

Watershed infarction during the first favism crisis in a Syrian child; A rare case report

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Case Report

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Abstract

Background: A watershed infarction is an ischemic event within the border zone regions of the brain. It can be associated with hematologic disorders including beta thalassemia and sickle cell disease. However, it has not been reported during a favism crisis.

G6PD deficiency is an X-linked recessive genetic disorder and one of the most prevalent enzyme deficiencies in humans, with a global prevalence of 4.9%. The most common triggers for hemolytic crises in G6PD deficiency are fava bean ingestion, infection and specific medications. We describe a rare case of a 3-year-old boy who developed a watershed infarction during his first favism crisis – an association has not previously reported.

Case Presentation: A 3-year-old male was admitted to our hospital with an acute hemolytic crisis (with a hemoglobin level of 3.3 g/dL) triggered by fava bean ingestion. After 6 hours of admission the patient developed neurological symptoms with normal vital signs and no hypotension. After several investigations, bilateral watershed infarction was confirmed by Magnetic Resonance Imaging. Fluid resuscitation and blood transfusion with intensive care were sufficient to improve the neurological symptoms and elevate hemoglobin level above 10 g/dL. The patient was discharged after 9 days of admission with full recovery.

Conclusion: According to our acknowledgement, this is the first reported case of watershed infarction triggered by favism, thus we aim to highlight the importance of accurate and frequent neurological examination for hemolytic crises patients to prevent adverse complications of delayed treatment.

Background

A watershed infarct refers to an ischemic event occurring within the border zone regions,^[1] and is characterized by distinctive features on brain imaging.^[2] Etiological factors for watershed infarction include: cardiac decompensation, vasculopathies, blood pressure dysregulation (both hypotension and hypertension), dyslipidemia, carotid stenosis, and hematologic disorders.^[2] Watershed infarction in patients with β -thalassemia,^[1] and sickle cell disease^[3] represent a rarely documented clinical entity. A causal association between this type of infarction and episodes of hypotension has been confirmed.^[2]

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is recognized as one of the most prevalent human enzyme deficiency disorders worldwide. Current epidemiological data indicate an overall global prevalence of approximately 4.9%.^[4] The highest frequencies of this condition are observed in specific regions, including the African continent, Asia, Latin America, and the Mediterranean basin.^[4, 5] It is an X-linked recessive genetic disorder; therefore, hemizygous males are more susceptible to severe clinical complications.^[5]

When exogenous triggers induce elevated oxidative stress in erythrocytes, a hemolytic crisis ensues, manifesting as acute hemolytic anemia.^[6] The primary triggers for hemolysis include a specific set of contraindicated medications, in addition to infections and the ingestion of fava beans, which are among the most common causative agents.^[5]

The onset of symptoms is not invariably concomitant with the initial exposure to fava beans, and the severity of the symptoms can be attributed to the disproportionate ratio between the volume of beans consumed and the patient's body mass.^[6]

The clinical presentation consistently demonstrates an underlying acute hemolytic anemia, constituting a pathognomonic feature of favism. Laboratory analysis is characterized by evident anemia.^[6]

The clinical spectrum encompasses specific, nonspecific, and rare manifestations. Pathognomonic symptoms of acute favism include jaundice secondary to hyperbilirubinemia from erythrocyte depletion, urine discoloration, tachycardia, and pallor. Nonspecific symptoms comprise abdominal pain, malaise, vomiting, nausea, and dizziness.^[6] The diagnosis of G6PD deficiency is confirmed through genetic testing.^[5] The therapeutic interventions consist of hydration with normal saline solution and urgent blood transfusion (packed red blood cells RBCs). Prevention is achieved through strict trigger avoidance and the provision of genetic counseling for families.^[5] In this article, we present the case of a 3-year-old male who developed a watershed infarction during his first favism crisis, which, to the best of our knowledge, has not been previously reported.

Case presentation

A 3-year-old male presented to the emergency department with sudden-onset jaundice, pallor, dark urine, fever, and fatigue, which have been started one day prior, following his first consumption of raw fava beans two days earlier. Family history was significant for favism in his mother and maternal uncle.

On examination, he was lethargic but responsive, with marked pallor and jaundice. Vital signs showed tachycardia (HR 160 b/m), tachypnea with hypoxia (oxygen saturation 88% improving with oxygen therapy), and mild hypotension (105/48 mmHg). Cardiac examination revealed a systolic murmur, and the radial pulse was of medium volume bilaterally. Abdominal and neurological exams on admission were unremarkable.

Laboratory findings confirmed severe hemolytic anemia, with a hemoglobin level of 3.3 g/dL, elevated reticulocytes (12%), and a total bilirubin of 7.5 mg/dL (primarily indirect 6 mg/dL). Urinalysis was positive for urobilinogen and showed heavy hemoglobinuria (+++). Blood urea nitrogen was elevated at 82 mg/dL, while serum creatinine, platelet count, blood glucose, prothrombin time (PT), and partial thromboplastin time (PTT) were within normal limits. Peripheral blood smear showed anisopoikilocytosis, schistocytes (helmet cells), bite cells, and nucleated RBCs. The patient received a bolus of normal saline and two doses of packed RBCs transfusion of 15 mL/kg per dose.

Six hours post-admission, the patient developed acute neurological deterioration featuring agitation, confusion, non-purposeful involuntary movements, orofacial dyskinesia (lip-smacking), and slowed speech. The Glasgow Coma Score (GCS) was 10/15.

Muscle strength was slightly reduced in the upper limbs, graded 3/5, and was severely weak (0/5) in the lower limbs.

Vital signs were normal, with a blood pressure of 102/53 mmHg. Blood glucose and serum electrolytes were within normal limits. Brain Computed Tomography (CT) scan was unremarkable.

Electroencephalography (EEG) showed background slowing without epileptiform activity. Cerebral spinal fluid (CSF) analysis was normal. Magnetic Resonance Imaging (MRI) with contrast revealed acute, bilateral, borderline zone (watershed) ischemic infarctions (Fig. 1), and Magnetic Resonance Angiography (MRA) revealed no vascular occlusion.

With intensive supportive care, including hemodynamic monitoring, maintaining hemoglobin levels above 10 g/dL, and keeping electrolyte values within the normal range, neurological improvement began within 72 hours. The patient regained full consciousness (GCS 15), with motor strength improved to a full 5/5 in the upper limbs and 4/5 in the lower limbs, and ambulation with a wide-based gait. Speech became clear and complete neurological recovery occurred within eight days, confirmed by normal examination and follow-up MRI with contrast, showing an improvement in the previous ischemic findings. The patient was discharged in good condition with complete recovery after 9 days of admission, showing a positive response to treatment. After two months of follow-up, with adherence to the G6PD deficiency diet, no complications, neurological symptoms, or new episodes of hemolysis were observed. The diagnosis was confirmed by assaying G6PD in the blood 3 months after the hemolytic crisis, which measured 0.51 U/g Hb (normal range 5-20.5).

Discussion

Watershed infarction resulting from hemolytic anemia was first reported by Dieter et al. in 1976.^[2] Since then, it has been frequently reported in the context of hemolytic disorders.^[1, 7] However, none of these cases was attributed to favism. Ischemic stroke has been studied and reported in several studies in association with hematologic diseases.^[3, 4, 8] Moreover, none of them was attributed to favism. There is limited information in the literature regarding the association between G6PD deficiency and cerebral infarction. Only a few studies have investigated how the coexistence of G6PD deficiency and sickle cell anemia affects the prevalence and clinical outcomes of stroke,^[8] however, their results were contradictory. Two studies have suggested an association between G6PD deficiency and unfavorable outcomes in stroke patients.^[4, 9] These findings were observed through screening for G6PD deficiency in stroke patients, rather than during ischemic stroke episodes triggered by favism. In this article, we report an extremely rare case of watershed infarction triggered by favism.

Some authors have studied the outcomes and risk factors of stroke in adults with hemolytic anemia,^[1, 4, 9] with elderly male patients considered a high-risk group.^[10] Other studies have demonstrated this relationship between stroke and hemolytic anemia in children.^[2, 3, 8, 9] Furthermore, hemolytic crises secondary to favism have demonstrated greater clinical severity in pediatric patients, and this was potentially attributable to their lower body mass.^[6] However, we present a case of a 3-year-old boy recovered from a severe favism crisis with no remarkable complications following appropriate treatment. The symptoms of watershed infarction appeared at hemoglobin level of 3.4 g/dL in a 25-year-old female,^[1] while neurological symptoms without any evidence of infarction or stroke appeared at hemoglobin levels 3 and 8.4 g/dL.^[6] The most common cause of watershed infarction in hemolytic anemia patients is hypotension,^[1, 2] although it occurs in cases of severe hemolytic crises due to severe anemia without hypotension,^[1] which coexisted with chronic intracranial carotid occlusion proved by MRA. However, we appreciate that severe anemia was the cause of the watershed infarction that occurred in our patient because the hemodynamics were within the normal limits at the time of symptom onset.

The diagnosis of G6PD deficiency is dependent on clinical presentations, laboratory findings, and family history.^[5, 6] Definitive diagnosis is performed through genetic testing,^[5, 8] or by measuring G6PD level, a method frequently employed in clinical practice.^[4, 6, 8] MRI is the diagnostic test of choice for watershed infarction,^[1, 7, 9] with hyper signal intensity^[1] on Flair and T2-weighted MRI.^[7, 10] MRA showed chronic occlusion of the left internal carotid artery in one reported case.^[1] EEG was conducted in one case and showed diffuse slow waves.^[2] The same author performed a lumbar puncture, and it was unremarkable. In this article, the diagnosis was based on clinical presentations and family history, and was confirmed by measuring G6PD blood level 3 months after the hemolytic crisis which found to be 0.5 U/g Hb. However, genetic testing is unavailable in our country. CT scan, lumbar puncture and MRA were performed in our case at the onset of neurological symptoms and were normal, EEG showed mild background slowing, and the diagnosis of watershed infarction was made by MRI which revealed regions of hyperintensity in the left and right watershed area on T2, Flair and DWI (Fig. 1). Cerebral stroke in hemolytic anemia tends to be asymptomatic,^[3] but it may present with neurological symptoms such as hemiparesis, headache, seizures,^[1, 2] aphasia and coma.^[2] The most optimal treatment of stroke in hemolytic patients is blood transfusion^[1] and fluid resuscitation.^[11] With the highlight of the importance of accurate blood amounts, particularly in children, to avoid repeated blood transfusions.^[11] In the presented case, the patient has undergone two episodes of packed RBCs of 15 mL/kg per dose. Most patients who have undergone appropriate treatment and follow-up revealed no complications during different periods of follow-up.^[1, 5] The follow-up period for stroke due to hemolytic disorders ranged from 2 weeks^[2] to several years,^[3] some of these follow-up periods revealed complications, including cortical blindness^[2] and, in some cases, death,^[3] while others did not report any complications. However, our patient was discharged after full recovery and followed up for three months without any complications or neurological dysfunctions.

Conclusion

To the best of our knowledge, this is the first reported case of watershed infarction triggered by favism. We emphasize the importance of accurate and frequent neurological examination of patients experiencing hemolytic crises until discharge, as well as the need for appropriate and early treatment to prevent significant adverse complications.

Abbreviations

G6PD

Glucose-6-phosphate dehydrogenase

RBCs

Red Blood Cells

PT

Prothrombin Time

PTT

Partial Thromboplastin Time

GCS

Glasgow Coma Score

CT

Computed Tomography

EEG

Electroencephalography

CSF

Cerebral Spinal Fluid

MRI

Magnetic Resonance Imaging

MRA

Magnetic Resonance Angiography

Declarations

Ethical approval and consent to participate

Not required for these case report.

Consent for publication

Written informed consent was obtained from the patient's parents for publishing these case report and the accompanying image. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

Competing interests

The authors declare that they have no conflicts of interest.

Guarantor

Mohammad Samih Khallouf and Bassam Nader are the guarantors of this work.

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Author Contribution

Sanaa Alakari: patient care, drafting, and the approval of the final manuscript
Nawar Mansour: design of the study, data collection, drafting, critical revision, corresponding and the approval of the final manuscript
Enas Akash: patient care, drafting, and the approval of the final manuscript
Ahlam Khosrouf: patient care, drafting, and the approval of the final manuscript
Bassam Nader: Co-supervisor, patient care, critical revision, and the approval of the final manuscript
Mohammed Samih Khallouf: The main Supervisor, patient care, critical revision, and the approval of the final manuscript

Acknowledgment

Not applicable.

Data Availability

All data of the patient generated during this study are included in this published article and its supplementary information files.

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Figures

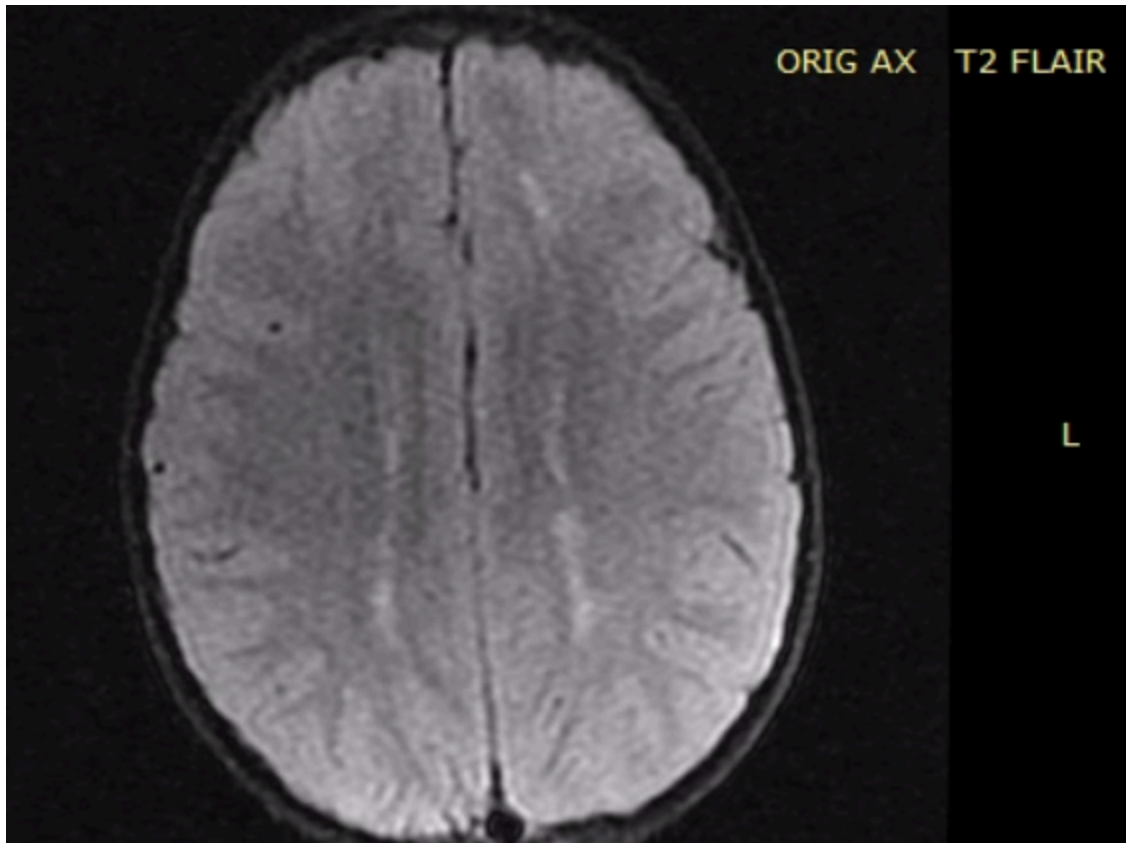


Figure 1

An axial T2 FLAIR MRI image, revealing an acute bilateral ischemic infarction in the watershed areas.