Fatal case of Reye's syndrome associated with H3N2 influenza virus infection and salicylate intake in a 12-year-old patient

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Abstract

We describe a fatal case of Reye’s syndrome in a 12-year-old male patient during an influenza A (H3N2) infection for which he received salicylates. In the current situation of the novel A/H1N1 virus pandemic, we believe that it is of high importance to emphasize the risks associated with salicylate intake to avoid the reappearance of Reye’s syndrome.

Keywords: Aspirin, encephalopathy, hepatopathy, viral infection

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Reye’s syndrome (RS) is a rare but severe and high-fatality-rate paediatric disease, characterized by an acute encephalopathy and pronounced cerebral oedema associated with liver disease with diffuse fatty infiltration [1]. The CDC case definition is: (i) acute non-inflammatory encephalopathy documented clinically by an alteration in consciousness and, if available, a record of cerebrospinal fluid containing eight leukocytes or fewer per mm³, or by a histological specimen demonstrating cerebral oedema without perivascular or meningeal inflammation; (ii) hepatopathy documented by either a liver biopsy or autopsy considered to be diagnostic of RS, or a three-fold or greater rise in the levels of either serum glutamate oxaloacetate transaminase, serum glutamic pyruvate kinase or serum ammonia; and (iii) no other reasonable explanation for the cerebral or hepatic abnormalities [2]. RS may occur at any age in childhood, although the frequency is higher in children under the age of 2 years [3]. The illness is typically biphasic with an apparent near recovery from a viral prodromal illness followed after a few days by vomiting and altered consciousness. Although the mechanism leading to RS remains unknown, it is often preceded by an acute viral infection, usually varicella, gastroenteritis or respiratory tract infection as a result of influenza virus [4]. Various factors (viral, toxic, drug-related and metabolic) were considered in the pathogenesis of RS, although only aspirin intake during the prodromal phase was statistically proven to be associated with RS [5–8]. Accordingly, warnings against aspirin administration to children were issued in the USA in 1980, and the incidence was reduced [9]. In Reye-like syndrome, and as a result of inborn errors of metabolism, hypoglycaemia, hypoketonaemia, elevated ammonia and organic aciduria are often evident. It is well known that fatty acid oxidation defects can manifest as Reye-like syndrome [10]. If the general population is not sensitized to this risk, RS may increase in the peculiar A/H1N1 pandemic situation. We report a fatal case of RS in a 12-year-old child who received aspirin during an influenza infection.

In February 2009, a 12-year-old boy was admitted to the hospital for neurological distress and gastrointestinal disease. For 4 days, he had been suffering from a viral syndrome, with fever (39°C) and nasal discharge, which was treated by self-administration of 250 mg of aspirin. Two days before hospital admission, he was no longer febrile but suffered from vomiting and complete digestive intolerance. The next day, he presented with haematemesis, which motivated admission to the emergency ward. Upon admission, his temperature was 35.8°C, his pulse was 110 per minute, and blood pressure was 128/73 mmHg. Laboratory analyses revealed major abnormalities, with hypoglycaemia (0.4 mM), acute hepatocellular deficiency with a prothrombin index < 10% (V factor 0.04), aspartate and alanine aminotransferase levels at 20 130 IU/L and 10 690 IU/L, respectively, and hyperammonaemia (255 µM). He was transferred into the paediatric intensive care unit, where a nasopharyngeal aspirate was collected and sent to the microbiology laboratory. Shortly after transfer, he presented alternative episodes of agitation, confusion and drowsiness, which were diagnosed as a hepatic
encephalopathy stage II–III. There was no measured intracranial hypertension. Biochemistry parameters showed hypotension (127 mM), hyperkalaemia (6.8 mM), lactic acidosis (5 mM) and renal deficiency, with a plasma urea level of 8.9 mM and a plasma creatinine level of 227 μM, which required dialysis. Treatment with suitable glycemic correction and fast recharge in sodium was administered. A few hours later, the patient developed a moderate polyneuropathy, which required mechanical ventilation. He had episodes of bradycardia and tachycardia with ventricular premature complexes. During the first 12 h after hospitalization, he presented a progressive deterioration of consciousness despite a suitable correction of glycaemia and serum sodium levels. In the early evening, neurovegetative disturbances appeared with mydriasis, which were initially reversible with osmotherapy and neuroanesthesia, and then irreversible 12 h after admission. A cranial Doppler examination demonstrated evidence of massive cerebral oedema. He died 2 days after admission.

Evidence for infection with A/H3N2 influenza virus was demonstrated via: (i) antigen detection by rapid influenza detection tests using immunochromatographic technology (Directigen EZ Flu A+B; Becton-Dickinson Biosciences, Franklin Lakes, NJ, USA); (ii) virus detection using a direct immunofluorescence test in the combined kit (anti-Adenovirus + Influenza A, B + Parainfluenza 1, 2, 3 + RSV; Argene, Verniolle, France); (iii) PCR detection by qualitative real-time RT-PCR [11]; (iv) subtyping by sequencing [12]; and (v) virus isolation onto Madin–Darby canine kidney cells.

Two liver biopsies were formalin-fixed and paraffin embedded. Serial sections were performed, with immunohistochemistry including anti-Ki 67 and anti-active caspase 3 antibodies, to assess cell proliferation and cell apoptosis, respectively (Fig. 1). Pathological lesions were diffuse and similar for the two biopsies (thirty portal tracts). Moderate mononuclear and polymorphonuclear infiltrates were present within the portal tracts but without destruction of the limiting plate and bile ducts. Major alterations were located within the hepatic lobules (zones 1, 2 and 3). Hepatocytes exhibited severe mixed micro-macrovacular steatosis associated with numerous lytic necrosis areas and apoptotic bodies. The proliferation index evaluated with anti-Ki67 antibody was low (i.e. 5–10% of hepatocytes). Anti-active caspase 3 was positive on up to 50% of hepatocytes, highlighting a massive apoptotic process. In muscle, enzymatic spectrophotometry measurements of the individual respiratory chain complexes revealed no decrease of complex I–V activity. A screen for mitochondrial DNA deletion and common mutations (m.3243A>G, m.8344A>G, m.8993T>G) was negative. Mitochondrial DNA quantification, performed by quantitative RT-PCR, showed no depletion (152% of age-matched controls). Moreover, manifestations of Reye-like syndrome usually occur before the age of 3 years [13].

The pathological findings were highly compatible with a RS in a patient who presented with a laboratory-confirmed acute H3N2 influenza A virus infection treated with aspirin. In addition, all CDC definition criteria of RS were fulfilled [2]. A low cerebrospinal fluid leukocyte count was not demonstrated because a cerebrospinal fluid tap test was not performed. Furthermore, additional criteria that may help to confirm the diagnosis were present in our case: age <15 years, hypoglycaemia, vomiting, peripheral zonal hepatic necrosis, lack of jaundice, metabolic acidosis and elevated prothrombin time. Clinical, pathological, virological and biochemical findings, together with the epidemiological context, unambiguously demonstrate that our patient presented with a RS from which he died. Written authorization has been obtained from the parents of the patient.

This recent case highlights that the prescription of aspirin or aspirin-containing medication to patients presenting with fever in the context of febrile illness compatible with viral infection such as influenza virus infection must be proscribed. In the early 1980s in the USA, warnings to physicians were associated with a clear decrease of RS [14]. A similar tendency was observed in the UK, with incidences varying from 0.3 per 100 000 in 1985–86 to 0.1 per 100 000 in 1990–91 [15,16]. No comparative data were available in France; however, in 1995–1996, the RS incidence was 0.08 per 100 000, in the same range as those in the USA and the UK [17]. We believe that the same warnings should be reiterated in
European countries to avoid an increase in the incidence of RS in the current context of the novel A/H1N1 influenza virus pandemic. Because self-administration of aspirin or aspirin-containing medications is frequent specifically during the winter season, it is of utmost importance to disseminate messages to the public concerning the possible dramatic consequences of aspirin intake during viral infections.

Transparency Declaration

None of the authors have conflict of interest to declare.

References


Surveillance of human astrovirus circulation in Italy 2002–2005: emergence of lineage 2c strains

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Abstract

By screening faecal samples collected over four consecutive years (2002–2005) from hospitalized children with diarrhoea in Palermo, Italy, astroviruses (HAstVs) were detected in 3.95% of the patients. The predominant type circulating was HAstV-1 but, in 2002, only HAstV-2 and -4 were identified. Interestingly, the HAstVs-2 detected appeared to be consistently different in 5' end of their open reading frame 2 from the previously described subtypes. These novel type 2 strains were included in a new 2c lineage based on the phylogenetic analysis and the presence of nine peculiar substitutions.

Keywords: Astrovirus, gastroenteritis, genotyping, Italy, sequence analysis

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Human astroviruses (HAstVs) are enteric viruses associated with gastroenteritis in young children in both developed and developing countries [1]. Their prevalence is usually in the range 2–9%, although some studies in developing countries report rates of up to 28.2% [1–5]. The pathogenic role of HAstVs is still disputed because they are frequently found (33–65% of the cases) in conjunction with other enteric

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