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## **What are the clues for an Inherited Metabolic Disorder in Reye syndrome ?**

### **A single centre study of 58 children**

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**Key words:** Reye Syndrome, Inherited Metabolic Disorder, Urea Cycle Disorders, Fatty-Acid Oxidation Disorders, ketogenesis defects, NBAS, deferasirox

**Short title:** Reye or Reye-like syndrome and Inherited Metabolic Disorders

**Abbreviations:** IMD: Inherited metabolic disorders ; CK: Creatinine kinase ; FAOD: Fatty-acid oxidation disorder ; PICU: Intensive care unit ; IQR: Interquartile range ; NGS: Next-generation sequencing ; PT: Prothrombine time ; UCD: Urea Cycle Disorder.

## **Abstract**

**Objectives.** Reye Syndrome is an acute encephalopathy with increased liver enzymes and blood ammonia, without jaundice. The prevalence of an underlying inherited metabolic disorder (IMD) is unclear, nor the clinical or biological factors directing toward this diagnosis. Our aims were to define these clues in a large series of patients.

**Patients and methods.** We retrospectively studied all patients with Reye admitted in our institution from 1995. We defined 3 groups: Group 1 with a confirmed IMD, Group 2 considered as free of IMD, Group 3 unclassified. Statistical analysis compared patients in Groups 1 and 2, to find criteria for a diagnosis of IMD.

**Results.** Fifty-eight children were included; 41 (71%) had a confirmed IMD, 12 (20%) were free of IMD, and 5 remained unclassified. IMDs included Urea Cycle Disorders (51%), Fatty-Acid Oxidation Disorders (24%), ketogenesis defects (5%), other mitochondrial energy metabolism defects (10%), NBAS mutation (7%), Glycosylation Disorders (2%). In Group 2, the trigger was a viral infection, or a drug, deferasirox in three children. Univariate analysis showed that onset before 2 years-old, recurrent Reye and the association with rhabdomyolysis were significantly associated with IMD. Blood ammonia was a poor discriminating marker. All children were admitted into the intensive care unit, 23% needed continuous venovenous hemodialysis and one died from brain oedema.

**Conclusion.** Metabolic tests should be performed early in all cases of Reye, regardless of triggers. As they can be inconclusive, we suggest to systematically go to Next-Generation Sequencing study. These children should be transferred early to a specialized unit.

## **1) Introduction**

Reye syndrome was first described in 1963 by the Austrian pathologist RD Reye, who described clinical and biological pattern including vomiting, consciousness disorder or convulsion, cytolysis and uniform pathological changes at autopsy especially cerebral swelling and a fatty infiltration of the liver. The Center for Disease Control and Prevention (CDCP) defined Reye syndrome in 1980 as "*i) an acute non-inflammatory encephalopathy that is documented clinically by a) an alteration in consciousness and, if available b) a record of cerebrospinal fluid containing 8 leukocytes/cu.mm or less, or a histologic specimen demonstrating cerebral oedema without perivascular or meningeal inflammation ; ii) an hepatopathy documented by either a) a liver biopsy or an autopsy considered to be diagnostic of Reye syndrome or b) a threefold or greater increase in the levels of the serum glutamic-oxaloacetic transaminase, serum glutamic-pyruvic transaminase or serum ammonia, iii) and no more reasonable explanation for the cerebral and hepatic abnormalities.*" (1,2). Liver biopsy, when done, revealed reversible fatty acid infiltration and mitochondriopathy (3,4). However, liver biopsy is rarely performed because of coagulation disorders, or is eventually inconclusive when performed later; the syndrome is then called "Reye-like" (5). In this article we will use "Reye" for Reye and Reye-Like syndromes.

"Reye" is rare, and occurs mostly in children, with few adult cases (6,7). The first symptoms develop 3-5 days after a catabolic event (mainly viral), with vomiting and encephalopathy or seizures, up to coma. Biology shows elevated ammonia, liver dysfunction (increased transaminases, clotting disorders, but normal bilirubin), hypoglycemia and metabolic acidosis. The outcome may be death or neurological sequelae (8).

"Reye" was frequently reported during 70's, and its association with aspirin and anti-emetic treatments has led learned societies to reduce the indication for these treatments allowing a decrease in reported cases (5). Initially considered as a disease, it should be rather considered as a syndrome resulting from unusual response to a catabolic trigger that may be favored by some virus, or drugs. Over the past 20 years it became obvious that "Reye" was also strongly associated with IMD (8–11). The main purpose of our study was to identify the clinical, biochemical or imaging characteristics hinting at an IMD in a large group of children hospitalized for "Reye".

## **2) Patients and Methods**

This was a retrospective study of children with a diagnosis of "Reye" followed up in Necker-Enfants malades Hospital. Data were collected from our in-house database *Dr*

*Warehouse* from which key words (here “Reye”) are extracted from patient’s records, from all the computer files of the different units of the hospital (ethics approval by the IRB CPP Ile-de-France) (12). Each folder extracted was retrospectively reassessed to confirm “Reye”’s diagnosis, defined as a liver disorder, increased transaminases (at least threefold) or decreased clotting factors (prothrombin time (PT) or Factor V less than 60% of normal), without increased bilirubin (less than 50  $\mu$ M), together with increased blood ammonia (more than 70  $\mu$ M) and encephalopathy (hypotonia, drowsiness, ataxia, coma). Children not meeting these criteria were excluded from the study. For all included children, characteristics reported in the study are those of the inaugural “Reye” episode. The investigations were performed in our reference center, and several affiliated laboratories.

We recorded:

- consanguinity, gestational age, birth parameters, psychomotor development, presence of previous “red flags”: hypoglycemia, increased transaminases, neurological symptoms...
- age at first “Reye” and number of “Reye” episodes,
- possible triggers: infection, drug, surgery, fasting, prolonged exercise...,
- clinical characteristics: vomiting, fever, drowsiness, seizures, hepatomegaly,
- biology: increased transaminases, coagulation disorders, ammonia, hypoglycemia (< 0.5 g/L), hyperlactatemia (> 2 mM), acidosis (pH < 7.3), rhabdomyolysis (Creatine kinase (CK) > 600 IU), acute renal failure,
- when available: lumbar puncture, brain imaging, liver ultrasound, liver biopsy, heart ultrasound,
- metabolic data: metabolic screening (plasma amino acids and acylcarnitine profile, urinary organic acids), gene sequencing or metabolic or mitochondrial Next-Generation Sequencing (NGS),
- management: need and duration of Pediatric Intensive Care Unit (PICU), ventilation, haemodynamic support, use of ammonia scavengers, continuous venovenous hemodialysis
- the genetically confirmed diagnosis of IMD (classically specific gene sequencing oriented by biochemical data, more recently metabolic and/or mitochondrial Next-Generation Sequencing (NGS)),
- evolution: psycho-motor delay, epilepsy, need for special education, death.

For analysis, patients were divided into 3 groups: Group 1, children with a genetically confirmed IMD; group 2, children for whom an IMD was unlikely based on clinical characteristics, a normal metabolic workup, and a negative genetic investigation when

performed; group 3, children in whom an IMD was strongly suspected but without genetic confirmation or lost to follow-up.

Main characteristics are reported as percentages for categorical variables, and median (interquartile range [IQR]) for quantitative variables. We assessed the association between these characteristics and an underlying IMD by comparing Group 1 and 2 with Fisher's exact test for categorical variables, and Student's t-test or logistic regression for quantitative variables. We also assessed sensitivity (Se), specificity (Spe) and positive and negative likelihood ratios (LR+/LR-) for variables of interest. A two-sided p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the open-source software R release v3.6.1 (<http://www.R-project.org>).

### 3) **Results**

Queries to *Dr Warehouse* extracted the records of 85 patients between 1995 and 2020, among whom we excluded 17 because of selection mistakes, and 10 who did not fulfill the "Reye" definition. Fifty-eight children (34 of them girls) were finally included. Their clinical and biochemical characteristics are summarized in Table 1. The majority, 41 patients (71%), belonged to group 1, 12 to group 2 and 5 to group 3.

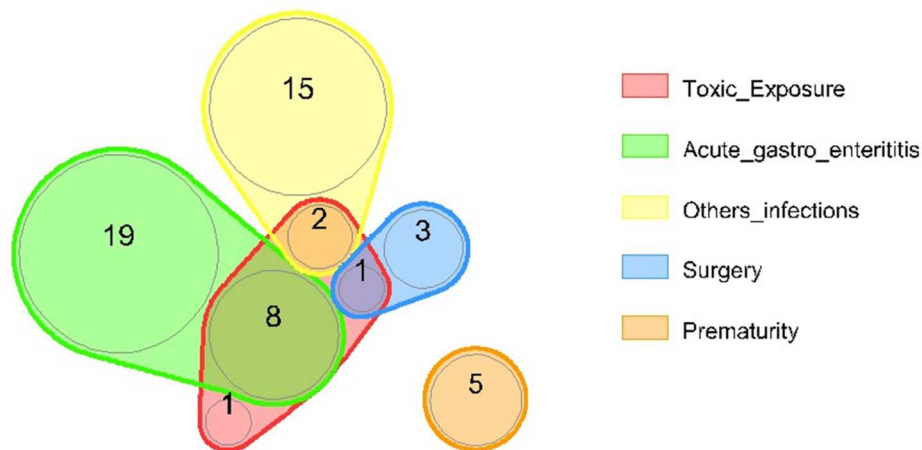
#### ***3.1 General characteristics***

Consanguinity was reported in 21% of the children. In most patients, pregnancy, birth and birth parameters were normal. A previous unexplained moderate psycho-motor delay was reported in 14% (P42 with severe epileptic encephalopathy, P50 with prematurity sequelae and P51 who had spinal muscular atrophy also presented psycho-motor delay but are not considered as unexplained). For 36%, symptoms such as unexplained increased transaminases, hypoglycemia, drowsiness during infection or after a vaccination, had been previously reported.

The first "Reye" event occurred at the median age of 12 months (IQR 7-24 months), in the first week of life for 9%, and before the age of 2 years for 84% of children. It happened after 5 years of age in 11% only. More than one "Reye" event was reported in 38%.

Six patients had a chronic disorder: Sickle Cell Anemia (Patients P47, P48, P49), spinal muscular atrophy (P51), severe neurological sequelae of prematurity (P50) and epileptic encephalopathy (P42).

A trigger before the onset of “Reye” was found in all children whatever the final diagnosis: 9% birth (catabolic event) ; 47% gastro-enteritis ; 31% another viral infection or fever ; 22% a drug, all known to be hepatotoxic (13–15) (aspirin, domperidone, metopimazine, metoclopramide, association of domperidone and metopimazine, deferasirox); 4% head trauma ; 4% surgery (scoliosis, adenoïdectomy). In 18% more than one trigger was reported (Figure 1).



**Figure 1.** Triggers preceding “Reye”.

Distribution of triggers preceding “Reye” among the 58 children: 27 acute gastro-enteritis (green), 17 other infections (yellow), 12 drug exposure (red), 4 surgery (brain trauma/scheduled surgery (blue), 5 birth (orange). 19% (11/58) of the children had associations with multiple triggers.

Among children in whom only 1 trigger was noticed, 88% (30/42) had an underlying IMD.

### 3.2 Clinical data and explorations

Neurological symptoms were systematically reported during the acute phase, sometimes with imprecision due to the retrospective approach of the study. Reported terms were hypotonia (9%), confusion (15%), drowsiness (30%) or coma (50%). Seizures were reported in 37% of the cases, vomiting in 81% and hepatomegaly was found in 67%.

The transaminases were increased in all patients, with a median of 18 times the normal value (IQR 6-77), with a predominance of AST for 88%. Most children had liver failure (98%), with a median PT of 34 % (IQR 16%-42%). Bilirubin was less than twice the normal range in all cases. All children had elevated blood ammonia with a median of 196  $\mu$ M (IQR 143-272). Lactates were increased in 88% of patients (median 4 mM (IQR 2.5-9.8), 56% had acidosis, 56% hypoglycemia. Rhabdomyolysis was found in 48% (CK median value 1324 IU, IQR 191-4072), and renal failure in 28%.

Liver ultrasound was performed on 31 children and showed hepatomegaly in 45% and hyperechogenicity (HE) compatible with steatosis in 52%. A follow-up ultrasound was

available in 11 patients, a few weeks after the acute episode: in 6 it was completely normal, in 5 there were mild transient abnormalities (hyperechogenicity, heterogeneity, hepatomegaly...).

In 3 patients only (P37, P43, P44), a liver biopsy was performed 4 to 8 days after the onset of symptoms. It showed inflammatory infiltrates (lymphocytic or polymorphic), clarified or ballooned hepatocytes and fibrosis in 2, and no necrosis. Steatosis was seen in 2 patients (micro-vesicular steatosis in 5% of hepatocytes, and extensive macro and micro-vesicular steatosis in 70% of hepatocytes).

Cerebro-spinal fluid (CSF) analysis was performed in 10 patients and was normal. Fifteen children underwent a brain CT during the acute phase, of whom only 2 had cerebral oedema. Thirty-two patients underwent Magnetic Resonance Imaging (MRI), 16 of whom had non-specific white matter signal abnormalities, one an increased lactate peak on spectroscopy.

Nearly all patients were admitted to PICU (median 6 days, IQR 3.5-10). Ventilation support was necessary for 46% (median 3.5 days, IQR 1.3- 7.3), and noradrenaline in 5 (median 3.5 days, IQR 2-5.5). Most patients were treated with ammonium scavengers and 23% needed continuous venovenous hemodialysis.

For 60% of children, the first line metabolic screening was consistent with IMD. In 9 children with a final diagnosis of IMD, the results were non-specific, but the samples were collected late. Genetic explorations confirmed the diagnosis of IMD in 71% of our 58 children (specific gene sequencing for 31 patients, metabolic NGS for 9 and mitochondrial NGS for 1).

### ***3.3 Outcome***

P53 died of brain oedema. In all other patients, blood ammonia and liver tests normalized within 2 weeks. Neurological sequelae were observed in 44% of the children, with a cognitive disability. However, 32% of them had previous neurodevelopmental symptoms. Five children developed epilepsy. Five patients needed special education, and 26% attended a specialized institution for children with severe psychomotor delay.

### ***3.4 Classification of patients according to clinical, biochemical and molecular results***

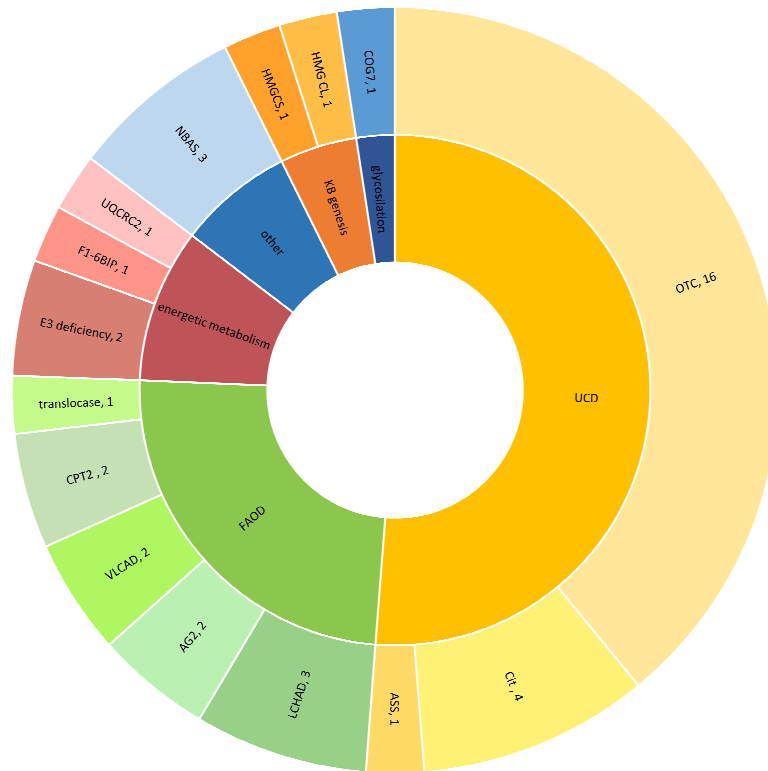
Group 1 included 41 children with genetically confirmed IMD. For 33 of them, IMD was diagnosed following the first Reye event and after two or more episodes for 8 patients (P13, 34, 36, 37, 38, 39, 40,41). Twenty-eight per cent of children were born from consanguineous union, and 51% had multiple Reye episodes (it should be noted that 18 children had repeated “Reye” despite the diagnosis of IMD and appropriate treatment, triggered by viral infection) (Supplementary data 1). Among the IMD diagnosed, we found (Figure 2):



- Urea Cycle Disorders (UCD) in 51%: Ornithine Transcarbamylase deficiency (OTC, n=16), Citrullinemia (Cit, n=4), Argininosuccinate Synthase deficiency (ASS, n=1),
- Fatty Acid Oxidation Disorders (FAOD) in 24%: Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD, n=3), Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD, n=2), Carnitine Palmitoyltransferase II (CPT2 n=2), Glutaric Aciduria type 2 (MADD, n=2), Translocase deficiency (n=1),
- ketogenesis defect in 5%: HMG-CoA lyase deficiency (HMGCL n=1), HMG CoA synthase deficiency (HMGCS n=1),
- other energetic metabolism defects in 10%: Fructose 1-6 bi-Phosphatase deficiency (F1-6bP, n=1), Dihydrolipoamide Dehydrogenase deficiency (E3, n=2) and biallelic *UQCRC2* pathogenic variants with mitochondrial complex III deficiency (n=1),
- biallelic *NBAS* pathogenic variants involved in infantile acute liver failure syndrome related to fever in 3 children,
- biallelic *COG7* pathogenic variants responsible for a rare Congenital Disorder of Glycosylation in one child.

**Figure 2.** Graphic representation of IMD diagnosed for the children in Group 1 (n=41)

■ UCD ■ FAOD ■ KB genesis ■ energetic metabolism ■ glycosilation ■ other



Group 2 included 12 children (Supplementary data 2). None had consanguineous background or recurrent event with a follow-up of 4 to 21 years.

“Reye” occurred after infection in 4 cases: varicella (P42, not genetically investigated, follow-up of 21 years), adenovirus, metapneumovirus and sepsis from unknown agent (P43, P44, P53, respectively; all had normal metabolic NGS). A drug in the context of catabolism (infection, surgery, trauma) was implicated in 5 cases: aspirin (P45, not genetically explored, follow-up of 11 years), association of two anti-vomiting drugs with overdose (P46, not genetically explored, follow-up of 11 years), deferasirox (P47, P48, P49, one with overdose, all had normal metabolic NGS). In 2 patients, “Reye” occur after a severe brain injury with intracranial bleeding, or scoliosis surgery in context of spinal muscular atrophy, both needed general anesthesia. None of them were genetically investigated but they never had recurrence with a follow-up of 6 and 7 years. “Reye” remained unexplained in P50, who had a severe epileptic encephalopathy related to a prematurity (normal metabolic and mitochondrial NGS, follow-up of 7 years).

Group 3 included 5 patients for whom the diagnosis of IMD remained possible (Supplementary data 3). Two were lost to follow up (P54 and P55) after the first negative genetic testing. In P54, metabolic investigations hinted at UCD, however *OTC* and *CPS* gene sequencing showed no pathogenic variant. P55 presented “Reye” after a brain injury and aspirin, first line tests suggested FAOD, but *CPTII*, *HADHA*, *HADHB*, and *HADHS* genes were normal. In 3 other patients, genetic explorations were still in progress at the last follow up: P56 from a consanguineous family, P57 with recurrent “Reye” and secondary myoclonic epilepsy with developmental delay, P58, a newborn with “Reye” and rhabdomyolysis.

### ***3.5 Statistical analysis*** (Table 1).

Univariate analysis showed that 3 characteristics were significantly associated with IMD: “Reye” before 2 years of age (88% in Group 1,  $p= 0.03$ ), recurrence of “Reye” ( $p= 0.01$ ), and rhabdomyolysis ( $p= 0.02$ ). “Reye” after the age of 5 years was associated with the absence of IMD ( $p= 0.012$ ). No difference was found in biological tests, and notably in blood ammonia. We also compared patients with UCD and FAOD or ketogenesis defects. Hypoglycaemia ( $p= 0.003$ ) and rhabdomyolysis ( $p= 0.04$ ) were strongly associated with FAOD or ketogenesis defects.

**Table 1.** Characteristics of the 58 children, of Group 1 and 2 and univariate analysis. (NS : Non significant)

	Total n= 58	Group 1 n=41	Group 2 n=12	Univariate analysis OR [IC95%] p value
Sex Ratio (male/female)	0.7 (24/34)	0.6 (15/26)	0.7 (5/7)	NS
Consanguinity	11/51 (22%)	10/36 (28%)	0/10	NS
Preexisting psycho-motor delay	10/42 (24%)	5/29 (17%)	1/10 (10%)	NS
Warning signs	13/36 (36%)	10/25 (40%)	0/8	NS
Age at onset in months (median, Q1; Q3)	12 (7;24)	12 (6;15)	24 (9;75)	<b>0.98 [0.96- 0.99] p = 0.03</b>
First week of life	5/56 (9%)	4/39 (10%)	0/12	NS
Before 2 years old	47/56 (84%)	36/39 (92%)	8/12 (67%)	<b>0.15 [0.28 - 1.12] p = 0.03</b>
After 5 years old	6/56 (11%)	1/39 (3%)	4/12 (33%)	<b>19.8 [1.16 - 1087] p =0.01</b>
>1 "Reye"	22/58 (38%)	21/41 (51%)	0/12	<b>0 [0 - 0.4] p = 0.01</b>
Triggers				NS
Birth	5/25 (9%)	4/38 (11%)	0/12	NS
Gastro-enteritis	26/55 (47%)	20/38 (53%)	3/12 (25%)	NS
Other infections	17/55 (31%)	12/38 (32%)	5/12 (41%)	NS
Drug	12/55 (22%)	6/38 (16%)	5/12 (42%)	NS
Surgery	2/55 (4%)	1/38	1/12	NS
Brain injury	2/55 (4%)	0/38	1/12	NS
"Reye" characteristics				
Vomiting	38/47 (81%)	27/33 (82%)	8/10 (80%)	NS
Fever	18/39 (46%)	14/27 (52%)	2/9 (22%)	NS
Seizure	16/43 (37%)	12/30 (40%)	3/10 (30%)	NS
Elevated transaminases	58/58 (100%)	41/41 (100%)	12/12 (100%)	NS
Acute liver failure	54/55 (98%)	38/38 (100%)	12/12 (100%)	NS
Hypoglycemia	23/41 (56%)	14/25 (56%)	5/12 (42%)	NS
Hepatomegaly	31/46 (67%)	23/32 (72%)	4/10 (40%)	NS
Blood ammonia (median in $\mu\text{mol/L}$ ; IQR)	196 (143-272)	197 (156-268)	178 (108-324)	NS
Rhabdomyolysis	13/27 (48%)	10/17 (59%)	0/6	<b>0 [0 - 0.86] p = 0.02</b>
Acidosis	15/27 (56%)	9/17 (53%)	5/7 (71%)	NS
Lactate > 2 mM	30/34 (88%)	20/23 (87%)	7/8 (88%)	NS
Acute renal failure	7/25 (28%)	2/16 (13%)	3/6 (50%)	NS
Explorations				
Ultrasound liver HE	18/33 (55%)	14/23 (61%)	3/7 (43%)	NS
White matter abnormality in MRI	16/32 (53%)	11/22 (50%)	1/4	NS
Lactate spike in spectroscopy	1/16	1/13	0/1	NS
Management				
PICU	23/24 (96%)	16/16 (100%)	6/7 (86%)	NS
Respiratory support	17/37 (46%)	9/24 (38%)	6/10 (60%)	NS
Hemodynamic support	5/37 (14%)	3/17 (18%)	2/7 (29%)	NS
Continuous venovenous hemodialysis	10/43 (23%)	5/29 (17%)	4/11 (36%)	NS
Prognosis				
Epilepsy	5/57 (9%)	2/41 (5%)	3/11 (27%)	NS
Psycho-motor delay	25/57 (44%)	19/41 (46%)	5/11 (45%)	NS
Adapted schooling	5/47 (11%)	4/36 (11%)	0/9	NS
Specialized establishment	12/47 (26%)	8/36 (22%)	4/9 (44%)	NS
Death	1/58	0/41	1/13	NS

ROC curves were graphically plotted, to assess the diagnostic performance and to define a threshold for blood ammonia and CK activity (supplementary data 5). ROC area for ammonia was 0.57, and no threshold could be defined. ROC area for CK was 0.8 and this defined a CK activity higher than 700 IU as suggestive of IMD, especially FAOD (Se 59%; Spe 100%).

We calculated sensitivity, specificity and positive and negative likelihood ratio (LR+/LR-) for some interesting variables (Table 2). Consanguinity, previous warning signs and

rhabdomyolysis showed a specificity of 100%. The variables with significant LR+ were consanguinity (6.2), warning signs (7.3), multiple “Reye” (13.3) and rhabdomyolysis (8.2).

**Table 2.** Sensitivity, Specificity, and Likelihood ratios defined for interesting variables [IC95%]

	Sensitivity	Specificity	Likelihood ratio +	Likelihood ratio -
Consanguinity	28% [14-45]	<b>100% [69-100]</b>	<b>6.2 [0.4-98]</b>	0.8 [0.6-1]
Preexisting psycho-motor delay	17% [6-36]	50% [19-81]	0.4 [0.1-1]	1.7 [0.9-3,1]
Warning signs	40% [21-61]	<b>100% [63-100]</b>	<b>7.3 [0,5-112]</b>	0.6 [0.4-0.9]
First week of life	10% [3-24]	<b>100% [73-100]</b>	2.9 [0.2-50.8]	0.9 [0.8-1]
Before or equal to 2 years old	<b>92% [79-98]</b>	36% [11-69]	1.5 [0.9-2.2]	0.2 [0.1-0.8]
After 5 years old	3% [0-14]	75% [43-94]	0.1 [0-0.9]	1.3 [0.9-1.8]
>1 “Reye”	51% [35-67]	<b>100% [73-100]</b>	<b>13.3 [0.9-205]</b>	0.5 [0.4-0.7]
Hypoglycemia	56% [34-76]	58% [28-85]	1.3 [0.6-2.9]	0.8 [0.4-1.5]
Rhabdomyolysis	59% [33-82]	<b>100% [54-100]</b>	<b>8.2 [0.6-121]</b>	0.5 [0.3-0.8]
Lactate > 2mM	<b>87% [66-97]</b>	12% [0,3-53]	1 [0.7-1.3]	1 [0.1-8.7]
Acute renal failure	13% [2-38]	50% [12-88]	0.3 [0.1-1.2]	1.8 [0,77-3,98]
Ultrasound liver HE	61% [38-80]	57% [18-90]	1.4 [0.6-3.6]	0.7 [0.3-1.6]
White matter abnormality in MRI	50% [28-72]	75% [19-99]	1.7 [0.4-6.8]	0.7 [0.4-1.4]

#### **4. Discussion**

From 1995, we admitted 58 children with “Reye” into Necker-Enfants malades, which means two to three new cases a year. “Reye” is therefore not so rare and we could confirm here that IMDs are the first cause of “Reye”, being found in 71% of our patients.

First associations between “Reye” and IMD were reported in the 80’s . Since then, retrospective studies showed that more than half of patients had an IMD (16). The larger proportion of our patients with IMD may be a referral bias to our specialized metabolic unit. Indeed, some children of this cohort were initially treated in elsewhere and addressed to Necker hospital as reference center for IMD, acute liver failure and liver transplantation. Like in the literature, UCD and FAOD were most frequent, OTC deficiency being diagnosed in more than a quarter of our patients (17,18). We found already reported defects, such as Fructose 1-6 Bi-Phosphatase deficiency (19), Ketone Bodies genesis disorders (20), mitochondrial complex III and E3 deficiencies (21–23). *NBAS* pathogenic variants have previously been found in recurrent acute liver failure or “Reye” (24). To our knowledge, ours is the first report of a glycosylation disorder in “Reye”. *COG7* pathogenic variants alter the Conserved Oligomeric Golgi

complexes necessary for protein glycosylation; only few cases are known, with growth failure, progressive and severe microcephaly, cardiac malformations, wrinkled skin and extreme hyperthermia episode with rapid demise (25,26).

We emphasize that recurrent “Reye”, “Reye” before the age of 2 years, and rhabdomyolysis were strongly associated with a diagnosis of IMD. Blood ammonia level was not a good discriminating marker. Hypoglycaemia was significantly associated with FAOD or ketogenesis defects due to their pathophysiology, but also with acute liver failure whatever the cause. A significant rhabdomyolysis, evidenced with CK levels, was strongly associated with FAOD or ketogenesis defects, although milder CK elevation could be observed after seizures or shock. IMD was also more often diagnosed in consanguineous families, when “Reye” occurred at birth, and when warning “red flags” signs were retrospectively found.

First line metabolic exploration including ammonia, CK, plasmatic amino acids and acylcarnitines, and urinary organic acids, should be systematically performed during the acute phase, as they may allow to initiate treatments and to orient specific genetic explorations. However, in this study, 9 of our patients with IMD had unspecific first line metabolic screening (1 F1-6bP, 2 OTC, 3 NBAS, 2 E3, 1 COG7), and were finally diagnosed by genetics explorations (NGS panels or exome). In Group 2, genetic investigations had not been systematically performed when “Reye” occurred without clinical or biochemical clues for an IMD and happened before the access of NGS. We retrospectively think that the patients in Group 2 have no genetic diseases as the “Reye” remained single with a long follow-up. However, we recommend to systematically extend exploration to genetic screening especially since NGS metabolic panel are more accessible.

A trigger was found before all episodes whatever the group, most frequently a virus (76%). Varicella and adenovirus had already been reported, but also influenza, rotavirus, parainfluenza, coxsackie, cytomegalovirus, herpes simplex (27,28),(8,29), and here for the first time, metapneumovirus.

The second, more frequent trigger was a drug. The link between salicylate and “Reye” is now unquestionable (30–34), as well as the responsibility of anti-vomiting drugs (10,35). Other drugs such as valproic acid (36,37), vigabatrin (38), chemotherapy (39) were not found here. But the occurrence of “Reye” in patients with sickle cell anemia treated with the oral iron chelator deferasirox was striking. It did not happen at the start of treatment but later on, after an infection. “Reye” was previously reported in 4 children on deferasirox for thalassemia; as in one of our patients, there were overdoses in two of them (40–43). Liver anoxia due to sinusoidal

sickling could be an additive factor in sickle cell anemia (44). Physicians caring for these patients should be warned about the risk and early symptoms of “Reye”, especially in the course of an infection or an accidental overdose.

We observed “Reye” after a head trauma and surgery, which has not been previously described. It might result from the combination of the catabolic stress and drugs, whether anesthetic or painkillers. However, in one case, we later diagnosed an IMD. Metabolic explorations should thus be comprehensive in all patients.

“Reye” should not be confused with fulminant hepatitis. The pathophysiology of the acute liver failure associated with “Reye” is a severe dysfunction of mitochondrial fatty acid oxidation, inducing the accumulation of non-esterified fatty acids in hepatocytes. The pathology shows steatosis, and not the extensive necrosis of toxic or infectious fulminant hepatitis (3,4). A liver biopsy is however rarely performed during the acute phase, and becomes barely informative after the first days, as steatosis is quickly reversible. It is thus important to highlight the main clinical difference, namely the absence of jaundice in “Reye”, as of the patient’s admission, to direct management and explorations. Liver transplantation is not a treatment for “Reye”. However, “Reye” is a potentially lethal disease, and patients should be admitted early into a paediatric intensive care unit experienced in the treatment of liver failure.

In this cohort conducted in France between 1995 and 2020, we observed an increase in “Reye” incidence: average 1.5/year between 1995 et 2006, 3.5/year between 2007 and 2020. This is probably not the reflect of a real increase in the incidence of “Reye” but the result of a better knowledge and awareness to this syndrome. Moreover, children with “Reye” syndrome were increasingly referred to our multi-specialty hospital (reference centers in IMD, liver diseases and liver transplantation). A multicenter study could allow to avoid this referral bias and to estimate more precisely the incidence of IMD in children with “Reye” syndrome.

None of the IMD diagnosed in this cohort was included in systematic neonatal screening in France during the period that goes from 1995 to 2020. Since January 2020, medium chain acyl-CoA dehydrogenase deficiency, known as possibly responsible of “Reye”, has been added in neonatal screening and seven others IMD will be screened in 2022. Expansion of newborn screening might reduce the incidence of “Reye” as inaugural presentation of these diseases, and the resulting neurologic sequelae.

In conclusion, “Reye” is not so rare, and is strongly associated with a diagnosis of IMD, even when a trigger is obvious. First line urgent metabolic testing includes, in blood : ammonia, CK, amino acids and acylcarnitines, and in urine : organic acids, but this may not be sufficient. We suggest systematically performing metabolic NGS investigations, including all genes known to be involved in “Reye”.

## **Acknowledgments**

The authors thank all the physicians and health professionals who cared for the patients.

## **Figures**

**Figure 1.** Triggers preceding “Reye”.

Distribution of triggers preceding “Reye” among the 58 children: 27 acute gastro-enteritis (green), 17 other infections (yellow), 12 drug exposure (red), 4 surgery (brain trauma/scheduled surgery (blue), 5 birth (orange). 19% (11/58) of the children had associations with multiple triggers.

Among children in whom only 1 trigger was noticed, 88% (30/42) had an underlying IMD.

**Figure 2.** Graphic representation of IMD diagnosed for children in Group 1(n=41)

## **Tables**

**Table 1.** Characteristics of the 58 children, of Groups 1 and 2, and univariate analysis.

**Table 2.** Sensitivity, Specificity, and Likelihood ratios for interesting variables.

## **Supplementary Datas**

**Supplementary data 1.** Characteristics of the children in Group 1

**Supplementary data 2.** Characteristics of the children in Group 2

**Supplementary data 3.** Characteristics of the children in Group 3

**Supplementary data 4.** ROC curve: diagnostic performance and optimal threshold of ammonia (A) and CK values (B) to suspect an IMD.

**A:** ROC area = 0.571, ammonia level is not a good discriminating parameter

**B:** ROC area = 0.799. A CK threshold of > 700 IU/L (Se 59% - Spe 100%) should guide the diagnosis towards an IMD



## **Supplementary datas**

Supplementary data 1. Characteristics of the children in Group 1

	Sex	consanguinity	age at first "Reye"	number of "Reye"	context	Elevated transaminases	lowest prothrombin time	higher ammoniaemia (µmol/L)	seizure	Hypoglycemia	lactate (mmol/L)	pH	AKF	CPK	HPM	liver ultrasound	brain MRI / SCAN	Heart Ultrasound	diagnosis	neurologic sequelae
Patient 1	F	0	13m	1	GEA	85N	low	170	1	-	-	-	-	-	-	-	-	-	OTC	PMD
Patient 2	F	0	1.5y	>3	-	high	low	370	-	-	-	-	-	-	1	HPM	MRI : WM anomaly	normal	OTC	PMD
Patient 3	M	0	2d	1	birth	3.7N	low	1000	1	1	6	7.29	1	-	1	HPM	MRI : SB and NGC anomaly, lactate spike	-	OTC	severe encephalopathy
Patient 4	F	1	5m	>1	GEA	high	low	196	-	-	-	-	-	-	1	HPM + HE	-	normal	OTC	PMD
Patient 5	F	-	9m	1	GEA	high	low	high	-	-	-	-	-	-	1	-	-	normal	OTC	0
Patient 6	F	0	2y	>1	-	high	low	high	-	-	-	-	-	-	-	normal	-	-	OTC	0
Patient 7	M	0	2y	1	fever + metoclopramide	10N	33%	200	-	0	2.45	-	-	-	0	HE	-	-	OTC	0
Patient 8	M	0	1y	1	GEA	high	low	150	-	-	-	-	-	-	-	HE	-	-	OTC	0
Patient 9	F	0	1y	2	fever	18N	19%	344	0	0	-	-	-	152	1	HPM	MRI : WM anomaly	-	OTC	PMD
Patient 10	F	0	7m	1	varicella	high	43%	198	1	0	high	-	-	-	1	HPM HE	MRI : WM anomaly	-	OTC	epilepsy
Patient 11	M	0	4d	1	birth	19N	20%	500	1	0	9.8	-	-	-	-	-	MRI : WM anomaly	normal	OTC	PMD
Patient 12	F	0	19m	>1	fever	high	low	280	0	-	-	-	-	-	1	-	-	-	OTC	0
Patient 13	F	0	13m	2	fever + aspirin	6N	20%	411	1	0	-	7.5	0	-	1	-	MRI : WM anomaly	-	OTC	PMD
Patient 14	F	0	13m	>3	GEA + aspirin	60N	37%	691	0	0	2.12	7.53	0	-	0	HPM HE	MRI and Scan : normal	-	OTC	0
Patient 15	M	-	2y	1	fever	high	low	217	1	-	high	-	0	0	1	HPM HE	-	-	OTC	PMD
Patient 16	F	0	3y	>1	GEA	5N	15%	139	0	1	2.3	7.39	0	-	0	-	-	-	OTC	0
Patient 17	M	0	1y	1	GEA + aspirin	50N	40%	220	1	-	-	-	-	-	-	-	-	-	Cit	compartmental disorder
Patient 18	F	1	1y	1	GEA	150N	8%	217	0	0	-	7.43	0	-	0	normal	Scan : normal	-	Cit	PMD
Patient 19	F	0	10m	>1	GEA	100N	low	high	0	-	-	-	-	-	-	HE	-	-	Cit	PMD
Patient 20	F	0	3y	3	GEA	high	54%	156	0	0	4.9	7.29	0	-	0	-	MRI : WM anomaly	-	Cit	0
Patient 21	M	0	15m	1	surgery	10N	low	264	0	-	1	7.4	0	-	1	-	Scan : normal	-	ASS	PMD
Patient 22	M	0	3d	1	birth	10N	24%	237	0	1	2.5	7.47	-	4523	-	normal	-	normal	CPT2	0
Patient 23	F	1	5m	>1	GEA	10N	low	high	1	1	0.8	-	0	2107	0	-	-	normal	CPT2	0
Patient 24	F	0	1y	2	pyelonephritis	9N	low	high	1	1	1.4	-	0	18 745	0	HE	-	normal	VLCAD	0
Patient 25	F	1	2d	1	birth	6N	low	125	0	1	10	acidosis	-	12792	1	-	-	normal	VLCAD	0
Patient 26	M	0	7m	1	fever	31N	35%	111	1	1	5	7.3	1	2718	1	-	Scan : normal	-	LCHAD	0
Patient 27	M	-	10m	1	GEA	high	low	160	1	1	2.1	7.29	-	27 000	1	HPM HE	MRI : WM anomaly	normal	LCHAD	PMD
Patient 28	F	0	4m	1	-	high	low	high	-	-	-	-	-	high	1	-	Scan : normal	normal	LCHAD	0
Patient 29	F	0	16y	1	GEA	1.5N	60%	177	0	1	3	7.1	0	2720	0	HE	-	normal	AG2	0
Patient 30	M	0	1y	1	GEA + domperidone	high	low	157	1	1	2.2	-	-	high	0	normal	MRI : WM anomaly	normal	AG2	left hemiparesis and PMD
Patient 31	M	-	1y	1	GEA	10N	74%	180	0	0	3.3	7.33	0	400 000	1	HPM	MRI : WM anomaly	normal	Translocase	0
Patient 32	M	1	1.2y	1	fever	high	42%	79	0	1	-	-	-	185	1	HPM	Scan : normal	normal	HMGCL	PMD
Patient 33	F	0	1y	2	GEA + metopimazine	10N	54%	71	0	1	3.4	7.25	0	209	1	normal	MRI and Scan normal	normal	HMGCS	0
Patient 34	M	1	-	>1	GEA	high	low	high	-	-	-	-	-	-	-	-	-	-	PDH-E3	0
Patient 35	M	1	-	>1	GEA	high	low	high	-	-	-	-	-	-	-	-	-	-	PDH E3	0
Patient 36	F	1	1.5y	2	GEA	55N	57%	210	0	1	13	6.97	-	85	1	HPM HE	-	normal	FI-6BIP	0
Patient 37	F	1	3m	5	GEA	high	35%	163	0	1	18	7.09	-	-	1	-	-	normal	UQCRC2	0
Patient 38	M	-	1y	>1	0	high	low	high	-	-	-	-	-	-	1	-	Scan : atrophic	normal	NBAS	severe encephalopathy
Patient 39	F	0	9m	4	fever	295N	9%	380	0	0	4.2	-	0	0	1	HPM	-	normal	NBAS	PMD
Patient 40	F	0	4m	>1	fever	50N	17%	109	0	0	2.7	7.45	0	0	1	HPM HE	Scan : C1-C2 anomaly	-	NBAS	0
Patient 41	F	1	2m	8	fever	high	low	186	-	-	-	-	-	-	1	-	-	normal	COG7	PMD

**Supplementary data 2.** Characteristics of the children in Group 2

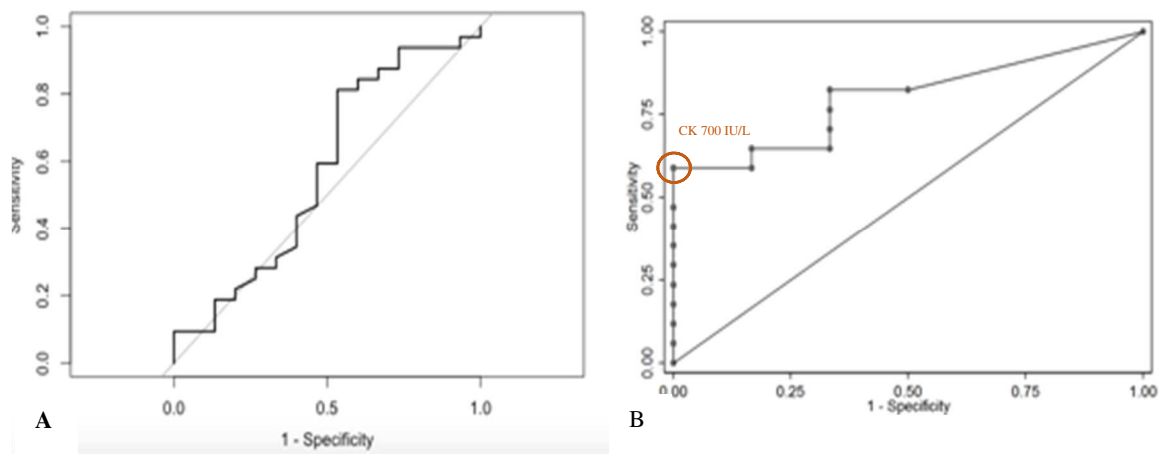
	sex	consanguinity	age at first "Reye"	number of "Reye"	preexisting diagnosis	context	Elevated transaminases	lowest prothrombin time	Highest ammonemia (μmol/L)	seizure	hypoglycemia	lactate (mmol/L)	pH	AKF	CPK	HPM	hepatic ultrasound	cerebral imaging	Heart ultrasound	Metabolic panel	Mitochondrial panel	neurologic sequelae
Patient 42	M	0	2y	1	epileptic encephalopathy	varicella	high	-	high	1	0	15	acidosis	1	-	-	-	Scan : atrophy	-	-	-	PMD
Patient 43	M	0	2y	1	0	adenovirus infection	150N	13%	80	0	1	-	-	-	-	1	HPM + HE	-	normal	neg	-	0
Patient 44	F	0	9m	1	0	metapneumovirus infection	323N	18%	132	0	0	2,5	7,46	-	0	0	normal	-	normal	neg	-	0
Patient 45	F	0	6m	1	growth delay	GEA + aspirin	5N	48%	84	1	1	3,97	-	-	-	-	-	-	normal	-	-	PMD
Patient 46	F	0	9m	1	0	GEA + domperidon + metopimazine	17N	34%	426	-	0	10,6	acidosis	0	-	0	HPM + HE	MRI : cortical lesions	normal	-	-	encephalopathy
Patient 47	M	0	12y	1	sickle cell anemia	GEA + deferasirox	4N	11%	240	-	0	11	-	0	38	0	-	Scan : normal	-	neg	-	0
Patient 48	F	-	5y	1	sickle cell anemia	deferasirox	58N	14%	416	0	1	-	acidosis	1	-	1	-	Scan : normal	normal	neg	-	0
Patient 49	M	0	11y	1	sickle cell anemia	GEA + deferasirox	3,5N	16%	280	0	0	4,5	7,23	1	-	0	normal	MRI and Scan normal	normal	neg	-	0
Patient 50	M	0	7m	1	severe prematurity	fever	50N	35%	75	1	1	1,9	7,42	0	-	0	HPM + HE	Scan : atrophy	-	neg	neg	epilepsy
Patient 51	F	-	10y	1	SMA	surgery	170N	-	148	0	0	-	-	-	0	0	normal	-	-	-	-	0
Patient 52	F	0	2y	1	0	brain injury	600N	15%	368	0	1	5	-	-	208	1	normal	Scan : subdural hematoma	-	-	-	PMD
Patient 53	F	0	6m	1	0	infection	high	-	178	0	0	-	7,23	-	558	1	-	-	Atrioventricular duct	neg	neg	death

M : Male. F : Female.. y : years. m : months. d : days. GEA : gastro-enteritis. ARF : Acute Renal Failure. HPM : Hepatomegaly HE : hyperchogenicity. Scan : Brain Scanner WM : White Matter. PMD : Psycho-Motor Delay.

**Supplementary data 3. Characteristics of the children in Group 3**

	Sex	consanguinity	age at first "Reye"	number of "Reye"	context	Elevated transaminases	lowest prothrombin time	higher ammonemia (µmol/L)	seizure	hypoglycemia	lactate	pH	ARF	CK	HPM	hepatic ultrasound	cerebral imaging	Heart ultrasound	AACp	OACu	Acylcarnitines profile	Metabolic panel	Mitochondrial panel	neurologic sequelae
Patient 54	M	0	16y	1	GEA	high	low	200	-	-	-	-	-	-	-	-	-	-	Glu 1000, Cit low, high orotate	-	-	-	-	0
Patient 55	F	0	3y	1	brain injury + aspirin	300N	35%	100	-	1	-	-	-	1500	1	-	MRI : WM anomaly	-	-	evocative of LCHAD deficiency	-	-	-	0
Patient 56	F	1	1,5y	1	GEA	77N	9%	high	1	1	5	7,37	1	174	1	HE	MRI : cortical anomaly	normal	-	-	-	running	-	PMD
Patient 57	M	0	1y	3	GEA	2N	48%	112	0	1	10	7,35	0	0	1	normal	-	-	unspecific anomaly	unspecific anomaly	unspecific anomaly	neg	running	0
Patient 58	M	0	3d	1	birth	5N	-	220	0	1	16	7,13	1	1148	1	normal	MRI : ventricular hemmorage	anomal veinous pulmonary return	unspecific anomaly	unspecific anomaly	unspecific anomaly	neg	-	0

M : Male ; F : Female ; y : years ; m : months ; d : days ; GEA : gastro-enteritis ; ARF : Acute Renal Failure ; HPM : Hepatomegaly ; HE : hyperechogenicity ; Scan : Brain Scanner ; WM : White Matter ; AACp : plasmatic amino-acid chromatography ; OACu : urinary organic acid chromatography ; PMD : Psycho-Motor Delay.



**Supplementary data 4.** ROC curve: diagnostic performance and optimal threshold of ammonia (A) and CK values (B) to suspect an IMD.

**A:** ROC area = 0.571, ammonia level is not a good discriminating parameter

**B:** ROC area = 0.799. A CK threshold of > 700 IU/L (Se 59% - Spe 100%) should guide the diagnosis towards an IMD.

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