Sponsored by the Swiss Society of Paediatrics (SSP) and the Federal Office of Public Health (FOPH)

Acute pediatric hepatitis of unknown origin

Disease surveillance

All children < 16 years with acute elevation of AST or ALT > 500 IU/ml, not due to hepatitis A-to-E

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Summary

Most cases of acute hepatitis of clinical significance in children are due to hepatitis viruses A to E. Since early 2022, an unusual increase in cases of acute hepatitis have been reported in children in many European countries and in the USA, with a few patients requiring liver transplantation. Despite intensive investigations, its etiology remains unclear to date. Using the SPSU, we aim to rapidly implement a nationwide surveillance system for acute non-A-to-E hepatitis in children. The aim of this study is to rapidly analyze its etiology, epidemiology, risk factors for occurrence and severity (liver failure, and transplantation), clinical presentation, complication, management, and outcome at hospital discharge.

Background and rationale

Most cases of acute hepatitis in children are mild and transient, and those of clinical significance are usually due to hepatitis viruses A to E. Since early 2022, an unusually high number of acute hepatitis of unknown origin have been reported, mainly in the United Kingdom[1], but also in the USA, France, Belgium, Spain, Italy, Norway, Romania, the Netherlands, New Zealand and Denmark[2]. As of May 6th, 2022, several cases in Switzerland would meet the WHO case definition[3].

This syndrome mostly affects previously healthy children aged 2-5 years but cases up to 16 years have been described[1; 2]. The most frequently reported symptoms are jaundice, vomiting, abdominal pain, pale stool, diarrhea, lethargy, and malaise[1; 2; 4; 5]. The reported frequency of fever varies between 0% to 55% [1; 2; 4; 6]. Between 7% to 10% of documented cases have required liver transplantation[2; 7].

Despite an extensive infectious, immunological and toxicological workup, the etiology of this entity remains unclear. There is no clear association with travel or recent vaccination. Adenovirus has been identified in about 60-70% of cases, either in blood, upper respiratory tract or stools. The most frequently identified adenovirus is adenovirus type 41[2; 4; 7]. However, it is not clear whether this simply reflects sustained circulation of adenoviruses in the pediatric community. Moreover, low viral load in blood[2; 4] and negative PCR on explant biopsies (personal communication) children having undergone liver transplant do not support the hypothesis of a primary adenovirus hepatitis. Similarly, SARS-CoV-2 has also be identified in some cases, but it could simply reflect community circulation. For example, out of the 114 cases reported in the UK, 60 (53%) were positive for adenovirus and 18 (16%) for SARS-CoV-2[2]. Other working hypotheses include a new viral variant of adenovirus or SARS-CoV-2, a coinfection, an immune-mediated hepatitis triggered by a viral infection in a relatively naïve pediatric population or a toxic agent.

Aims of the study

Therefore, we aim to rapidly implement a nationwide surveillance system for acute non-A-to-E hepatitis in children <16 years with the following aims:

Primary aim

- Identify the epidemiology of acute non A-to-E hepatitis

Secondary aims

- Identify the etiology of acute non A-to-E hepatitis
- Characterize the clinical presentation of acute non A-to-E hepatitis
- Identify risk factors for occurrence of acute non A-to-E hepatitis
- Analyze risk factors for a severe course (liver failure and liver transplantation)
- Analyze management of acute non A-to-E hepatitis with a view to streamline and rationalize management

Methods

Observational, multicentric surveillance with reporting of all children and adolescents meeting the following criteria.

Two step approach: 1) declaration of cases through the monthly SPSU card; 2) filling of a specific, individualized, anonymized case-report form (see attached) by physician in charge.

Case definition

In order to allow for international comparisons, we will follow the World Health Organisation (WHO) accepted case definition[3]:

• **Confirmed**: N/A

• **Probable**: A person presenting with an acute hepatitis (non-hepatitis viruses A, B, C, D and E*) with aspartate transaminase (AST) or alanine transaminase (ALT) over 500 IU/L, who is 16 years old or younger, since 1 October 2021.

Inclusion criteria

- Age ≤ 16 years of age
- acute elevation of AST or ALT>500 IU/ml

Exclusion criteria

- A to E acute viral hepatitis

Study Design

1. Communication

Our center has communicated at a national level with the following specialities

- pediatric gastroenterologists (through the Swiss Society for Pediatric Gastroenterology, Hepatology and Nutrition [SSPGHN])
- pediatric infectious diseases specialists (through the Pediatric Infectious Diseases Group of Switzerland [PIGS])
- pediatric immunologists (through the Swiss Society for Allergy and Immunology [SSAI])
- pediatric emergency specialists (through the Pediatric Emergency Medicine Switzerland [PEMS])
- pediatric intensive care specialists (through the pediatric group of the Swiss Society of Intensive Care Medicine [SSICM])
- general pediatricians (through Pédiatrie Suisse [PS])
- adult hepatologists (through the Swiss Association for the Study of the Liver [SASL]

2. Reporting, data collection and questionnaire:

Upon identification of a case of acute hepatitis by a pediatrician or pediatric gastroenterologist to the SPSU in the monthly report, they will enter the data into SPSU questionnaire, which will contain all data needed to be reported through the TESSy reporting system, in order to streamline data collection by the BAG.

All data is anonymized and does not contain any identifiable information.

Through this system, we aim to capture all patients meeting inclusion criteria. Patients admitted to one of the SPSU participating hospitals will be reported through the usual SPSU surveillance system.

Study initiation

01.07.2022

Duration of study

Five years (2022-2027) with an option for extension

Literature

1. Marsh K, Tayler R, Pollock L, Roy K, Lakha F, Ho A, Henderson D, Divala T, Currie S, Yirrell D, Lockhart M, Rossi MK, Phin N (2022) Investigation into cases of hepatitis of unknown aetiology among young children, Scotland, 1 January 2022 to 12 April 2022. Euro Surveill 2710.2807/1560-7917.ES.2022.27.15.2200318
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5. UK Health Security Agency. Guidance. Increase in acute hepatitis cases of unknown aetiology in children.
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