# POST-VACCINATION GIANT CELL HEPATITIS WITH AUTOIMMUNE HEMOLYTIC ANEMIA

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**Abbreviations key:**

| Abbreviation | Full term |
|---|---|
| GCH | Giant cell hepatitis |
| AIHA | Autoimmune hemolytic anemia |
| OPV | Oral Polio Vaccine |
| DPT | Diphtheria-Pertussis-Tatanus |
| MCV | Mean corpuscular volume |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| IVIG | Intravenous immunoglobulins |
| PCR | Polymerase chain reaction |
| HAV | Hepatitis A virus |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| CMV | Cytomegalovirus |
| EBV | Ebstein Barr virus |

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|---|---|
| RBCs | Red blood cells |
| MMF | Mycophenolate mofetil |
| COVID-19 | Corona virus disease-2019 |

**ABSTRACT**

Giant cell hepatitis (GCH) with autoimmune hemolytic anemia (AIHA) is a rare entity in children. GCH is commonly described in infants. Vaccination has been incriminated as a trigger of development of AIHA in infants and children. However, vaccination has not been reported, till the time of writing the manuscript, to trigger the combination of Giant cell hepatitis with autoimmune hemolytic anemia.

GCH with AIHA is usually fatal. Immunosuppressive treatment with conventional drugs offers some temporary response. We, herein, report a case of GCH with AIHA in a 4-month old male infant, following receipt of oral polio vaccine (OPV) and intramuscular diphtheria-tetanus-pertussis (DPT) vaccine. The patient was resistant to standard immunosuppressive combinations, and rescue therapy with Rituximab was used.

**Key words:** Giant cell hepatitis, autoimmune hemolytic anemia, vaccination, rituximab

## INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is an acute, self-limited childhood disease with good response to treatment. However, on very rare occasions, it is accompanied by giant cell hepatitis (GCH), which is progressive and often fatal **1, 2.** We, herein, report an infant with GCH and AIHA, following vaccination with oral polio vaccine (OPV) and intramuscular diphtheria-tetanus-pertussis (DPT) vaccine, who failed to respond initially to conventional immune therapy, but achieved complete remission after a trial of CD20 monoclonal antibody (rituximab).

## CASE REPORT

A four-month old infant was referred to Cairo University Children's hospital, Cairo, Egypt, on the 10$^{th}$ of October 2016 with acute onset of intense pallor, jaundice and dark-colored urine 3 days following his 4-month vaccination with OPV and DPT at the primary health center. The patient was fully conscious, had mild jaundice, the liver was felt 1 cm below the right costal margin, and there were no palpable abdominal masses or lymph nodes.

Laboratory investigations showed severe anemia (hemoglobin 5.4 gm/dl) with high mean corpuscular volume (MCV) of 112 fl, his reticulocyte index was 22% and direct anti-globulin test was positive. Total serum bilirubin was 2.1 mg/dl, with a direct fraction of 0.5 mg/dl, liver transaminases were mildly elevated (ALT: 125 IU/L and AST: 52 IU/L) while other liver functions were normal.

Blood samples were drawn from the patient for cross-matching but, all trials to get matched packed RBCs failed. Therapy using intravenous immunoglobulins (IVIG) failed as well. Then, pulse steroid therapy was initiated using intravenous methylprednisolone 30 mg/kg. Once the patient's hemoglobin stabilized without packed RBCs transfusion, steroids were tapered. Unfortunately, hemolysis recurred. Intravenous methylprednisolone was resumed with slower tapering schedule.

Along the course of the patient's illness, liver transaminases were continuously rising, exceeding 20 times the upper limit of normal (Fig. 1). Ischemic hepatitis was a very remote possibility. Serology and PCR results for HAV, HBV, HCV, CMV, EBV and HIV were negative. Thorough history taking excluded the recent use of hepatotoxic drugs. Autoantibodies tested negative.

Finally, a liver biopsy was performed and a diagnosis of GCH was made.

Remission of hemolysis could not be sustained with high dose steroids. Mycophenolate mofetil (MMF) in a dose of 600 mg/m$^2$/dose twice daily was added for 12 weeks without notable improvement (Fig. 2).

Finally, Rituximab was added to the treatment plan. The patient received one cycle in the form of 4 weekly doses (375 mg/m$^2$) in addition to steroids and MMF. Because reactivation of Hepatitis B virus may occur, we screened our patient for Hepatitis B infection before the first infusion. Sepsis screening was done. We aimed to ensure that our patient was sepsis-free before starting Rituximab. Rituximab resulted in remission of his AIHA with gradual improvement in liver transaminases.

Because the patient suffered complications from prolonged high dose steroids, steroids were tapered over a period of 3 months till they were discontinued completely. He was kept on his twice daily MMF doses for a whole year. Since May 2017 up to the time of writing this manuscript, the patient has been in full hematological remission, and normalization of his liver transaminases was achieved 4 months after therapy with Rituximab. He is attending the hematology outpatient clinic on monthly basis. With the emergence of the COVID-19 pandemic he has been followed by phone calls. Lately, gradual withdrawal of MMF is being done.

**DISCUSSION**

The combination of GCH with AIHA is considered a very rare distinct disorder that carries a poor prognosis. GCH is commonly described in infants **1, 2.** Vaccination has been incriminated as a trigger of development of AIHA in infants and children. However, according to our knowledge, this is the first case of combined GCH with AIHA to be reported following vaccination with OPV and DPT.

Miloh et al reported a case of GCH in a 3-month-old infant who previously presented with AIHA. The AIHA responded well to steroids therapy, however, the GCH was refractory to treatment. He was given Rituximab as a rescue therapy when his liver condition deteriorated. The medication was very well tolerated and the patient's condition remained fine without recurrence of AIHA or liver disease **3.**

In 2010, Baran et al described a similar condition in a 3 month-old-infant who presented with a skin rash diagnostic of varicella infection followed by an AIHA and evidence of hepatic disease. Acyclovir

was started in the active skin rash, IVIG was given to suppress the immune hemolysis. Methylprednisolone was started after resolution of varicella infection without notable response, and the patient's liver condition decompensated. Liver biopsy confirmed the diagnosis of GCH. Immune therapy was started without any improvement. Finally, Rituximab was given with only partial clinical and

biochemical response. On a follow-up visit, the patient presented with bacterial sepsis and died of septic shock **4.**

Paganelli et al described 4 cases of GCH with AIHA who were successfully treated with Rituximab. All patients suffered a severe course of the disease with poor control on standard and aggressive immunosuppressive medications. Finally, Rituximab was started in the 4 patients in a dose of 375 mg/ $m^2$ every week for 4 successive weeks. Although the initial cycle of Rituximab induced remission in all patients, 3 out of 4 patients required further additional cycles because of relapses. Patients have been followed up many years after their initial presentation, they were all alive with their native liver **5.**

In 2014, Bakula et al reported 5 cases of severe GCH with AIHA. First line therapy with steroids and AZA proved ineffective in all patients but one, who initially responded but suffered a relapse after 4 months, developed hemophagocytic lymphohistiocytosis and died 2 months following a liver cell transplantation. The remaining 4 patients achieved full remission after 4 to 6 doses of Rituximab **6.**

**In conclusion,** GCH with AIHA is a rare disorder that does not respond well to conventional immunosuppressive therapy. We, herein, report a case of GCH and AIHA following vaccination with OPV and DPT. The patient showed partial response to conventional immunosuppression, while full remission was achieved using Rituximab. We conclude that Rituximab should be considered for patients with GCH and AIHA who do not respond to conventional immunosuppression.

**DECLARATION OF CONFLICT OF INTEREST:**

No potential conflicts of interest were disclosed.

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All authors have contributed significantly in this work, and all authors are in agreement with the content of the manuscript.

Mai Abdel Salam: The clinical work & writing the manuscript.

Ahmad El-Hennawy: Examining the pathology of the liver biopsy and writing the final report.

Hanaa El-Karaksy: Directing the case work-up with possible differential diagnoses & final revision and editing of the manuscript.

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**FIGURE LEGANDS:**

**Figure 1:** Course of ALT (IU/L) and AST (IU/L) vs. treatment over time

**Figure 2:** Course of hemoglobin level in gm/dl and reticulocyte index % vs. treatment over time