Congenital Amegakaryocytic Thrombocytopenia Type II Presenting with Multiple Central Nervous System Anomalies

Ellis Eshuis-Peters[1] Anne Brigitta Versluys[2] Marijn Fijke Stokman[3] Saskia Nanette van der Crabben[3] Sebastiaan W. A. Nij Bijvank[4] Gerda van Wezel-Meijler[5]

[1] Department of Neonatology, University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, The Netherlands
[2] Department of Pediatric Hematology, University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, The Netherlands
[3] Department of Medical Genetics, University Medical Center Utrecht, Utrecht, The Netherlands
[4] Department of Obstetrics and Gynaecology, Isala, Zwolle, The Netherlands
[5] Department of Neonatology, Isala, Zwolle, The Netherlands

Address for correspondence Ellis Eshuis-Peters, MD, Department of Neonatology, University Medical Center Utrecht, Wilhelmina Children's Hospital, 85090, 3508 AB Utrecht, The Netherlands (e-mail: E.Peters-3@umcutrecht.nl).

Neuropediatrics 2016;47:128–131.

Abstract

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare autosomal recessive bone marrow failure, caused by *MPL* gene mutations. The combination of CAMT and central nervous system abnormalities is uncommon. We describe a case with a homozygous missense *MPL* gene mutation and polymicrogyria, underdevelopment of the cerebellum, and multiple intracranial hemorrhages.

Keywords

- congenital
- amegakaryocytic
- thrombocytopenia
- CAMT
- MPL
- CNS

Introduction

Congenital amegakaryocytic thrombocytopenia (CAMT) is a rare, autosomal recessive bone marrow failure, characterized by early-onset isolated hypomegakaryocytic thrombocytopenia later evolving into pancytopenia.[1] Most children present with purpura or petechiae shortly after birth. Homozygous (or compound heterozygous) mutations in the myeloproliferative leukemia virus oncogene (*MPL*) affect the normal production of the thrombopoietin (TPO) receptor protein, resulting in an abnormal TPO receptor. Consequently megakaryocytes cannot bind and are not stimulated to increase in size, number, and ploidy, resulting in thrombocytopenia. As TPO also has a crucial role in maintaining the number of hematopoietic stem cells, a defect in its receptor leads to pancytopenia.[2] Due to the inadequate binding to the TPO receptor plasma TPO levels are very high. *MPL* is the only known gene associated with CAMT.

A CAMT-like phenotype can be caused by mutations or (chromosomal micro-) deletions of the *RUNX1*, leading to myelodysplastic syndrome (MDS) and congenital thrombocytopenia.[3] Patients with CAMT are at an increased risk for MDS and acute myeloid leukemia (AML).[4]

Based on the course and outcome of the disease CAMT is divided into: Type I, characterized by persistent thrombocytopenia and early progression to bone marrow failure and pancytopenia, and type II, characterized by transient increase of platelet counts up to nearly normal values during the first year of life and an onset of bone marrow failure at age 3 or later (OMIM #604498).[5]

The differentiation of type I and II is mainly based on the type of *MPL* gene mutation and the clinical course. Nonsense deletions and frameshift *MPL* mutations lead to a total loss of the TPO receptor and the clinical presentation of CAMT type I. Missense and splice site *MPL* mutations seem to be responsible for CAMT type II with a residual function of the TPO

received
September 21, 2015
accepted after revision
December 16, 2015
published online
February 8, 2016

DOI http://dx.doi.org/10.1055/s-0036-1571800.
ISSN 0174-304X.

receptor.[6] The only curative treatment for CAMT is hematopoietic stem cell transplantation.

Little is known about the co-occurrence of CAMT and central nervous system (CNS) abnormalities.[5,7–9] We report a novel case of a child presenting with CAMT type II and congenital brain anomalies.

Case Study

The boy, first child of healthy Caucasian parents, was born by cesarean section at 36^{+1} weeks gestation. Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. Birth weight was 2,700 g, head circumference 32.9 cm (both p50).

Antenatal ultrasonography at 33^{+2} weeks gestation had revealed an enlargement of the right lateral ventricle, suspect for a porencephalic cyst (►**Fig. 1**). Physical examination immediately after birth revealed multiple petechiae. Blood tests showed hemoglobin of 7.8 mmol/L (range, 8.1–14.3 mmol/L), platelets 8.0×10^9/L (range, 150–390 $\times 10^9$/L), and leukocytes 10.9×10^9/L (range, 9.0–38.0 $\times 10^9$/L). Cranial ultrasonography performed shortly after birth showed dilated lateral ventricles with a large right-sided porencephalic cyst. He required platelet transfusions during the first weeks, resulting in a temporary rise of the platelet count.

Differential diagnoses included viral infections, alloimmune or autoimmune thrombocytopenia, AML1, and genetic syndromes; thrombocytopenia absent radius (TAR) syndrome, Wiskott–Aldrich syndrome (WAS), *COL4A1* or *COL4A2* mutation and CAMT. Screening for congenital infections was negative, human platelet antigen alloantibodies were negative in both mother and child and maternal platelet count was normal. TPO was elevated (590 E/L). Sequencing of *RUNX1* (AML1), *COL4A1, COL4A2,* and WAS revealed no abnormalities. Presence of both radial bones excluded TAR syndrome. A single nucleotide polymorphism array was performed, showing various regions of homozygosity > 5 Mb, possibly indicating parental consanguinity. Within one of these homozygous regions (10.24 Mb) the *MPL* gene was contained. A bone marrow aspirate, performed 3 weeks after birth, showed a decreased number and an immature morphology of the megakaryocytes (►**Fig. S1, Supplementary Materials** [available in the online version only]). The other cell lines showed a moderate activity. This combination is highly suspect for CAMT.[10] Sanger sequencing of the *MPL* gene showed a known homozygous pathogenic missense mutation, c.305 G > C p.(Arg102Pro), confirming CAMT type II.

The boy developed a progressive hydrocephalus. A Rickham reservoir was implanted, and daily cerebrospinal fluid punctions were performed. After a few days there was a drop in hemoglobin value and he developed therapy-resistant seizures. Cranial ultrasonography showed, besides the porencephalic cyst, multiple parenchymal and ventricular hemorrhages. Magnetic resonance imaging (MRI) confirmed the porencephalic cyst on the right side and multiple intracranial hemorrhages. It additionally showed polymicrogyria, hypoplasia of the basal ganglia and thalami, absent myelination of the posterior limb of the internal capsule, a hypoplastic pons and hypoplasia, and dysplasia of the cerebellar vermis and hemispheres with multiple hemorrhages (►**Fig. 2a–c**).

Based on the severe MRI findings the prognosis was considered grave with severe motor and cognitive impairments, behavioral and visual problems, and epilepsy. Further treatment was focused on comfort and pain management. He died two months after birth.

Postmortem examination confirmed most of the MRI findings, including the hydrocephalus, multiple hemorrhages, porencephalic cyst and small basal ganglia, and thalami. No conclusive statements could be done on the presence of PMG and cerebellar hypoplasia.

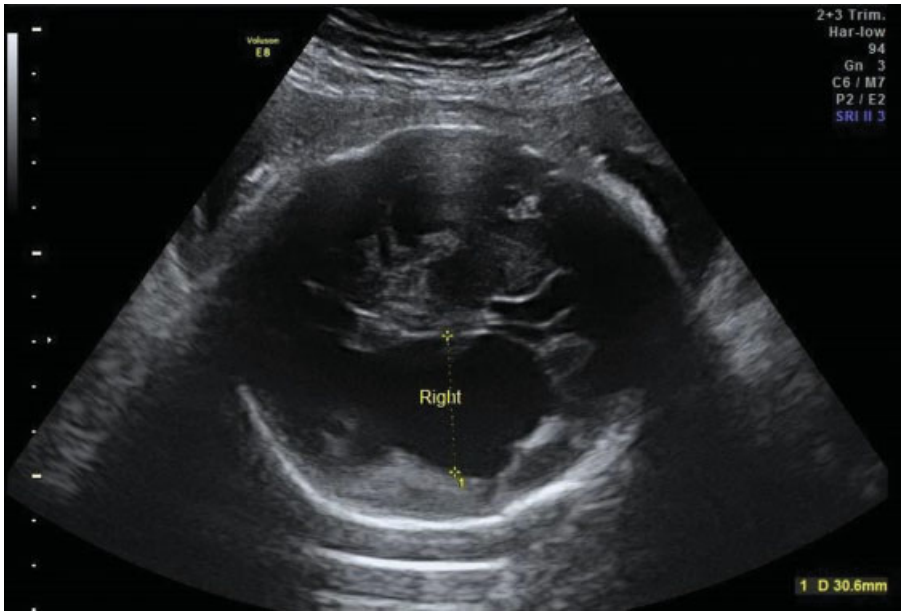

Fig. 1 Antenatal cranial ultrasound image in the transverse plane at a gestational age of 33^{+2} weeks, showing severe, irregular dilatation of the right lateral ventricle, and a normally sized left ventricle, suspect for a large right-sided porencephalic cyst.

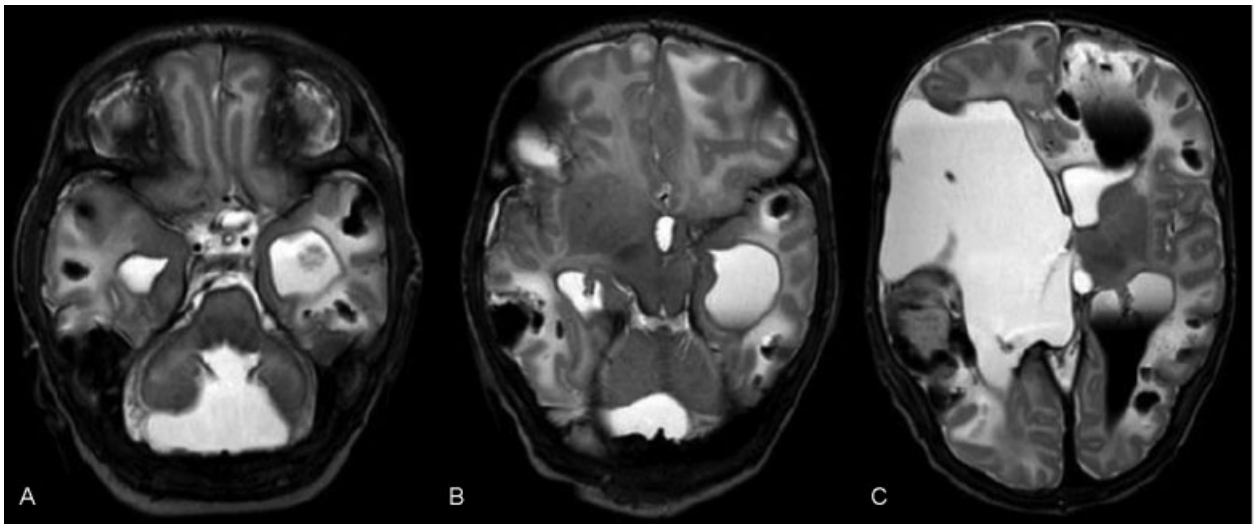

Fig. 2 (**a–c**) MRI performed at week 7 of life. T2-weighted transverse images: (a) hypoplasia and dysplasia of the cerebellum, ventricular dilatation. (b) Dysplastic cerebellum, right-sided polymicrogyria (PMG). (c) Large porencephalic cyst on the right, PMG in the left parietal region. All images show in addition multiple hemorrhages.

Discussion

CAMT is a rare inherited bone marrow failure syndrome, usually presenting with severe thrombocytopenia at birth due to ineffective megakaryocytopoiesis. In 2011, 96 patients with CAMT were presented.[11] Four more case reports have been published since.

Ihara et al were the first to describe a mutation in the *MPL* gene in patients with CAMT. Since then 41 different *MPL* mutations have been detected in CAMT patients.[5,6,10–13] No other mutations than *MPL* gene mutations have been identified.[6,11]

Besides the porencephalic cyst, our patient showed polymicrogyria, hypoplasia of the basal ganglia and thalami, and cerebellar hypoplasia. The association of CAMT and CNS abnormalities is uncommon. Six other cases presenting with CNS abnormalities have been described.[3,7–9] In 1970, Hoyeraal et al described two brothers with CAMT and cerebral and cerebellar hypoplasia, no mutation analysis was performed.[7] In 1999, Ihara et al described vermian hypoplasia in a girl with CAMT. A compound heterozygous mutation (frameshift) in the *MPL* gene was found, confirming CAMT type I.[8] More recently, King et al described in a series of 20 children with CAMT two children, monozygotic twins, with CNS abnormalities. One showed cortical dysplasia and polymicrogyria, the other lissencephaly and pachygyria. Chromosomal analysis was normal, analysis of the *MPL* gene was not performed.[5] The last report of Martinón-Torres et al in 2011, described a female with CAMT and cerebellum agenesis with hypoplasia of the corpus callosum and brainstem. A homozygous *MPL* gene mutation (missense), R102P, was found, confirming CAMT type II.[9] Ballmaier et al described a summary of all CAMT cases from 1990 onwards. Of all CAMT cases with a *MPL* gene mutation only 3.8% showed brain malformations.[11] Our patient is the second CAMT type II case described with cerebral anomalies.

The cause of CNS abnormalities in patients with CAMT is still unclear. It can be assumed that brain abnormalities in fetuses with CAMT are antenatally acquired, related to multiple hemorrhages resulting from thrombocytopenia. As *MPL* is expressed in cells of the megakaryocytic lineage progenitor, early hematopoietic progenitor, brain, and fetal liver, it has also been suggested that deficiency of the *MPL* gene may directly affect fetal brain development.[8] Studies have shown that the TPO receptor is not only expressed in platelets, but also in hematopoietic precursor cells and in neurons in various locations within the brain.[9,14] Another mechanism of brain abnormalities may therefore be disruption of the TPO receptor. TPO acts in the brain as a counterpart of erythropoietin (EPO), a hematopoietic growth factor with neuroprotective properties.[15] TPO is proapoptotic in the brain. The apoptosis induced by TPO appears to be restricted to maturating neuronal cells. Considering the structural similarity of the receptor binding domain in EPO and TPO, TPO may bind to the neuronal EPO receptor.[15] This may be the third factor influencing brain development in patients with CAMT. Further studies are needed to better understand the CNS function of TPO, especially in humans as former studies were performed in animals.[15]

Besides the porencephalic cyst our patient had multiple CNS abnormalities. We assume that these abnormalities were related to multiple hemorrhages, occurring early during the fetal period and resulting in disturbed development of the rapidly developing brain.[16] However, as outlined above the *MPL* gene mutation and disruption of the TPO receptor function may also have played a role. Evaluation of the presence of other candidate variants in the regions of homozygosity, that might be associated with the cerebral anomalies seen in our patient, did not reveal homozygous variants. The mutation in our patient, c.305G $>$ C, is the most frequently detected *MPL* gene mutation in patients with CAMT. It is classified as type II, in which the

receptor retains some function.[12] Our patient lived too shortly to show the increase in platelet count and distinguish between the two subtypes based on platelet count. Besides a hemoglobin drop during active intracerebral bleeding, the other hematopoietic cell lines remained stable.

Like our patient, most children with CAMT present with purpura or petechiae after birth. Intracranial hemorrhage is observed in a minority and is not strongly correlated with the platelet count. King et al described only 2/20 children with intracerebral hemorrhage after vaginal birth. They also described 4/20 children with ventricular dilatation and 1 child with a temporal lobe cyst, suspecting an antenatal intracerebral hemorrhage. Only one child, born after cesarean section had both antenatally and postnatally acquired hemorrhages like our patient. She had a homozygous nonsense mutation, classified as type I mutation.[5] Our patient had a large porencephalic cyst, suggesting an intracerebral hemorrhage or hemorrhagic infarction of antenatal origin. Seven weeks after birth he developed massive intracranial hemorrhages, despite several platelet transfusions. Postmortem examination showed cortical hemorrhages and iron depositions in the lateral ventricles, due to hemorrhages. To our knowledge, this is the second case of a CAMT type II with neurological complications and the first CAMT type II case with multiple, severe CNS abnormalities.

Besides supportive care with platelet and red cells transfusions the only definitive treatment for children with CAMT is hematopoietic stem cell transplantation. The optimal timing for transplantation is not known.

Conclusion

We describe a neonate with CAMT and severe intracranial abnormalities, antenatally and postnatally acquired. Sanger sequencing of the *MPL* gene showed a known homozygous pathogenic missense mutation, c.305 G > C p.(Arg102Pro), confirming CAMT type II. He died 2 months after birth.

Acknowledgment
None.

References

1 Savoia A, Dufour C, Locatelli F, et al. Congenital amegakaryocytic thrombocytopenia: clinical and biological consequences of five novel mutations. Haematologica 2007;92(9):1186–1193
2 Stoddart MT, Connor P, Germeshausen M, Ballmaier M, Steward CG. Congenital amegakaryocytic thrombocytopenia (CAMT) presenting as severe pancytopenia in the first month of life. Pediatr Blood Cancer 2013;60(9):E94–E96
3 Christensen RD, Wiedmeier SE, Yaish HM. A neonate with congenital amegakaryocytic thrombocytopenia associated with a chromosomal microdeletion at 21q22.11 including the gene RUNX1. J Perinatol 2013;33(3):242–244
4 Alter BP. Bone marrow failure syndromes in children. Pediatr Clin North Am 2002;49(5):973–988
5 King S, Germeshausen M, Strauss G, Welte K, Ballmaier M. Congenital amegakaryocytic thrombocytopenia: a retrospective clinical analysis of 20 patients. Br J Haematol 2005;131(5):636–644
6 He X, Chen Z, Jiang Y, Qiu X, Zhao X. Different mutations of the human c-mpl gene indicate distinct haematopoietic diseases. J Hematol Oncol 2013;6(X):11
7 Hoyeraal HM, Lamvik J, Moe PJ. Congenital hypoplastic thrombocytopenia and cerebral malformations in two brothers. Acta Paediatr Scand 1970;59(2):185–191
8 Ihara K, Ishii E, Eguchi M, et al. Identification of mutations in the c-mpl gene in congenital amegakaryocytic thrombocytopenia. Proc Natl Acad Sci U S A 1999;96(6):3132–3136
9 Martinón-Torres N, Vázquez-Donsión M, Loidi L, Couselo JM. CAMT in a female with developmental delay, facial malformations and central nervous system anomalies. Pediatr Blood Cancer 2011; 56(3):452–453
10 Ballmaier M, Germeshausen M. Advances in the understanding of congenital amegakaryocytic thrombocytopenia. Br J Haematol 2009;146(1):3–16
11 Ballmaier M, Germeshausen M. Congenital amegakaryocytic thrombocytopenia: clinical presentation, diagnosis, and treatment. Semin Thromb Hemost 2011;37(6):673–681
12 Ballmaier M, Germeshausen M, Schulze H, et al. c-mpl mutations are the cause of congenital amegakaryocytic thrombocytopenia. Blood 2001;97(1):139–146
13 Germeshausen M, Ballmaier M, Welte K. MPL mutations in 23 patients suffering from congenital amegakaryocytic thrombocytopenia: the type of mutation predicts the course of the disease. Hum Mutat 2006;27(3):296–X
14 Ivanova A, Wuerfel J, Zhang J, Hoffmann O, Ballmaier M, Dame C. Expression pattern of the thrombopoietin receptor (Mpl) in the murine central nervous system. BMC Dev Biol 2010;10:77
15 Ehrenreich H, Hasselblatt M, Knerlich F, et al. A hematopoietic growth factor, thrombopoietin, has a proapoptotic role in the brain. Proc Natl Acad Sci U S A 2005;102(3):862–867
16 Volpe JJ. Cerebellum of the premature infant: rapidly developing, vulnerable, clinically important. J Child Neurol 2009;24:1085–1104