A case of paroxysmal cold hemoglobinuria with influenza A (H1N1) virus infection

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Abstract

Background: Despite many reports emphasizing that paroxysmal cold hemoglobinuria (PCH) is an unusual disease, in recent years, PCH has become recognized as a relatively frequent cause of childhood acute transient autoimmune hemolytic anemia (AIHA). Although most cases of PCH involve an antecedent upper respiratory infection, the causative agent often remains unidentified. PCH combined with influenza A (H1N1) virus infection has not been previously reported.

Case presentation: A 2-year-old patient and both of her parents were of Filipino decent. The patient presented to our hospital with a 3-day fever, abdominal pain, and dark red urine. The patient was diagnosed with PCH because the Donath-Landsteiner antibody test (DLT) was positive. On the 12th day following admission, her influenza A (H1N1) antibody levels were elevated compared with the levels at the time of admission, and the patient was diagnosed with influenza A (H1N1) infection. After a 2-week period, she was discharged, with no further evidence of hemolysis.

Conclusion: Influenza virus infection is a common disease. If physicians encounter children with hemolytic anemia and hemoglobinuria during an epidemic of influenza virus infection, these professionals need to consider the onset of PCH in the differential diagnosis and should examine the DLT for a diagnosis of PCH.

Keywords

autoimmune hemolytic anemia, childhood, Donath-Landsteiner test, influenza A (H1N1) virus infection, paroxysmal cold hemoglobinuria
Background

In recent years, paroxysmal cold hemoglobinuria (PCH) has become recognized as a relatively frequent cause of acute transient autoimmune hemolytic anemia (AIHA) in childhood [1]. The causative antibody is of the IgG immunoglobulin class and is a biphasic hemolysin that is detected by incubation in the cold followed by incubation at 37°C in the presence of complement, which is called the Donath-Landsteiner test (DLT) [1, 2]. Although most cases of PCH involve an antecedent upper respiratory infection, the causative agent often remains unidentified [2]. We report a case of PCH combined with influenza A (H1N1) virus infection. PCH combined with influenza A (H1N1) virus infection has not been previously reported.

Case presentation

A 2-year-old patient and both of her parents were of Filipino decent. She and her family had lived in Japan for 1 year and were healthy. The patient presented to our hospital with a 3-day fever, abdominal pain, and dark red urine. Upon admission, she was pale and exhibited jaundice. A complete blood count revealed leukocytes 10,860/µL (neutrophils 59.7%), hemoglobin 6.8 g/dL, hematocrit 19.4%, platelets 530,100/µL, reticulocytes 12.6%, blood urea nitrogen 17.8 mg/dL, creatinine 0.25 mg/dL, haptoglobin <10 mg/dL, total bilirubin 1.53 mg/dL, indirect bilirubin 1.29 mg/dL, lactate dehydrogenase 2138 IU/L, aspartate aminotransferase 97 IU/L, alanine aminotransferase 16 IU/L, C3 106 mg/dL, C4 47 mg/dL, and CH50 43.2 U. The antinuclear antibody and cold agglutinin tests were negative. The direct antiglobulin test was positive for anti-C3c (3+) and anti-C3d (4+) alone, whereas no IgG, IgM, or IgA antibody was detected on the red cells with specific antisera. The indirect antiglobulin test was negative. The direct DLT was positive.

The direct DLT was performed as follows [1, 3]. ABO-compatible, author-donated serum was used as a negative control and as a source of fresh complement, if needed. A specimen was carefully drawn and kept at 37°C until the serum was separated. The patient’s serum and red blood cells (RBCs) were incubated, without additional complement, at 0°C for 30 minutes and then at 37°C for 60 minutes, 0°C for 30 minutes, and 37°C for 60 minutes, without exposure to cold. The negative-control sera were similarly incubated with the patient’s RBCs. An identical set of tubes was also incubated at 0°C for 30 minutes and then at 37°C for 60 minutes, 0°C for 30 minutes, and 37°C for 60 minutes, without exposure to cold. All tubes were centrifuged and examined for the presence of hemolysis at the end of the incubation periods. A positive result was judged by hemolysis in the tests in which only the patient’s serum and RBCs had been cooled and rewarmed, with no hemolysis evident in the tests that had remained at 37°C or 0°C throughout (Table 1). The patient was diagnosed with PCH.

The patient was nursed to avoid cooling her body temperature because she was antipyretic on the second day after her admission. The patient was treated with drip infusion due to poor oral intake and treated with prednisolone (1 mg/kg/day) for a period of 3 days. No transfusion was required. The urine occult blood became negative on the 5th day after her admission. The direct antiglobulin test was negative 12 days after her admission.

The rapid antigen detection method for flu A and B was negative at the time of
admission. The patient’s influenza A (H1N1) antibody levels were elevated on the 12th day following admission compared with the levels at the time of admission (over 10 vs. 20 times: reference range [N]; under 10 times). She had never received the influenza vaccine and was infected with influenza virus. Her influenza A (H3N2) and influenza B antibody levels were not elevated on the 12th day following admission compared with the levels at the time of admission (under 10 vs. under 10 times; N: under 10 times). Her mycoplasma antibody levels were not elevated on the 12th day following admission compared with the levels at the time of admission (under 40 vs. under 40 times; N: under 40 times), and her parvovirus B19 antibody levels were not elevated on the 12th day following admission compared with the levels at the time of admission (0.35 vs. 0.35 times; N: under 0.8 times). The patient was diagnosed with influenza A (H1N1) infection.

After a 2-week period, the patient was discharged, with a hemoglobin level of 10.4 g/dL and no further evidence of hemolysis. One month later, she was asymptomatic.

Discussion

Although many reports emphasize that PCH is an unusual disease, in recent years, PCH has become recognized as a relatively frequent cause of childhood acute transient AIHA [1]. The reason why most likely relates to greater awareness of the disorder and more frequent use of the DLT [1]. We describe the first case of PCH with influenza A (H1N1) virus infection.

The patient had never received the influenza vaccine and was infected with influenza virus. Although the rapid antigen detection method for flu A and B was negative at the time of admission, her influenza A (H1N1) antibody levels were already elevated (over 10 times; N: under 10 times) at the time of admission. Nevertheless, the patient had not received the influenza vaccine, and only her influenza A (H1N1) antibody levels were elevated on the 12th day following admission compared with the levels at the time of admission (more than 10 vs. 20 times; N: less than 10 times). We diagnosed her with influenza A (H1N1) infection because other infections had been excluded.

Although PCH is considered to be self-limited and transient, deaths have been reported [1]. Because severe intravascular hemolysis is usual during the acute phase of the disease, the transfusion of RBCs may be necessary [1]. Physicians should pay attention to the progression of anemia in the acute phase of PCH. In the present case, no transfusion was required. Corticosteroids are often administered, although their effectiveness is difficult to evaluate because of the transient nature of the hemolysis [1]. In the present case, although the patient was treated with prednisolone (1 mg/kg/day) for a period of 3 days, this treatment might not have been necessary.

The patient had lived in Japan for 1 year and presented to our hospital in February of 2009. A novel influenza A (H1N1) virus strain was identified in Mexico in March of 2009 and rapidly spread worldwide [4]. In the current case, we concluded that the patient was not infected with a novel influenza A (H1N1) strain based on differences in the time of onset. Two previous reports described pandemic influenza A (H1N1) combined with AIHA. One case was that of a 22-month-old boy with Evans syndrome [5], and the other case was that of a 60-year-old woman with cold agglutinin syndrome [6]. However, PCH combined with influenza A (H1N1) virus infection (including the novel type) has not been previously reported.
A limitation of our study is that we did not examine the indirect DLT or the antibody titer for syphilis. Because we examined the direct DLT for the diagnosis of PCH, we might have examined the indirect DLT. Although the patient had no symptoms of syphilis, we should have examined the antibody titer for syphilis. We diagnosed her with influenza A (H1N1). However, the rapid antigen detection method for flu A and B was negative at the time of admission, and her influenza A (H1N1) antibody levels were slightly elevated on the 12th day following admission compared with the levels at the time of admission (more than 10 vs. 20 times; N: less than 10 times). We hypothesized that the patient’s antibodies were slightly elevated because she had never received the influenza vaccine and was infected with influenza virus.

In the case reported here, the patient was of Filipino decent and was living in Japan. There does not appear to be any particular racial consistency in the development of PCH [1]; however, the Japanese climate is colder than that of the Philippines. The patient’s immigration and exposure to a colder region than her home country may have contributed to the development of a new disease. Upon discharge, she returned to the Philippines. The recurrence of PCH has been reported [3, 7], including the recurrence of PCH in a boy following physical cooling for the treatment of fever [7]. We have asked the hospital in the Philippines for a follow-up.

In the future, through the evaluation of more cases with sufficient laboratory data and tests (including the DLT), a more complete classification should be possible. This classification can be applied to a study of the prognosis of this rare condition.

Conclusion

Influenza virus infection is a common disease. If physicians encounter children with hemolytic anemia and hemoglobinuria during an epidemic of influenza virus infection, these professionals need to consider the onset of PCH in the differential diagnosis and should examine the DLT for a diagnosis of PCH.

Consent

Written informed consent was obtained from the patient’s guardian for publication of this study and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations

PCH: paroxysmal cold hemoglobinuria; AIHA: autoimmune hemolytic anemia; DLT: Donath-Landsteiner test;

Competing interests

The authors have no competing interests.
Authors’ contributions

AK and HM treated the patient. The patient was followed up by HM. AK, HM, HM and SK were involved with drafting of the manuscript. All of the authors have read and approved the final manuscript.
References

同意書

岩手県立中央病院 佐々木 崇 雄

今後、私の児童が研究に参加することに対して、
小児科 加賀 元栄 医師からその研究の意義と目的ならびに具体的な方法
について十分な説明を受け、不明な点については質問し十分に医療スタッフと話し合
い、同意書に署名をいただきました。

研究に私の子どもが参加することに同意します。

平成21年3月18日

説明者（医師氏名）（署名） 小児科 加賀 元栄

新生児の氏名

新生児の親権者氏名（署名） Joanna Marie (こどもとの様柄 Metha)
Additional files provided with this submission:

Additional file 1: PCH BMC2 table.doc, 33K
http://www.biomedcentral.com/imedia/9970870721094173/supp1.doc