies were conducted to make the MADD diagnosis (acylcarnitines produced from the oxidation of palmitate deuteric (16^{-2} H_{3-} palmitate) in cultured fibroblasts).

Treatment of our patients frequently included extracorporeal removal therapy, especially if they had endogenous intoxication (50%). This finding is similar to other series published (30% or more).[8,14,15] The most frequent technique used was veno-venous eodiafiltration, which has proved efficacy.

These therapies could be avoided in some cases by using drugs. This becomes even more important when technical and methodological limitations to perform effective dialysis in the neonate delays the start of treatment. We reported one hyperammonemic patient with severe CIT I who responded well to treatment with intravenous phenylacetate and benzoate, and did not require more aggressive measures. Another patient that we followed for Propionic Aciduria had an episode of metabolic decompensation with hyperammonemia, and responded to *N*-carbamoylglutamate.

Death occurred generally in the first year of life (5/6), two of te in first days of life. All of te were initially admitted to the NICU, representing a 33.3% (6/18) rate of mortality in this group (initial NICU admission and IEM). This figure is similar to other published numbers for patients with these circumstances.[8,16]

We frequently observed a good neurological outcome between survivors, especially if the diagnosis was made, or helped by NBS. The early diagnosis with proper and immediate action is vital for a good subsequent neurological outcome.[17–19]

We think it must be taken into consideration to perform expanded newborn screening 24 h after milk intake and this screening must be improved in some pathologies with new biochemical markers that increase the sensibility and specificity of the screening.

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