Case Report

The Hypoxia Trap: Worsening Sickle Cell Disease in the Setting of Tetralogy of Fallot

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Keywords

Tetralogy of Fallot, Sickle Cell Disease, Pediatric Stroke, Thrombosis, Exchange Transfusion, Cyanotic Congenital Heart Disease

Abstract

Background: Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease and predisposes affected children to thrombotic complications due to chronic hypoxia and polycythemia. Sickle cell disease (SCD) further increases the risk of vaso-occlusion through erythrocyte sickling and endothelial dysfunction. The coexistence of TOF and SCD is rare and creates complex diagnostic and therapeutic challenges with significant risk of catastrophic neurological events.

Case presentation: We report a 14-month-old female with known TOF who presented with acute left-sided hemiparesis, fever, and seizures. Brain computed tomography with angiography revealed extensive bilateral ischemic infarctions with complete thrombosis of both middle cerebral arteries and occlusion of the right internal carotid artery. Haematological evaluation confirmed previously undiagnosed SCD with an HbS fraction of 60.2%. Despite intensive therapy including oxygen, intravenous hydration, hydroxyurea, antiepileptic drugs, and exchange transfusion that reduced HbS to 28.9%, the child developed progressive encephalopathy and died. Chronic hypoxia from TOF combined with SCD-related sickling likely precipitated catastrophic cerebrovascular thrombosis.

Conclusion: This case highlights the synergistic thrombotic risks of TOF and SCD, emphasising the critical need for routine hemoglobinopathy screening in children with cyanotic heart disease, especially in high-prevalence regions. Early diagnosis, proactive use of vasopressors to optimise oxygenation, and multidisciplinary management are essential to improve outcomes. Aggressive preventive interventions are essential to reduce morbidity and mortality in patients presenting with these rare coexisting pathologies. Enhanced screening awareness, stroke-preventing strategies and timely surgical intervention for TOF could improve prognosis in this rare, high-risk dual pathology.

Introduction

Tetralogy of Fallot is the most frequent cyanotic congenital heart disease encountered in pediatric practice and comprises four cardinal anatomical abnormalities: ventricular septal defect, overriding aorta, right ventricular hypertrophy, and right ventricular outflow tract obstruction [1]. Chronic cyanosis, recurrent hypoxic spells, and compensatory polycythemia predispose affected children to thromboembolic complications, including cerebrovascular accidents [1].

Sickle cell disease is a common hereditary hemoglobinopathy in geographically distributed regions such as India and sub-Saharan Africa and is characterized by recurrent erythrocyte sickling, hemolysis, and microvascular occlusion [8,11]. Cerebrovascular disease is a major cause of morbidity and mortality in children with SCD, arising from hypoxia-driven endothelial dysfunction and thrombosis [8,11].

The coexistence of TOF and SCD is exceptionally rare but poses a unique clinical challenge due to synergistic amplification of hypoxia-induced sickling and hyperviscosity-related thrombosis [2,3]. Only a limited number of reports describe this dual pathology, and standardized management guidelines are lacking [3,14].

We report a 14-month-old child with TOF who presented with acute massive bilateral cerebral infarction and was subsequently diagnosed with previously unrecognized SCD. This case underscores the importance of early identification of coexisting thrombotic risk factors, routine hemoglobinopathy screening in cyanotic congenital heart disease, and coordinated multidisciplinary management, particularly in resource-limited settings [3,14].

Case description

A 14-month-old female child was referred to a Tertiary care center in Central India with complaints of acute-onset, non-progressive left-sided hemiparesis for three days. This neurological deficit was associated by high-grade fever, non-projectile vomiting, and an episode of generalized tonic-clonic seizures two days before admission. There were no antecedent trauma, urinary retention, or other complaints suggestive of cranial nerve involvement.

Her history was notable for recurrent respiratory tract infections and bluish discolouration of the body and extremities, leading to a diagnosis of Tetralogy of Fallot (TOF) with an associated atrial septal defect (ASD) at theage of 6 months. The child had been started on prophylactic propranolol (1 mg/kg/day), and surgical intervention was planned. Birth and developmental histories were unremarkable, and family history revealed one spontaneous abortion without further significance.

Upon reviewing investigations from the previous hospital, cranial computed tomography (CT) revealed confluent hypodense areas with loss of grey-white differentiation in the right frontoparietal-temporal region, along with a midline shift of 6 mm to the left, which is overall suggestive of acute infarction. Echocardiography demonstrated a significant subaortic ventricular septal defect (VSD) with 50% override, bidirectional shunt, infundibular pulmonary stenosis, and an ostium secundum-type ASD measuring 6 mm.

On admission, the child was hemodynamically stable, with a regular heart rate of 115 beats per minute, a respiratory rate of 35 breaths per minute, blood pressure of 100/60 mmhg (within the 90th–95th percentile for age), and an oxygen saturation of 77% on room air. Physical examination revealed pallor, cyanosis, and a grade 4 systolic ejection murmur at the left parasternal border. Neurological assessment showed a Glasgow Coma Scale (GCS) score of 12/15 (E4V3M5), normal cranial nerve function, left-sided hypotonia, grade 2/5 motor power in the left upper and lower limbs, areflexia, and absent left plantar response. Sensory examination indicated loss of pain, touch, and temperature sensation on the left side. No meningeal signs were present. Abdominal examination showed the presence of firm, non-tender splenomegaly (4 cm) along with hepatomegaly (3 cm).

The patient was admitted to the pediatric intensive care unit and initiated on intravenous fluids (100 ml/kg/day normal saline), supplemental oxygen (3 L/min via nasal cannula), decongestive therapy (hypertonic saline), and anti-seizure medication (levetiracetam 20 mg/kg loading dose, followed by 10 mg/kg twice daily). Given the early presentation of stroke in a patient with TOF, an evaluation for thrombophilia was initiated. Complete blood count showed hemoglobin of 12.5 g/dl, haematocrit of 38%, and reticulocyte count of 6%. Peripheral smear revealed sickled erythrocytes, confirmed by a positive sickling test. Biochemical parameters, coagulation profile, and homocysteine levels were normal. High-performance liquid chromatography (HPLC) confirmed the sickle cell disease, with an HbS fraction of 60.2% (Table 1).

Table 1: Baseline clinical and laboratory investigations at presentation.

Parameter	Baseline Result
HbS	60.2%
HbF	24.6%
HbA0	4.1%
HbA2	1.0%
Sickling test	Positive
Hemoglobin	11.1 g/dl
RBC count	4.46 million/µl

Parameter	Baseline Result
MCV	83.4 fl
MCH	24.9 pg
RDW	31.8%
WBC count	17.0 ×10³/µl
Platelet count	163 ×10³/µl
Reticulocyte count	6.7%
Peripheral Blood Smear	Sickle cells, fragmented RBCs, tear-drop cells, nRBCs
CRP	27.1 mg/L
Sodium	152.9 mmol/L
Potassium	5.41 mmol/L
Creatinine	0.48 mg/dl
Homocysteine	9.16 µmol/L

Initial hematological and biochemical parameters at admission demonstrating elevated HbS fraction, positive sickling test, reticulocytosis, and inflammatory markers, with peripheral smear showing sickled and fragmented erythrocytes consistent with sickle cell disease.

Parental HPLC screening revealed sickle cell trait in both parents. Hydroxyurea (15 mg/kg/day) was started to reduce sickling. Given the high HbS fraction and for secondary stroke prevention, Partial exchange transfusion was performed (around 300ml) under strict asepsis protocol. Post-transfusion HPLC showed an HbS fraction of 28.9% (Table 2).

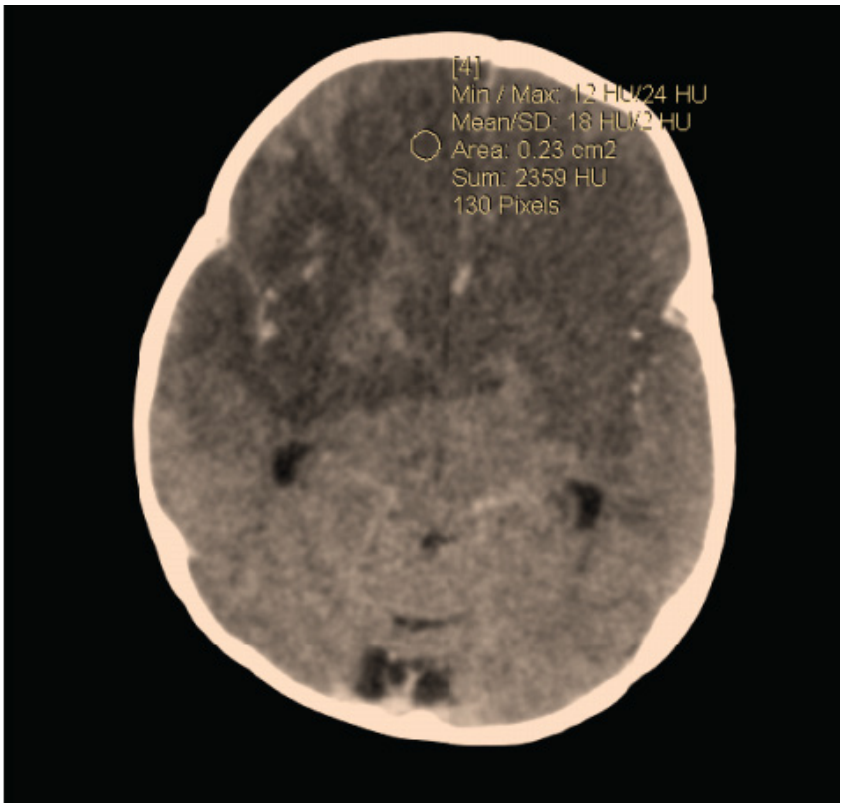
Table 2: Changes in hemoglobin fractions on high-performance liquid chromatography before and after exchange transfusion.

Hemoglobin Fraction	Pre-exchange HPLC (%)	Post-exchange HPLC (%)
Hbs	60.2	28.9
Hbf	24.6	12.8
Hba0	4.1	46.6
Hba2	1.0	1.9

Comparison of hemoglobin fractions demonstrating a marked reduction in HbS from 60.2% to 28.9% following exchange transfusion, with a corresponding increase in HbA0, indicating effective replacement of sickled erythrocytes and improved hemoglobin profile.

However, within hours, the patient developed intractable seizures, requiring escalation of anti-seizure therapy (midazolam infusion 0.1 mg/kg/hour). She progressed to global hypotonia and encephalopathy (GCS 7/15). A Repeat CT head and carotid angiography were performed, which demonstrated a large, relatively defined wedge-shaped hypodense area with loss of grey-white matter differentiation in the bilateral MCA and ACA territory regions, involving the bilateral frontoparietal lobes, basalganglia, and anterior limbs of the internal capsules. Hyperdense bilateral MCA vessels and bilateral A2 segments of the ACA were visualized, consistent with acute-subacute infarction. There was partial effacement of the left lateral ventricle due to mass effect. The angiography revealed complete long-segment non-visualization of the right internal carotid artery (ICA) from its origin, with the absence of the right middle cerebral artery (MCA) and only faint opacification of the A1 segment of the right anterior cerebral artery (ACA), indicating thrombosis. There was also complete non-opacification of the left MCA from its origin, consistent with thrombosis. Other supra-aortic branches, vertebral and basilar arteries, were unremarkable, and the venous sinuses appeared normal in calibre and opacification (Figure 1).

Figure 1: Neuroimaging demonstrating extensive bilateral large-vessel ischemic stroke.



Axial contrast-enhanced computed tomography (CECT) of the brain shows bilateral frontoparietal hypodense infarcts with loss of gray–white matter differentiation involving the middle cerebral artery (MCA) and anterior cerebral artery (ACA) territories. CT angiography reveals long-segment non-visualisation of the right internal carotid artery and bilateral MCAs, consistent with acute large-vessel thrombotic ischemic stroke.

Despite aggressive supportive care, including mechanical ventilation and inotropic support, the patient succumbed to her illness on day 5 of admission. Resource constraints, including limited access to real-time neurological monitoring, bedside palliative shunt expertise, likely contributed to the challenges in managing post-transfusion complications and delayed TOF correction. This case highlights the complex interplay and synergistic and compounding effects of hypoxia due to dual TOF and SCD.

Informed consent for the publication of this case report was obtained from the patient's parents.

Discussion

The unusual co-occurrence of TOF and SCD in a 14-month-old child poses a clinical challenge due to the synergistic thrombotic risks of these conditions [2,3]. TOF results in chronic hypoxia (spo2 77% in our case) and secondary polycythemia (hematocrit 38%), ultimately increasing blood viscosity and predisposing to thrombosis [1,3].

SCD increases this risk through hypoxia-induced erythrocyte sickling, hemolysis, and microvascular occlusion, as seen in the patient's high HbS (60.2%) [8,11]. The intricate interaction of these disorders produced a vicious cycle of hypoxia-inducedsickling, which led to a devastating neurological injury that included bilateral middle cerebral artery thrombosis and a large-scale cerebral infarction [9,12].

The delayed diagnosis of SCD, despite a known TOF diagnosis at 6 months, highlights an important gap in hemoglobinopathy screening practices [3]. In a high-prevalence country like India, routine hemoglobinopathy screening at CCHD diagnosis is essential to detect SCD early [11,14]. Had SCD been detected earlier in this case, preventive interventions such as hydroxyurea, folate supplementation, or pneumococcal vaccination could have reduced the risk of sickling and vaso-occlusive crisis [10,13].

Although the patient's haematocrit is elevated, it indicates that polycythaemia exacerbated hyperviscosity, which was not measured during previous treatment [1]. In individuals with TOF, routine haematocrit and oxygen saturation monitoring may help direct prompt measures to reduce thrombotic risk [4].

The proactive use of vasopressors to maximise oxygenation and minimise sickling is a novel therapeutic approach that has been suggested in this instance. When cyanotic episodes occur in TOF, vasopressors such as phenylephrine are used to raise systemic vascular resistance (SVR), which lessens right-to-left shunt and increases pulmonary blood flow [3,4]. Chronic hypoxia probably caused sickling in this patient, which led to cerebral thrombosis [9]. Proactive vasopressor therapy may have improved systemic oxygenation, reduced sickling, and promoted left-to-right shunting through the VSD by increasing SVR, even outside of acute episodes [5]. Although there is evidence to support the use of vasopressors in the acute management of TOF [3,4], their wider application in TOF-SCD patients to avoid hypoxia-driven consequences has not been investigated. Risks

including elevatedcardiac afterload need to be considered, and pilot studies are required to determine treatment effectiveness [5]. Exchange transfusion helped lower the post-surgical HbS to 28.9%, which is consistent with recommendations for preventing subsequent stroke [6]. However, post-procedural seizures suggest complications, such as hemodynamic shifts or inadequate neurological monitoring, because of the limited availability of real-time EEG [12]. Standardised protocols for exchange transfusion in pediatric SCD-CCHD patients, including accurate volume calculations, continuous monitoring, and pre-procedural stabilisation, could reduce such risks [14]. Limited availability or a lack of patient awareness may be the cause of delays in TOF surgical correction, underscoring the need for robust awareness campaigns and effective capacity building [7]. An earlier approach, such as BT shunt placement or even complete repair, may have improved outcomes [7].

Review of the limited available literature on the coexistence of tetralogy of Fallot and sickle cell disease demonstrates a consistently high burden of morbidity related to thrombotic and neurological complications. Iannucci et al. reported long-term outcomes in five children with sickle cell disease and cyanotic congenital heart disease, including tetralogy of Fallot [2]. They observed frequent Vaso-occlusive events, cerebrovascular complications, and the need for intensive multidisciplinary care. Unlike the patients described in this series, the undiagnosed sickle cell disease in our patient, together with delayed surgical correction of tetralogy of Fallot, likely contributed to the markedly adverse outcome, reinforcing the importance of early evaluation and timely surgical intervention in such high-risk children [7].

To improve outcomes, we propose: (1) Mandatory Screening: CCHD cases should have HPLC screening for hemoglobinopathies done at diagnosis in high-prevalence areas [11,14]. (2) Timely Surgical Correction - Focus on performing early TOF repair to alleviate chronic hypoxia and polycythemia, which could lower the chances of sickling crises [7]. (3) Standardised Protocols: Develop universal guidelines for exchange transfusion and anti-seizure management in SCD-CCHD patients [6,14]. (4) Vasopressor Research: To evaluate proactive vasopressor use in TOF-SCD patients to optimise oxygenation [5]. (5) Public Health Measures: Promote awareness of SCD and genetic counselling in CCHD clinics [13,14].

Conclusion

This case demonstrates the disastrous combination of TOF and SCD, which is fuelled by thrombosis and sickling brought on by hypoxia in a 14-month-old girl. Particularly in high-prevalence areas like India, this example emphasises the vital necessity of frequent hemoglobinopathy screening in children with cyanotic congenital heart disease. Thrombotic risks could be reduced by proactive use of vasopressors, optimised exchange transfusion protocols, early TOF correction, and routine hemoglobinopathy screening. To improve results, public health activities and customised practices are needed in settings with limited resources. Consensus recommendations for this uncommon dualdisease should be established, and the efficacy of proactive vasopressor use should be validated in future research.

Author's Disclosures

Declaration of Conflict of Interests

The authors declare that there are **no conflicts of interest** regarding the publication of this manuscript.

Ethical Approval

This study was conducted in accordance with the ethical principles for medical research involving human subjects as outlined in the **Declaration of Helsinki**. Ethical approval for the publication of this case report was obtained from the Institutional Ethics Committee. Written informed consent for publication was obtained from the patient's parents/legal guardians.

Credit Author Statement

All authors contributed equally to the writing, development, and finalization of the case report.. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Funding Statement

This research received **no specific grant** from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability Statement

All data supporting the findings of this study are included within the article. Additional clinical details are available from the corresponding author upon reasonable request, subject to institutional and ethical considerations.

Acknowledgements

The authors thank the patient's family for their cooperation and consent for publication of this case report.

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