Atypical Reye syndrome: three cases of a problem that pediatricians should consider and remember

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Abstract. Introduction: Reye syndrome is a rare acquired metabolic disorder appearing almost always during childhood. Its etiopathogenesis, although controversial, is partially understood. The classical disease is typically anticipated by a viral infection with 3-5 days of well-being before the onset of symptoms, while the biochemical explanation of the clinical picture is a mitochondrial metabolism disorder, which leads to a metabolic failure of different tissues, especially the liver. Hypothetically, an atypical response to the preceding viral infection may cause the syndrome and host genetic factors and different exogenous agents, such as toxic substances and drugs, may play a critical role in this process. Reye syndrome occurs with vomiting, liver dysfunction and acute encephalopathy, characterized by lack of inflammatory signs, but associated with increase of intracranial pressure and brain swelling. Moreover, renal, and cardiac dysfunction can occur. Metabolic acidosis is always detected, but diagnostic criteria are not specific. Therapeutic strategies are predominantly symptomatic, to manage the clinical and metabolic dysfunctions. Case reports: We describe three cases of children affected by Reye syndrome with some atypical features, characterized by no intake of potentially trigger substances, transient hematological changes and dissociation between hepatic metabolic impairment, severe electroencephalographic slowdown and slightly altered neurological examination. Conclusions: The syndrome prognosis is related to the stage of the syndrome and the rapidity and the adequateness of intensive care treatments. The analysis of the patients leads to a greater awareness of the difficult diagnosis of this not well completely known syndrome.

Key words: Acute Liver Failure, Children, Encephalopathy, Pediatric Intensive Care Unit, Reye Syndrome.

Introduction

Reye syndrome (RS) is a rare acquired metabolic disorder appearing almost always during childhood; Continued surveillance data into the 1990s has shown a marked drop of Reye syndrome and associated fatalities and contemporary rates have dropped to around 0.79 in 1 000 000 children (1). Nevertheless, the severity of this disease and its mortality rate - death occurs in about 30-40% of cases from brainstem dysfunction - implies that its existence nowadays should not be ignored and that its etiology and pathophysiology must still be investigated.

RS is characterized by acute encephalopathy and fatty degeneration of some parenchymas, especially the liver one. Since the first report of 1963 (2), there has always been evidence of the association of the syndrome with an antecedent infectious event, generally with episodes of influenza A or B or chickenpox; however, the etiology remains unknown and in particular the direct pathogenic action of an infectious agent or the presence of a hereditary metabolic disorder has never been strongly demonstrated.

The pathogenetic hypothesis prevailing in the last years considers the syndrome as the result of an unusual response to the preceding viral infection, which is
determined by host genetic factors modified by some exogenous triggering agents (3): among these, acetylsalicylic acid is frequently reported by different controlled studies (1, 3-5).

In 1990 The CDC has defined Reye syndrome using the following criteria (6): acute, non-inflammatory encephalopathy that is documented clinically by an alteration in consciousness and, if available, a record of the cerebrospinal fluid (CSF) containing less than or equal to 8 leukocytes/cu.mm or a histologic specimen demonstrating cerebral edema without perivascular or meningeal inflammation; hepatopathy documented by either a liver biopsy or an autopsy considered to be diagnostic of Reye syndrome or a threefold or greater increase in the levels of the serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), or serum ammonia; no more reasonable explanation for the cerebral and hepatic abnormalities. The third criterion for the diagnosis of RS is fundamental, because there are different metabolic disorders that may simulate clinically, biochemically, and histologically the syndrome, requiring complex investigations. Indeed, a few years ago the presence of an underlying hereditary metabolic defect (in particular, the oxidation of fatty acids, the urea cycle or the catabolism of branched amino acids) was highlighted in about a quarter of the cases initially incorrectly classified as RS and subsequently reanalyzed (7). Therefore, the possibility of a congenital metabolic disorder must be excluded in all patients with a clinical presentation similar to RS with atypical connotations if they are very young or if they have a family and/or pathological history positive for a Reye-like syndrome. An accurate diagnostic evaluation of the suspected RS cases is consequently necessary because of the importance of the preventive and therapeutic program for a specific underlying congenital metabolic alteration. Instead, for the “classic” RS therapeutic strategies are predominantly symptomatic, to manage the severe alterations. The use of glycerol, mannitol and desametazone could be useful in countering endocranial hypertension and inflammation; on the other hand, non-steroidal anti-inflammatory drugs could not be employed because they can worsen the clinical picture (8). For both RS and Reye-like syndromes, as for most Pediatric Intensive Care Unit (PICU) management diseases (9), the prognosis varies according to the severity of the clinical picture and the rapidity and the adequateness of treatments.

We report the cases of three children admitted to our PICU for a suspected RS with peculiar aspects.

Case Reports

Case 1

B. C., male, 5 years old, had incoercible vomiting arisen for about 48 hours in full well-being. The history showed an episode of viral infection of the upper airways during the previous week and no intake of salicylates or other drugs. He was sent to our PICU with the suspicion of poisoning by mushrooms or other hepatotoxic substances because of the presence of hypertransaminasemia (AST/ALT = 9694/10268 U/L), hyperamylasemia (260 U/L), hyperlipasemia (1238 U/L), leukopenia (White Blood Cells = 2210/mm³) and thrombocytopenia (Platelets = 68000/mm³). On physical examination, the hepatic margin was at 1.5 cm from the costal arch and the child was eutrophic, slightly drowsy, but well oriented in time and space. The tests carried out excluded the intake of hepatotoxic substances, confirmed hypertransaminasemia, hyperamylasemia, leuko-thrombocytopenia, and detected hyperammonemia (202 μg/L) and alterations in the hemocoagulation tests (Activated Partial Thromboplastin Time = 64 s).

CSF analysis showed normal values of glucose, proteins, and cells content. Culture tests, inflammatory markers, serologies for hepatitis A, B, C, cytomegalovirus (CMV) and Epstein Barr virus (EBV) and bone marrow aspirate were negative. The first electroencephalogram (EEG) performed documented the presence of widespread wide voltage delta waves; subsequent checks - in the fourth and eighth day - demonstrated a gradual normalization of brain electrical activity, achieved on the eighth day of hospitalization. Liver ultrasound and computed tomography (CT) of the abdomen confirmed the modest hepatomegaly, highlighting structural parenchymal anomalies as in steatosis. The liver biopsy allowed to outline the anatomopathological picture, characterized by ballooning degeneration of the hepatocytes with small microvacuolar areas.
Subsequent checks documented a rapid decrease of transaminases and the normalization of the hematological values in 5 days. The child was discharged in good general conditions.

Case 2

D. S., female, 4 years old, was hospitalized for symptoms of suspected meningoencephalitis, characterized by repeated vomiting and lethargy with two temperature peaks at 39° C during the 36 hours preceding the admission. An episode of chickenpox emerged from the medical history during the previous month, but not the intake of salicylates or other drugs. Physical examination revealed painful hepatomegaly (liver margin 4.5 cm from the costal arch) and confirmed the tendency to drowsiness.

Laboratory tests revealed hypertransaminasemia (AST/ALT = 12500/9500 U/L), increased serum LDH (28000 U/L), hyperammonemia (150 μg/L), leukopenia (White Blood Cells = 1500/mm³), mild thrombocytopenia (Platelets = 120000/mm³) and severe deficiency of coagulation factors (Prothrombin Activity <15%), subsequently corrected with fresh frozen plasma. The CSF analysis, the culture tests and the serologies for hepatitis A, B and C, CMV and EBV were negative. The EEG record found mild diffuse alterations (theta waves and rare medium voltage delta waves) and liver ultrasound showed a probable steatosis (liver of increased size and inhomogeneous structure, brighter than normal).

The clinical and laboratory picture improved progressively until the regression of the abnormalities after 6 days of hospitalization.

Case 3

C. F., male, 3 years old, was admitted to our PICU because of worsening drowsiness for about 24 hours. The child had been hospitalized three days earlier at another hospital for high fever (>39° C) and generalized seizure. The tests showed hypertransaminasemia, increased serum LDH and presence of thickening of the right lung base on the chest X-rays. CSF analysis showed normal values.

The practitioners then started parenteral antibiotic treatment with ceftriaxone and oral acetyl-salicylic acid therapy (200 mg x 4/day, equal to 60 mg/kg/day). After about 48 hours of hospitalization, it was decided to transfer the child to our ward for deterioration of the state of consciousness. At the entrance, the child appeared drowsy and disoriented, but capable of locating pain stimuli and spontaneously opening eyes in response to external stimuli; furthermore, the hepatic margin was identified at the transverse umbilical line. Thoracic auscultation and chest X-rays confirmed the presence of a thickening area in the middle-basal right, associated with a modest pleural effusion. The tests carried out found haemocoagulative alterations (Prothrombin Activity = 25%; Activated Partial Thromboplastin Time = 50 s) and mild hyperammonemia (126 μg/L) and confirmed the elevation of serum enzymes (AST/ALT = 5168/7254 U/L; LDH = 5501 U/L).

The EEG at admission time showed widespread changes, characterized theta waves and frequent delta waves of wide voltage, while cerebral the CT scan excluded relevant brain alterations in progress.

Culture tests, serologies for hepatitis A, B and C, CMV, EBV, Echoviruses, Coxsackie virus (A4, A9, B1 and B6 type), poliovirus, orotic aciduria and 2,4-dinitro-phenyl-hydrazin tests were negative.

The child underwent intravenous fluid therapy, restricted to his needs, with 5% fructose, steroid anti- edema treatment (dexamethasone 0.3 mg/kg/day for 6 days, 0.15 mg/kg/day for 2 days), antibiotic therapy with ceftriaxone (80 mg/kg/day) for 8 days and intravenous administration of vitamin K (2 mg x 2).

The neurological condition of the patient progressively improved until normal recovery after about 9 days of admission to PICU. EEG performed 15 days after the onset of symptoms was within normal limits. Subsequent blood chemistry checks showed a rapid normalization of ammonia and blood coagulation tests and a slower decrease in serum LDH, AST and ALT. Liver ultrasound, performed only before discharge, excluded abnormalities of the structure and size of the parenchyma. Pre-discharge chest X-rays showed complete resolution of the pleuro-pulmonary inflammatory process.

Discussion

Reye et al. in 1963 described the clinical features of 21 children with encephalopathy and hepatic steatosis; these patients presented with an initial
non-specific malaise, generally caused by an infectious process of the upper airways and, after a symptom-free interval, persistent vomiting followed by severe neurological symptoms (stupor and coma, sometimes seizures) (2). Subsequently, other Authors reported different cases characterized by a sequence of signs and symptoms superimposable to that outlined by Reye and by peculiar laboratory alterations (10-13). The similarity of this metabolic disorder with other known nosographic entities (Table 1) made it necessary to formulate restrictive diagnostic criteria, above all for the understanding of the most atypical cases. The guidelines proposed by the CDC in 1985, updated in 1990, for the diagnosis of RS include the exclusion of known etiopathogenetic factors, such as congenital metabolic diseases, for encephalo-hepatopathy. Some decades later, indeed, there is still no scientific certainty on the cause of the syndrome (14); only the association of most cases with various viral infections (influenza A or B, varicella-zoster, parainfluenza virus, adenovirus, CMV and Herpes Simplex virus infections) was confirmed (5,15) and the role of additional cofactors was highlighted (drugs: acetylsalicylic acid; toxins: aflatoxin) for the disease in the populations analyzed (15-19). However, in RS were found histological and cytological parenchymal alterations which are sufficiently indicative for diagnosis (15). Indeed, the disease is associated with perilobular microvacuolar fatty infiltration of hepatocytes. Electron microscopy has allowed to identify cytological markers of the disease: the proliferation of the smooth endoplasmic reticulum, the loss of glycogen, the proliferation of peroxisomes and the presence of swollen and pleomorphic mitochondria. The mitochondrion seems to be the main site of the lesion: the unknown causal element would determine the opening of pores of the internal mitochondrial membrane and consequently the swelling and alteration of its functionality. Thus, the disassociation of oxidative phosphorylation, the inactivation of mitochondrial enzymes, fundamental for the intermediate metabolism (such as carbamylphosphate synthetase and ornithine transcarbamylase of the urea cycle, pyruvate dehydrogenase), and the accumulation of more or less toxic unused metabolites (ammonium, fatty acids) are established (15, 20) .

The end result is the appearance of signs and symptoms that also characterize congenital metabolic diseases caused by enzyme mitochondrial dysfunctions. It is therefore necessary to perform the most suitable determinations on blood and urine to exclude hereditary alterations of the metabolism at the onset of diseases similar to RS, characterized above all by one or more of the following suspicious anamnestic elements (7, 21): disease onset before age 3, especially in the first year of life; previous history of recurrent episodes of vomiting associated with stressful events, growth difficulties, encephalopathy or psychomotor alterations; BRUE; family history of SIDS or RS simulating disease or recurrent undefined encephalopathy; absence of prodromal viral disease; RS precipitated by prolonged fasting or combinations of diet or other unusual stressful event.

The cases we have observed have clinical features that are remarkably reminiscent of RS (vomiting, neurological and EEG alterations, hypertransaminasemia, hyperammonemia, haemocoagulative changes, normal liquor) (Table 2), although in all of them it is possible to highlight some aspects not typical of the syndrome. In cases 1 and 3 it is easy to note the disassociation between hepatic metabolic impairment, the severe electroencephalographic slowdown on the one hand and the neurological examination that is slightly altered and not worsening on the other. According to Huttenlocher’s classification (22), RS encephalopathy can occur in 4 successive stages of severity: stage I: modest cognitive impairment, drowsiness, confusion or irritability; stage II: disorientation, psychomotor agitation or stupor, decortication and possible alterations of the autonomic nervous system; stage III: coma with decerebration; stage IV: absence of brain activity and brain stem reflexes (severe brain swelling). The alterations of the neurological examination of the three patients were mild and self-limiting, constituting an expression of Huttenlocher stage I.

EEG records, performed repeatedly in our patients, however, have demonstrated the simultaneous presence of a slowdown in brain electrical activity, generally related to more severe levels of encephalopathy for severe intracranial hypertension. The normalization of EEG findings also took place gradually.
Table 1. Differential diagnosis of Reye Syndrome.

|                                      | RS | Viral hepatitis | Drugs or other toxic substances* | Congenital metabolic disorders** |
|--------------------------------------|----|----------------|----------------------------------|----------------------------------|
| Infectious (viral) prodromes         | +  | +              | -                                | +/-                              |
| Previous intake of:                 |    |                |                                  |                                  |
| Drugs                               | +/-| -              | ++                               | -                                |
| Salicylates                         | +  | -              | -                                | -                                |
| Encephalopathy                      | ++ | +/-            | -                                | +                                |
| Hypertransaminasemia                | ++ (Always) | ++     | +                                | +                                |
| Hyperbilirubinemia                  | -  | +              | +                                | +/                               |
| Haemocoagulative alterations        | ++ (Usually) | +/-   | -                                | +/                               |
| Serum LDH increase                  | ++ | +/-            | -                                | +/                               |
| Hyperammonemia                      | ++ (Usually) | +/-   | -                                | ++                               |
| Hypoglycemia                        | +  | +/-            | -                                | -                                |
| Normal CSF                          | ++ (Always) | ++     | +                                | +/-                              |

* Drugs: 6-mercaptopurine, methotrexate, halothane, acetaminophen, anti-TB drugs.
Other toxic substances: lead, aflatoxins.

**Metabolic disorders: altered urea cycle, altered fatty acid metabolism, altered metabolism of branched-chain amino acids, fructose intolerance.

Table 2. Comparison between our case reports and classical Reye Syndrome.

|                                      | RS | Case 1 (B.C.) | Case 2 (D.S.) | Case 3 (C.F.) |
|--------------------------------------|----|---------------|---------------|---------------|
| Age (years)                          | 3-14| 5             | 4             | 3             |
| Infectious (viral) prodromes         | Yes| Yes           | Yes           | Perhaps (+/-) |
| Previous intake of salicylates       | Yes| No            | No            | Yes           |
| Vomiting                             | Yes| Yes           | Yes           | No            |
| Clinical neurological changes         | Yes| Yes (+)       | Yes           | Yes (+)       |
| EEG alterations                      | Yes| Yes (+++)     | Yes           | Yes (+++)     |
| Jaundice                             | No | No            | No            | No            |
| Hypertransaminasemia, LDH increase   | Yes| Yes (+)       | Yes           | Yes           |
| Hyperammonemia                       | Yes| Yes           | Yes           | Yes (+/-)     |
| Haemocoagulative alterations         | Yes| Yes           | Yes (+)       | Yes (+)       |
| Leukopenia and/or thrombocytopenia    | No | Yes           | Yes           | No            |
| Hyperamylasaemia                     | Yes (in case of pancreatitis) | No | No | No |
| Hypoglycemia                         | Yes| No            | No            | No            |
| Normal CSF                           | Yes| Yes           | Yes           | Yes           |
and over a period of time certainly longer than that in which the decrease in ammonia occurred, a determin-
ing factor of the extent of cerebral edema and therefore of the progression of encephalopathy (23). On the other hand, no factors were found useful to explain the EEG alteration of our little patients.

Indeed, the absence of vomiting at the onset of neurological disorders of patient 3 is interesting; this symptom, generally associated with the appearance of the encephalopathic phase of the RS, is indicated as the most explicit manifestation of the endocranial pressure increase, probably at the basis of brain suffering of the RS. The history of our patients suggests the interaction between known or suspected infectious agents and unknown host factors; in fact, there is no evidence in cases 1 and 2 of an intake of substances that may have interacted with the infectious process in the triggering of the metabolic disorder. Instead, Case 3 confirms the role repeatedly attributed by the literature (3, 17) to acetylsalicylic acid of co-responsibility in the realization of RS in children.

The absence of negative prognostic factors (age of onset less than 3 years, severity of coma, severe hypoglycaemia, seizures, very high hyperammonemia) (5,15,24), in our patients confirmed their clinical course, characterized by the benign evolution of the syndrome (rapid normalization of liver and brain function) and the absence of outcomes at discharge and follow-up.

The transient hematological changes (leukopenia and thrombocytopenia) found in two patients (cases 1 and 2) constitute an element that is difficult to interpret and, in any case, not typical of the classic RS.

The cases we describe are lacking in some diagnostic assessment (liver biopsy or more specific metabolic tests), but they highlight the awareness of the difficult diagnosis and classification of RS, despite the guidelines and classifications proposed internationally.

It is possible to hypothesize that a still unknown specific genetic predisposition determines a syndrome that simulates RS after the triggering action of particular exogenous agents in children in whom the execution of main metabolic tests and/or the absence of anamnestic elements allow to exclude the presence of a known congenital enzyme disorder.

Conclusions

RS is a rare acquired metabolic disorder appearing almost always during childhood. The undefined etiology of RS, its inconstant association with acetylsalicylic acid and the clinical atypia, also reported by us, make it necessary to search for further elements to understand this still mysterious metabolic disorder. Moreover, the reduction in the incidence of cases that has been encountered in recent years is not a good reason to decrease the attention towards a potentially fatal disease.

Conflict of Interests: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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