

# Epileptic Seizure, Postictal Hemiparesis, and Hyperleukocytosis

Global Pediatric Health  
Volume 3: 1–5  
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DOI: 10.1177/2333794X16681934  
gph.sagepub.com



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## Abstract

**Introduction:** Acute ischemic stroke (AIS) is a rare event in infancy. Besides vasculopathy, thrombophilia, or cardiac disorders, cancer and chemotherapy are known predisposing factors for AIS. Leukemia can be associated with different abnormal coagulation parameters, but severe bleeding or thrombosis occurs rarely. **Clinical Course:** We report the case of a 2-year-old boy who was presented to our emergency ward after a prolonged seizure with right sided postictal hemiparesis. Cranial computed tomography scan revealed a large infarction and edema due to thrombosis of the left carotid artery, the middle cerebral artery, and the anterior cerebral artery. Laboratory workup showed 196 g/L leukocytes with 75% myeloid blast cells. Immediate exchange transfusion, hydration, and chemotherapy with cytarabine were started. During the hospital course intracranial pressure increased and the patient developed a unilateral dilated pupil unresponsive to light. Cranial computed tomography scan revealed a new infarction in the right middle cerebral artery territory. Refractory increased intracranial pressure and brain stem herniation developed, and the child died 3 days after admission to hospital. **Conclusion:** Seizures with postictal hemiparesis due to cerebral infarction can be a rare manifestation of acute myeloid leukemia. Leukocytosis and cancer-induced coagulopathy are main reasons for thrombosis and/or hemorrhage. High leukocyte counts need immediate interventions with hydration, careful chemotherapy, and perhaps exchange transfusion or leukapheresis. In the presence of thrombosis, anticoagulation must be discussed despite the risk of bleeding due to hyperfibrinolysis and low platelet counts. Mortality may be reduced by awareness of this rare presentation of leukemia and prompt institution of leucoreductive treatment.

## Keywords

pediatric stroke, hyperleukocytosis, epileptic seizure, acute myeloid leukemia, emergency medicine, hematology/oncology

Received November 8, 2016. Accepted for publication November 8, 2016.

## Introduction

Acute ischemic stroke (AIS) in children is a rare event with an incidence of 1 to 8 per 100 000 children per year. Leading symptoms are hemiparesis, facial palsy, and dysphasia. Seizures occur in the first hours in up to 50%. Besides vasculopathy, thrombophilia or cardiac disorders, cancer, and chemotherapy are known predisposing factors for AIS.<sup>1,2</sup> While solid tumors primarily are associated with venous thromboembolism, malignant hematologic disorders like acute leukemia cause hemorrhagic and thrombotic complications in both venous and arterial vessels.<sup>3</sup> In childhood, thrombotic complications due to leukemia are rare.<sup>4</sup>

## Clinical Course

We report the case of a 2-year-old boy who presented to our emergency department after a generalized tonic-clonic afebrile seizure with postictal impaired consciousness and right sided hemiparesis. Since 3 days he suffered from recurrent vomiting, diarrhea, and weakness. Immediate

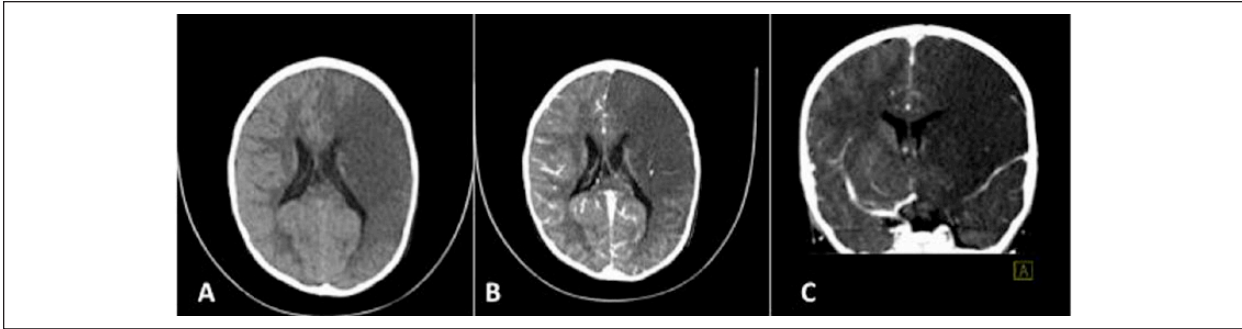
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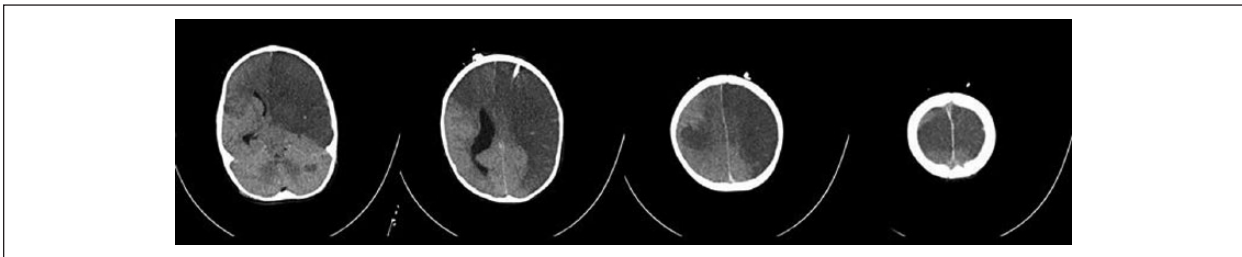
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**Figure 1.** Cranial CT scan with (A) and without contrast (B) at admission to hospital shows a large left-sided infarction and midline shift due to complete occlusion of the left carotid artery, ACA, and MCA.



**Figure 2.** Nonenhanced cranial CT scan 24 hours after admission shows a new large right-sided infarction.

cranial computed tomography (CT) scan and CT angiography revealed a large left-sided ischemic infarction with edema and midline shift due to thrombotic occlusion of the carotid artery, the middle cerebral artery (MCA), and the anterior cerebral artery (ACA). Laboratory workup showed 196 g/L leukocytes with 72% blast cells, 6.3 g/dL hemoglobin, 84 g/L platelets, and a lactate dehydrogenase of 3599 U/L. Acute myeloid leukemia (AML) M5 was diagnosed morphologically. Coagulation testing showed a beginning disseminated intravascular coagulopathy (DIC) with low thromboplastin time (40%; normal value = 70% to 120%), normal activated prothrombin time (32 seconds; normal value = 25-42 seconds), low fibrinogen levels (124 mg/dL; normal value = 160-400 mg/dL), and high D-dimers (63.6  $\mu$ g/mL; normal value = <0.6  $\mu$ g/mL). Due to high leukocyte count, immediate hydration with 3 L/m<sup>2</sup> body surface area and exchange transfusion were started. Thrombolysis, interventional thrombectomy, and anticoagulation were discussed within our interdisciplinary pediatric stroke team but dismissed based on the high bleeding risk and probable low efficiency in leukocyte thrombi. After 8 hours of leukapheresis and hydration, the leukocyte count decreased to 60 g/L, and chemotherapy with low-dose cytarabine was started.

Neuromonitoring was performed including intracranial pressure measurement. Despite swelling of the left hemisphere, maximum intracranial pressure in the first

2 days was 18 mm Hg. Standard care with 30° head of bed elevation, normotonia, normoglycemia, normothermia, normonatremia, sedation, and muscle relaxation was performed. Twenty-four hours later leukocytes rose again and the patient now showed a dilated left pupil unreactive to light. Repeat cranial CT scan revealed a second AIS on the right side but no new vessel occlusion (see Figures 1 and 2). On day 3 both pupils were dilated and unresponsive to light due to brain stem herniation, intracranial pressure increased to maximum 59 mm Hg. Decompressive craniectomy had been discussed and dismissed in our pediatric stroke team as the long-term prognosis of a large bi-hemispheric infarction in a patient with malignant disease was regarded as dismal. Due to poor prognosis no further therapy was initiated and the patient died a few hours later.

Over the next several days further coagulation test results were received and showed a low protein C (26%; normal value = 70% to 140%) and S (45%; normal value = 70% to 140%) activity, factor VIII levels were high (172%; normal value = 50% to 150%), and genetic testing revealed a heterozygous MTHFR polymorphism (C677T). Leukemic blasts expressed CD33, CD15, HLADR, CD56, CD36, CD4, moAB7.1, CD38, CD99, and CLL1 and a mutation in the FTL3 gene in codon 835 was found.

## Diagnosis

Fatal ischemic stroke in acute myeloid leukemia presenting with epileptic seizure and postictal hemiparesis.

## Discussion

Pediatric AIS is a rare but potentially life-threatening event in childhood. The underlying causes can be multifactorial. Due to a lot of stroke mimics, AIS is very often misdiagnosed or diagnosed with time delay.<sup>1,2,5</sup> Hemiparesis, facial palsy, and dysphasia are main symptoms. Epileptic seizures are rarely a primary symptom but occur in contrast to adult stroke in nearly 50% of patients during the acute phase.<sup>2,6</sup> In our patient a prolonged epileptic seizure with postictal right-sided weakness and hemiparesis were the first symptoms. Due to these symptoms an immediate cranial CT scan was performed and showed a large left-sided infarction with complete obstruction of the internal carotid artery, the MCA, and the ACA. Due to leukocytosis and low hemoglobin levels and platelet count, an acute myeloid or lymphatic leukemia was suspected. Coagulation testing showed a beginning DIC.

Several cases of acute arterial thrombosis as first manifestation of cancer, mainly leukemia, in adults<sup>7-13</sup> and only few reports in children<sup>4,14-17</sup> have been published. To our knowledge, this is the first case of stroke in a pediatric patient with an underlying AML FAB M5. Coagulopathy can occur in all AML patients but is mainly associated with AML FAB M3 (acute promyelocytic leukemia) and can be either associated with bleeding symptoms or thrombosis.<sup>18</sup> Hypercoagulability is associated with a high leukocyte count (white thrombus), higher expression of tissue factor, and cancer procoagulant on the blast cells leading to activation of coagulation cascade and thrombosis. Overall, thrombosis remains a rare event (12% in adults, 1.1% in children) while hemorrhage due to fibrinogenolysis, DIC caused by high annexin II levels, higher proteolysis, and cytokine release (IL-1, TNF- $\alpha$ ) occurs more often.<sup>17,19</sup> Breccia et al could demonstrate that thrombotic events are more likely associated with specific immunologic and molecular parameters (CD2, CD15 expression, FLT3-ITD mutation).<sup>20</sup> In our patient, an FLT3-ITD mutation that is presumed to be an additional risk factor for the development of ischemic stroke and a heterozygous MTHFR polymorphism (C677T) was found. No further thrombosis risk factors were found in our patient. The low protein C and S levels and high factor VIII levels are signs of activation and consumption in the coagulation cascade.

The additional bleeding risk associated with AML also can complicate possible therapeutic strategies.<sup>19</sup> Use of recombinant tissue plasminogen activator (rtPA) is often limited by time delay, low platelet count, and underlying bleeding risk in AML. Due to low plasminogen levels in AML, therapeutic effects of thrombolysis could be impaired and higher doses as usual probably are needed, associated with increased bleeding risk. With underlying leukocytosis, thrombus material may largely be composed of leukocytes (white thrombus) instead of fibrin and platelets that may further limit rtPA effectiveness.

The use of a stent retriever seems to be a feasible method for therapy of AIS in childhood.<sup>21</sup> Mechanical thrombectomy could be postulated as a method to reopen vessels occluded by leukocyte thrombi but up to now no data exist for its use and outcome. Up to now interventional thrombectomy is only used in addition to rtPA with the same bleeding risk as with rtPA alone.<sup>22</sup> In our patient, rtPA was no option due to the time delay with already demarcation of the infarction area and unacceptable bleeding risk that also limited the use of low-molecular-weight heparin or unfractionated heparin. Furthermore, we supposed that anticoagulation would not prevent further thrombus formation due to leukostasis. Immediate hydration and exchange transfusion reduced the leukocyte count to 60 g/L until chemotherapy with cytarabine according to the current BFM (Berlin-Frankfurt-Münster) protocol was started. Despite immediate leucoreductive therapy our patient suffered a second ischemic stroke. The recurrent stroke most probably was caused by leukostatic or embolic occlusion of the right-sided ACA und MCA with once again increasing leukocyte count, although the CT angiography did not reveal occluded vessels on this side. Beside leukostasis the cell death of leukocytes induced by hydration and chemotherapy may have resulted in an additional release of procoagulative substances and further activation of the coagulation cascade.

It remains to be discussed if low-dose anticoagulation would have reduced the risk of secondary thrombosis. We believe that the patient's bleeding risk would have been unacceptably high under this treatment due to the AML associated high bleeding risk and developing DIC. Craniotomy as therapy for refractory increased intracranial pressure might be a possible therapeutic option considering the high plasticity and good rehabilitation capacity of young brains. However, there was the decision not to perform craniotomy due to the mentioned high bleeding risk associated with the underlying AML and the dismal prognosis with large size of the infarcted area in both hemispheres.

## Conclusion

Epileptic seizures are an unusual presenting symptom of pediatric arterial ischemic stroke. The differential diagnosis should include AML with hyperleukocytosis. Standard treatments of ischemic stroke may not be effective due to the leucocyte-rich nature of thrombi in this disease. Time delay to diagnosis and treatment seems to be of utmost importance as leukoreductive treatment may not be sufficiently successful when started with delay.

## Author Contributions

MO: contributed to conception and design; contributed to acquisition; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

KK: contributed to conception and design; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

F Heinen: contributed to conception and design; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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KR: contributed to conception and design; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

LG: contributed to conception and design; contributed to acquisition; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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