Clinical Presentation, Treatment and Prognosis in Children with Reye-like Syndrome

Reye-like Sendromu Olan Çocuklarda Klinik Prezentasyon, Tedavi ve Prognoz

Reye-like Sendromu Olan Çocuklar / Children with Reye-like Syndrome

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Özet

Konya Eğitim ve Araştırma Hastanesinde tedavi edilen Reye like Sendromu olan hastaların mortalite oranlarını ve prognozlarını araştırmak için retrospektif bir çalışma yaptık. Yaşları 5 ay ile 7 yaş arasında olan 22 çocuk çalışmaya dahil edildi. Tüm hastalar vücut sıvısı, kan dolaşımı, solunum, vücut ısısı ve intrakraniyel basıncını idare etmek için destekleyici yöntemlerle tedavi edildi. Temel prezentasyon özellikleri ateş (% 72,7), kusma (% 63,6), anormal davranış ve ajitasyon (% 72,7) ve ani başlayan bilinç bulanıklığıdır (%100). Çalışmaya alınan hastalarda etiyoloji; viral hastalık, gastroenterit, metabolik hastalık, intoksikasyon ve yabancı cisim aspirasyonuna bağlı hipoksi. Hastalığı atlatan çocuklarda nörolojik defisit izlenmemiştir. Hastalarımızda mortalite oranı % 31,8 idi. Sonuç olarak, Reye like sendromu nadiren görülür; fakat nedeni bilinmeyen ensefalopatilerde, özellikle eğer viral enfeksiyon, kusma ve ilaç alım öyküsü varsa ayırıcı tanının bir parçası olmalıdır. Tedavi protokolümüz Reye like sendromu olan çocuklarda güvenilir ve etkilidir.

Anahtar Kelimeler

Reye-Like Sendromu; Ensefalopati; Tedavi; Etiyoloji

Abstract

We performed a retrospective study to explore the mortality rates and prognosis of the Reye like syndrome in patients treated at Konya Research and Education Hospital. Twenty two children with ages between 5 months and 7 years old were included in this study. All patients were treated with intensive supportive methods to manage body fluid, blood circulation, respiration, body temperature, and intracranial pressure. The main presenting features were history of fever (72.7%), profuse vomiting (63.6%), abnormal behavior and agitation (77.2%), and sudden onset of unconsciousness (100%). The etiologies of patients included viral illness, gastroenteritis, metabolic disorders, intoxication and hypoxia due to foreign body aspiration. No neurological deficit was seen in the children who survived the disease. In our patients the mortality rate was 31.8%. In conclusion, Reye like syndrome occurs only rarely but should be a part of the differential diagnosis of any encephalopathy of unknown origin and above all if there is a history of ingestion of drugs, previous viral infection and vomiting. Our treatment protocol is safe and effective in children with Reye like syndrome.

Keywords

Reye-Like Syndrome; Encephalopathy; Treatment; Etiology

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Introduction

Reye's syndrome is a rare but severe illness that occurs mainly in children and adolescents with a mean mortality rate of about 40% that seems to be higher in males than females [12]. The syndrome was clinically characterised for the first time during 1963 by the Australian pathologist R. D. Reye, [16] but sporadically was described previously. The term RS was replaced by the term Reye like syndrome, while its possible cause were viral infections, metabolic disorders, salicylates, other exogenous agents including a number of toxins, drugs and other chemicals [17]. The etiological cause is presently unknown, but generally the syndrome is preceded by a viral episode, with an intermediate free interval with a mean of 3-5 days [17]. Frequently influenza A or B and chicken pox are involved, but also other previous viral infections, especially those affecting the respiratory tract are possible, and recently it has been supposed that Rotaviruses can be involved, too [6, 17].

Therapeutic approaches are prevalently symptomatic in order to counteract the occurring severe alterations [7, 18] and the prognosis depends on syndrome stage and on the timeliness and adequateness of intensive care treatments. An attempt at monitoring of neurologic, respiratory, cardiovascular, coagulative, metabolic and water and electrolyte balance situation is necessary for possible interventions [19]. Mannitol, glycerol and dexamethasone may be employed in order to counteract endocranial hypertension, and inflammatory manifestations [9]. However the mortality rate averages 40%, and in survivors, severe neurologic sequelae can be present in 30% of the cases [2, 13].

We performed a retrospective study to explore the mortality rates and prognosis of the Reye like syndrome in patients treated at Konya Research and Education Hospital.

Material and Method

Subjects

Twenthy two children with ages between 5 months and 7 years old were included in this study. All of them were admitted into the emergency room in the Konya Research and Education Hospital and transferred to the Paediatric Intensive Care Unit in accordance with their clinical condition. All the cases were recollected from the Paediatric Intensive Care Unit data file, searching by diagnosis in a period of 2 years (october 2010-april 2012).

Reye like syndrome was determined as one in which there is acute, noninflammatory encephalopathy, manifested clinically by alterations in the level of consciousness and documented, when such results are available, by the presence of cerebral edema with imaging of the brain as well as hepatic dysfunction and fatty infiltration of visceral organs. The exclusion criteria were inflammatory encephalopathy, malignancies and intracranial hemorrhage.

The inclusion criteria used in this study were: 1) Children of all ages, 2) During or while recovering from gastroenteritis or viral illness (most commonly influenza), 3) Repetitive vomiting, fever and altered behaviour and the presence of lethargy, confusion, irritability, aggressiveness, 4) Unexplained non-inflammatory encephalopathy, 5)Elevated serum hepatic transaminases, plasma ammonia and creatinine kinase with normal serum bilirubin levels, 6) Normal cerebrospinal fluid examinations.

The study protocols were approved by the institutional review board of Konya Training and Research Hospital.

Laboratory Investigation

In addition to detailed neuroimaging analysis, we included following clinical characteristics in this study: Demographic features (age at clinical onset, gender), preceding infections, family history of metabolic disorders, and duration of follow-up.

In general, routine laboratory tests included blood cell count, electrolytes, liver enzymes, creatinine, urea, glucose, viral serology, serum bilirubin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase, creatinine kinase, lactate dehydrogenase, blood gas analysis and plasma ammonia concentration. Cerebrospinal fluid (CSF) examinations included cell count, protein, glucose, gram stain and bacterial cultures. These studies are obtained immediately after admission.

All patients were treated with intensive supportive methods to manage body fluid, blood circulation, respiration, body temperature, and intracranial pressure. Our patients treatment scheme is shown in table 1. All subjects received high dose dexamethasone treatment as well as brain hypothermia, semi-Fowler's position and phenobarbital.

Table 1. Patients treatment protocol

1. Fluid and electrolyte balance
2. Intravenous administration of 25% human albumin (0,5-1 gr/kg/dose, 30 minute intravenous infusion) followed by furosemide (2 mg/kg/dose, intravenous bolus).
3. Dexamethasone;
1-3 days 2 mg/kg/day
4-7 days 0,5 mg/kg/day
4. Semi-Fowler's position
5. Brain hypothermia
6. Phenobarbital;
5 mg/kg/day, 2 dose/day
7. İf needed vitamin K and fresh frozen plasma

Results

Twenty two Reye-like syndrome who were admitted to pediatric intensive care unit were enrolled in the study. The age range of the patients was from 5 months to 7 years (mean age 1,7 ± 1,6 years). The etiologies of patients included viral illness, gastroenteritis, metabolic disorders, cyanide intoxication and hypoxia due to foreign body aspiration.

Nine patients were males and thirteen females. The main presenting features were history of fever (72.7%) and profuse vomiting (63.6%), which was soon followed by abnormal behavior and agitation (77.2%), and sudden onset of unconsciousness (100%). Frank convulsions or history of seizures was found in 6 (27.2%) cases. There was no history of rash or other overt signs of any exanthematous viral illness. The period of time between the initiation of the symptoms and admission corresponded to an average of 5 days (range: 3-9 days). None of the children was given salicylates or any other medications. Subjects presenting symptoms, imaging findings and outcome are shown in table 2. Physical examination showed encephalopathy in all the cases. Encephalopathy ranged from a somnolent state to coma.

Table 2. Patients presenting symptoms, imaging findings and outcome

No of patients	fever	Vomiting	convulsion	Abnormal behavior	coma	Cerebral edema	consequence
1	+	-	-	-	+	-	Survived
2	+	-	+	+	+	+	Survived
3	+	+	-	+	+	X	Died
4	+	+	-	-	+	+	Survived
5	-	-	+	+	+	X	Died
6	-	-	-	+	+	-	Survived
7	+	+	-	-	+	+	Survived
8	-	+	-	+	+	+	Survived
9	+	-	+	+	+	+	Survived
10	+	+	-	+	+	+	Survived
11	+	+	-	+	+	X	Died
12	+	+	-	+	+	+	Survived
13	-	+	-	+	+	+	Died
14	+	-	+	+	+	+	Survived
15	+	+	+	+	+	+	Survived
16	+	+	-	+	+	+	Survived
17	+	+	-	+	+	+	Survived
18	+	-	-	+	+	+	Died
19	-	+	-	+	+	+	Survived
20	+	-	-	-	+	+	Died
21	-	+	+	-	+	+	Died
22	+	+	-	+	+	+	Survived

Biochemical alterations were observed in all patients. Serum bilirubin was normal in all cases (mean 0,44± 0,20 mg/dL). Serum ALT and AST activities were elevated; Gamma glutamyl transferase was elevated only in one case: 158 IU/L and alkaline phosphatase activity were at normal values in all cases. Hypoglycemia was determined only in two patient.

Serum prothrombin time was elevated in four patients and treated with vitamin K and fresh frozen plasma. Serum ammonia level was determined in the 20 cases and was elevated (normal range: 27,2-102 µg/dl). Blood gas analysis revealed metabolic acidosis in all patients, except one case. Laboratory analysis of the subjects are shown in table 3.

Table 3. Laboratory analysis of the subjects

	Minimum	Maximum	Mean	St. Deviation
Age (years)	0,4	6,6	1,77	1,69
Glucose (mg/dl)	43	279	136,68	66,19
Urea (mg/dl)	10	265	46,14	52,7
Creatinin (mg/dl)	0,34	2,34	0,78	0,51
Albumin (g/dl)	2,2	4,9	3,6	0,55
T. bilirubin (mg/dl)	0,2	0,9	0,44	0,20
AST (U/L)	55	2104	473,77	535,57
ALT (U/L)	35	542	200,9	184,07
ALP (U/L)	72	343	190,41	81,68
GGT (U/L)	18	158	51,14	29,18
Creatinine kinase (U/L)	132	42045	3293,05	8806
WBC (K/uL)	4,56	32,1	11,68	6,99
HGB (g/dl)	8,2	15,9	11,52	1,71
PLT (K/uL)	60	679	287	158,32
PTT (second)	15,0	46,0	28,82	7,99
partial thromboplastin time (PT) (second)	10,9	21	13,86	2,98

AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl transferase, ALP:alkaline phosphatase, PTT: parsiyel tromboplastin zamanı,

Brain MRIs were performed on admission or shortly after admission on most of the patients. Brain MRIs were showed brain edema in 17 (89.4%) patients, while 2 patients had normal results. None of the patients had hemorrhage or syrinx on the MRIs. Of three children, brain MRIs were not available because of unstable subject conditions.

Three patients who showed renal failure with elevated creatinine levels presented a bad evolution and finally died. Four patients died during the first week of admission. The rest of the patients ameliorate their clinical and biochemical conditions and abandoned the Hospital in good condition. No neurological deficit was seen in the children who survived the disease. In our patients the mortality rate was 31.8%.

Discussion

In Reye-like syndrome, acute encephalopathy is associated with severe liver damage. There is a marked increase in serum aminotransferases, which seemingly meets the Centers for Disease Control diagnostic criteria of Reye syndrome [3]. However, biochemical and histologic findings characteristic of classical Reye syndrome are lacking. Reye syndrome is a biphasic illness that occurs predominantly in children and adolescents. It is a prodromal viral illness followed by protracted vomiting and subsequent neurological changes occurring at the time of apparent recovery.

It is important to recall that infection or microbial toxins production can act as preparatory or inducing factors of physiopathological phenomena characterising Reye syndrome [1]. Moreover infective agent and/or pre-existent metabolic disorders (latent also) predispose to the chemically induced syndrome [14]. In particular, according to Glasgow and Middelton [8] some viruses can affect Kupffer cells with a consequent endotoxemic condition, accompanied by proinflammatory cytokines and especially of TNFα release [10]. These phenomena down regulate gene expression of major cytochrome P-450 enzymes that are very important for metabolism of many endogenous and exogenous products, with a consequent damage of main mitochondrial functions [15].

Although Reye like syndrome is associated with a complex variety of metabolic disturbances, [4, 5] both death and the neurologic sequelae in survivors are attributed to the insult to the central nervous system. Therefore, therapy is focused on maintaining an adequate cerebral perfusion pressure while providing the support required to minimize the associated metabolic dysfunction. All patients with Reye like syndrome should be monitored closely in an intensive care setting, as their clinical condition can deteriorate rapidly, even in mild cases. The Reye like syndrome is treated with intensive supportive methods to manage body fluid, blood circulation, respiration, body temperature, and intracranial pressure. Correction of metabolic abnormalities (hypoglycemia, hyperammonemia, and metabolic acidosis) and coagulation disorder is important. Our patients were treated with intensive supportive methods to manage body fluid, blood circulation, respiration, body temperature, and intracranial

pressure. All subjects received high dose dexamethasone treatment, brain hypothermia, semi-Fowler's position and phenobarbital. We didn't prefer mannitol to reduce intracranial pressure because of its electrolyte imbalance and acute kidney injury effects. In our study, three patients who showed renal failure with elevated creatinine levels presented a bad evolution and finally died. Four patients died during the first week of admission. The rest of the patients ameliorate their clinical and biochemical conditions and abandoned the Hospital in good condition. No neurological deficit was seen in the children who survived the disease. Lemberg et al. found mortality rate 41.7% in Reye like syndrome [11]. In our patients the mortality rate was 31.8%. The mortality rate of Reye like syndrome in our department is very low when compared with other reports.

In conclusion, our treatment protocol is safe and effective in children with Reye like syndrome. Reye like syndrome occurs only rarely but should be a part of the differentiating diagnosis of any encephalopathy of unknown origin and above all if there is a history of ingestion of drugs, previous viral infection and vomiting. Early recognition of the signs and symptoms and early treatment is imperative to reduce morbidity and mortality in children with Reye like syndrome.

Competing interests

The authors declare that they have no competing interests.

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