

Case study

Massive acute hemolysis in two siblings with glucose dehydrogenase deficiency and parvovirus B19 infection

ABSTRACT

Aims: A previous study reported hemolytic crisis in patients with erythron ~~erythro-~~enzymopathy. Here, we report two further cases of massive acute hemolysis with ~~methemoglobinemia~~ **methemoglobinemia** in two siblings with glucose dehydrogenase deficiency and parvovirus B19 (PAVB) infection.

Presentations of case: The first was his 8-year-old brother, who developed mild hemolysis with liver dysfunction and survived. The second patient was a 10-year-old boy, who developed liver and kidney failure and died. To elucidate the mechanisms through which PAVB can cause liver and kidney failure, we analyzed cytokines and virus burden.

Conclusion: Physicians should be aware that severe hemolysis may occur in patients with hematological abnormalities and PAVB infection.

Keywords: [parvovirus B19, acute hemolysis, erythroenzymopathy, methemoglobinemia, household infection]

1. INTRODUCTION

A previous study reported hemolytic crisis in patients with erythroenzymopathy. Here, we report two further cases of massive acute hemolysis with ~~methemoglobinemia~~ **methemoglobinemia** in two siblings with glucose dehydrogenase deficiency and parvovirus B19 (PAVB) infection. The first was his 8-year-old brother, who developed mild hemolysis with liver dysfunction and survived. The second patient was a 10-year-old boy, who developed liver and kidney failure and died. To elucidate the mechanisms through which PAVB can cause liver and kidney failure, we analyzed cytokines and virus burden.

2. PRESENTATION OF CASE

Case 1. An 8-year-old boy with glucose dehydrogenase deficiency (G6PD) presented with pyrexia and brown urine without rash. No oxygen supplementation was required, and only a mild increase in methemoglobin (2.9%; normal, <1.5%) was detected. A mild increase in both aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (146 U/l and 16 U/l, respectively) was observed, with no elevation of creatinine or blood urea nitrogen (BUN). On day 5 of admission, a rapid decrease in hemoglobin occurred (11.5 g/dl to 4.1 g/dl). Erythrocyte and maintenance fluid transfusion was initiated. He was discharged from hospital on day 12 without complications. Analysis of blood samples from day 7 on hospitalization revealed parvovirus B19 (PAVB)-specific IgM, IgG, and DNA. PAVB DNA genome level was 4.6×10^4 copies/ml, and a mild increase was observed in cytokines (neopterin, sTNFR1, sTNFR2) and tau protein (30.5 nmol/l, 1190 pg/ml, 8150 pg/ml, and 940 pg/ml, respectively)

Case 2. The 10-year-old male sibling of Case 1, who also had a known diagnosis of G6PD, had presented with pyrexia and brown urine without rash two days after Case 1 became ill. Pulse oximetry revealed desaturation that was unresponsive to oxygen supplementation. Blood analysis showed an increase in methemoglobin, AST, ALT, lactate dehydrogenase, creatinine and BUN (12.3%, 13670 U/l, 7890U/l, 10967IU/l, 7.19mg/dl and 128mg/dl respectively). He was therefore referred for specialist management of liver and kidney failure. On day 2 of admission, a rapid decrease in hemoglobin (10.6 g/dl to 5.9 g/dl) and reactive leukocytosis occurred. Despite hemodialysis and erythrocyte and maintenance fluid transfusion, he progress to anuria and death secondary to pulmonary congestion and hemorrhage occurred on day 6 of hospitalization. Analysis of blood samples from day 3 on admission revealed PAVB IgM and DNA. IgG was negative. PAVB DNA genome level was 5.3×10^8 copies/ml, and high levels of cytokines (neopterin, sTNFR1, sTNFR2) and tau protein were detected (1700 nmol/l, 19800 pg/ml, 93800 pg/ml, and 544 pg/ml, respectively) (Table).

Table 1 : Cytokines, tau protein, and PAVB virus load in Cases 1 and 2.

	Virus load*	IL-18**	IL-6**	sTNFR1**	sTNFR2**	Tau protein**	Neopterin***
Case 1.	4.6×10^4	700	4	1190	8150	940	30.5
Case 2.	5.3×10^8	2230	91	19800	93800	544	1700

*copies/ml, **pg/ml, ***nmol/l. IL; interleukin, TNF; Tumor Necrosis Factor

3. DISCUSSION

These cases illustrate that PAVB infection may be associated with massive acute hemolysis with methemoglobinemia. G6PD is a common erythrocyte enzymatic defect, which is generally asymptomatic. However,

oxidative stress may induce acute hemolytic crisis. (1) ~~Methemoglobinemia~~ **methemoglobinemia** can result from exposure to a variety of oxidants, many of which can also induce hemolytic crisis in G6PD patients. (2) The pathogenic link between liver and kidney failure and oxidative hemolysis in PAVB infection is unclear. (3) Although previous authors have analyzed cytokines in PAVB infection to elucidate autoimmune disease, chronic fatigue syndrome, and myocarditis, to our knowledge no prior report has investigated their role in hemolysis. (4, 5) In our patients, cytokines and viral load were highest in Case 2. Hypercytokinemia and massive viremia may have a profound effect on prognosis.

4. CONCLUSION

Physicians should be aware that severe hemolysis may occur in patients with hematological abnormalities and PAVB infection. Further studies of erythroenzymopathy patients are warranted to determine both the mechanisms through which PAVB causes liver and kidney failure and the existence of predisposing factors, as well as the incidence of this condition in this population.

8. ETHICAL APPROVAL (WHERE EVER APPLICABLE)

The study protocol was approved by the Institutional Review Board of the Japanese Red Cross Wakayama Medical Center (no. 581).

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

9. REFERENCES

1. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet*. 2008;371:64-74.
2. Jain AK, Sircar S, Jain M, Adkar S, Waghmare C, Chahwala F. Increased morbidity in acute viral hepatitis with glucose-6-phosphate dehydrogenase deficiency. *Indian J Gastroenterol*. 2013;32:133-134.
3. Chan TK, Todd D. Haemolysis complicating viral hepatitis in patients with glucose-6-phosphate dehydrogenase deficiency. *Br Med J*. 1975;1:131-133.
4. Naciute M, Mieliauskaite D, Rugiene R, et al. Parvovirus B19 infection modulates the levels of cytokines in the plasma of rheumatoid arthritis patients. *Cytokine*. 2017;96:41-48.
5. Page C, Francois C, Goeb V, Duverlie G. Human parvovirus B19 and autoimmune diseases. Review of the literature and pathophysiological hypotheses. *J Clin Virol*. 2015;72:69-74.