Early Infantile Diagnosis of Hereditary Hemorrhagic Telangiectasia Complicated by Child Abuse

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We report a rare case of hereditary hemorrhagic telangiectasia (HHT) in a 4-month-old female infant with findings of child abuse. She presented with poor feeding, vomiting, and irritability after a short fall from the bed. Initial evaluation found subdural hematomas, persistent hypoxia, failure to thrive, a frenulum tear, facial lacerations, and bruising. The patient was admitted, and an extensive workup led to the diagnosis of brain and pulmonary arteriovenous malformations and finally the diagnosis of HHT. The subdural hematomas, cutaneous injuries, and oral injury were highly suspicious for child abuse and were reported to Child Protective Services and law enforcement for investigation simultaneous to the medical work-up. Her hospital course was complicated by progressive hypoxemia with radiographic evidence of several large pulmonary arteriovenous malformations, for which she underwent successful embolization. Her head injury was indeterminate for physical abuse in the setting of a medical condition predisposing to intracranial hemorrhage. A few weeks later, she was readmitted with repeat abusive injuries in the form of femur fractures. This case demonstrates the unique diagnostic dilemma when 2 diagnoses are occurring simultaneously—HHT and child abuse—and showcases the importance of a detailed family history, genetic testing, strong multidisciplinary collaboration with a holistic approach and medically informed Child Protective Services systems to ensure accurate diagnoses and safe disposition. *(J Pediatr 2024;12:200111).*

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber disease, is an autosomal-dominant disorder caused by mutations in genes encoding major constituents for transforming growth factor-β family signaling: endoglin (*ENG*), activin receptor-like kinase 1 (*ACVRL1*), and mothers against decapentaplegic homolog 4 (*SMAD4*).[1] HHT is characterized by arteriovenous malformation (AVMs) found in multiple organs, including the skin, mucous membranes, lungs, brain, and the gastrointestinal tract.[2] AVMs are direct shunts between arteries and veins without intervening capillary beds.[2] There are significant challenges to early diagnosis based on history and physical examination alone, as signs and symptoms evolve through late childhood and early adult life.[3] To date, there are only a handful of case reports of pulmonary and brain AVMs manifesting with such severe sequelae in children as young as 4 months.[4-6]

AVM evolution during childhood occurs at a variable rate, although it is well known that progression can be stimulated by trauma, puberty, and pregnancy.[7] Shunting increases over time, resulting in localized venous hypertension, reducing perfusion pressure to the involved and adjacent tissues, leading to tissue ischemia and hemorrhage.[8] Extensive extracranial AVMs and those with large fistulas can cause cardiac volume overload, leading to high output cardiac failure.[8] This is a case presentation of an infant with severe manifestations of brain and pulmonary AVMs who ultimately required coil embolization and whose diagnosis was complicated by child abuse. Even though AVMs are in the differential for abusive head trauma, there are no case reports, to our knowledge, of the diagnostic dilemma of HHT and child abuse in the same child.

Case Presentation

A 4-month-old, ex-34-week gestational age, 3-kg (<0.01 percentile for age) twin presented for evaluation of poor feeding, poor growth, and irritability. The parents reported a fall from a 3-foot bed onto hardwood floor 3-4 days before admission with no loss of consciousness, seizures, or altered mental status at that time. She subsequently developed emesis, lethargy, and persistent bilateral eye deviation to the right, which prompted evaluation. Computed tomography of the head demonstrated bilateral multifocal subdural

AVM	Arteriovenous malformation
CAPS	Child advocacy and protective services
CML	Classic metaphyseal lesion
CPS	Child Protective Services
ENG	Endoglin
HHT	Hereditary hemorrhagic telangiectasia
SpO_2	Oxygen saturation

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hematomas, predominantly along the posterior left cerebral hemisphere. Because of concerns that the reported history was not consistent with the radiographic findings and the presence of cutaneous and oral injuries concerning for abuse, a report was made to Child Protective Services (CPS) and law enforcement for investigation.

On admission to the pediatric intensive care unit, the patient had mild hypoxia responsive to low-flow nasal cannula oxygen to maintain normal pulse oximetry (oxygen saturation [SpO_2]). On physical examination, she had bruising to her left medial eyelid, a left lateral eyelid abrasion, a scabbed laceration below her left lower lip, healing frenulum lacerations, left medial tibia bruise, and left shoulder bruising. Her Glasgow Coma Scale score was 15, and she was described as "active, alert, vigorous cry." Initial workup included radiograph of the chest and skeletal survey.

The skeletal survey showed possible proximal left tibia classic metaphyseal lesion (CML) and probable right distal tibia CML. An ophthalmologic examination showed no retinal hemorrhages. The hospital's child advocacy and protective services team (CAPS) explained the high suspicion of abuse to CPS and law enforcement even in the setting of a probable medical condition as their investigation commenced.

The family history was significant for a maternal history of pulmonary hypertension secondary to pulmonary AVMs during pregnancy, requiring a cardiac catheterization intervention peripartum. Hematology was consulted to evaluate for coagulopathy or increased bleeding risk. Her laboratory findings at admission were significant for normocytic anemia with a hemoglobin of 7.6 g/dL, normal platelet count, and normal coagulation studies. The anemia was believed to be caused by subdural hematoma combined with nutritional deficiencies resulting from her failure to thrive. Her bilirubin level was normal, and there was no evidence of schistocytes, effectively ruling out a hemolytic process. On the basis of medical history, clinical findings, family history, screening laboratory testing, and the absence of continuing or persistent bleeding while in the hospital, the hematologists concluded that there was no concern for a primary bleeding disorder.

The patient had persistent and progressive hypoxemia without evidence of respiratory distress and without a known cyanotic congenital heart defect. On hospital day 2, SpO_2 fell to the high 70s-low 80s on high-flow nasal cannula with fraction of inspired oxygen of 1.0. No focal abnormalities were noted on radiograph of the chest. Respiratory support progressed to invasive mechanical ventilation as the result of refractory hypoxia with minimal improvement in SpO_2 to the low 80s. Repeat echocardiogram after intubation showed mild flattening of the interventricular septum and an abnormal saline contrast (bubble) study suggestive of pulmonary AVMs from the right lung. She developed hemodynamic instability and a pulmonary hypertension crisis, for which she was started on inhaled nitric oxide, and milrinone with temporary improvements in saturations to the 90s. Computed tomography of the chest angiogram confirmed right upper and right middle lobar pulmonary AVMs (**Figure 1**).

Subsequent brain magnetic resonance angiogram showed an AVM of the brain in the medial left temporal lobe with suspected arterial supply from the left middle cerebral artery as well as left temporal lobe encephalomalacia concerning for an evolving infarct in the left MCA II territory (**Figure 2**). The location of the bilateral subdural hematoma did not fit the typical picture of a ruptured brain AVM, and this was conveyed to CPS and law enforcement, as abuse could not be ruled out. At this point, the primary diagnosis on the

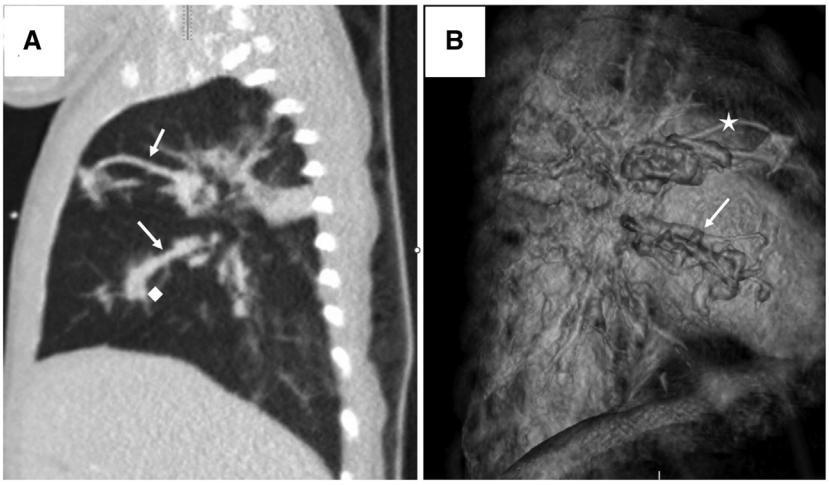

Figure 1. **A,** Pulmonary AVM on sagittal maximum intensity projection images of the right lung on a nongated contrast-enhanced CT angiogram of the chest; shown here are the feeding arteries (*arrows*) and AVM nidus (*diamond*) to the right middle and lower lobes. **B,** Pulmonary AVM on virtual reality images of the right lung on a nongated contrast-enhanced CT angiogram of the chest; shown here are the feeding arteries (*arrows*) and draining veins (*star*). *CT*, computed tomography.

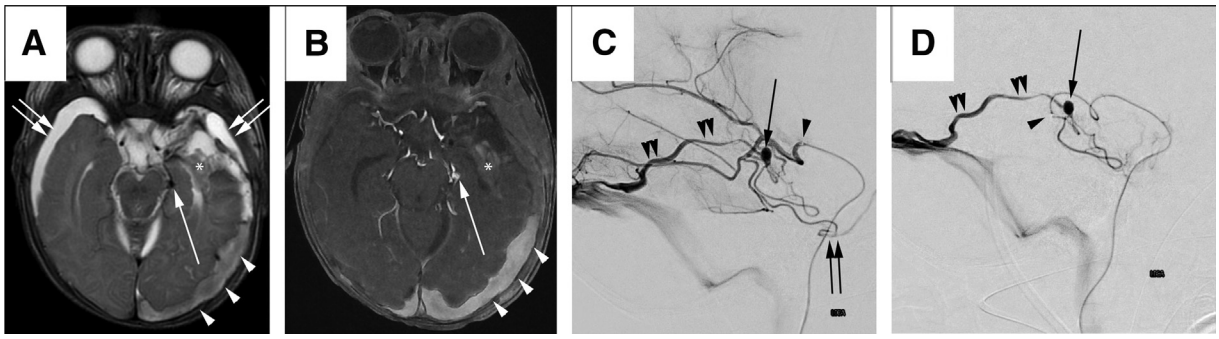

Figure 2. **A,** T2 axial magnetic resonance and **B,** time-of-flight magnetic resonance angiography showed bilateral subdural hygromas (*double arrows*) and left larger than right posterior subdural hematomas (*arrowheads*), encephalomalacia of the left temporal pole (*asterisk*), and a 2-mm aneurysm in the left ambient cistern (*arrow*). Direct microcatheter angiography of the left PCA (*arrowhead*, **A**) and of the main left (PCA) temporal branch supply (*arrowhead*, **D**) to a left medial temporal pial fistula, shows a 2-mm aneurysm (*arrow*, **C, D**) at the point of arteriovenous shunting into a single draining cortical vein extending posteriorly with egress via the left transverse sinus. A separate temporal branch of the left PCA supplies a second pial fistula on the undersurface of the left temporal pole (*double arrows*, **C**). *PCA*, posterior cerebral artery.

differential was HHT with a high suspicion of abuse. She underwent a full genetic and inborn errors of metabolism workup, which confirmed a pathogenic sequence change detected in the *ENG* gene (c.1646 G > A [p.Cys549Tyr]) in the heterozygous state, consistent with the diagnosis of HHT.

Her clinical course was significant for progressive hypoxemia refractory to medical therapy. Right heart catheterization with angiography revealed multiple diffuse pulmonary AVMs of the right middle and lower lobes (**Figure 3**). The right upper lobe and base of the right lower lobe appeared to have normal vasculature and no left lung pulmonary AVMs were visualized. Four 5-mm vascular occluder plugs (LOBO-5) and four 6-mm × 20-mm detachable coils (Balt) were deployed into multiple segmental and subsegmental branches supplying the pulmonary AVMs, with marked immediate improvement in oxygen saturation noted (**Figure 3**). The postcatheterization course was complicated by a precipitous drop in hemoglobin with

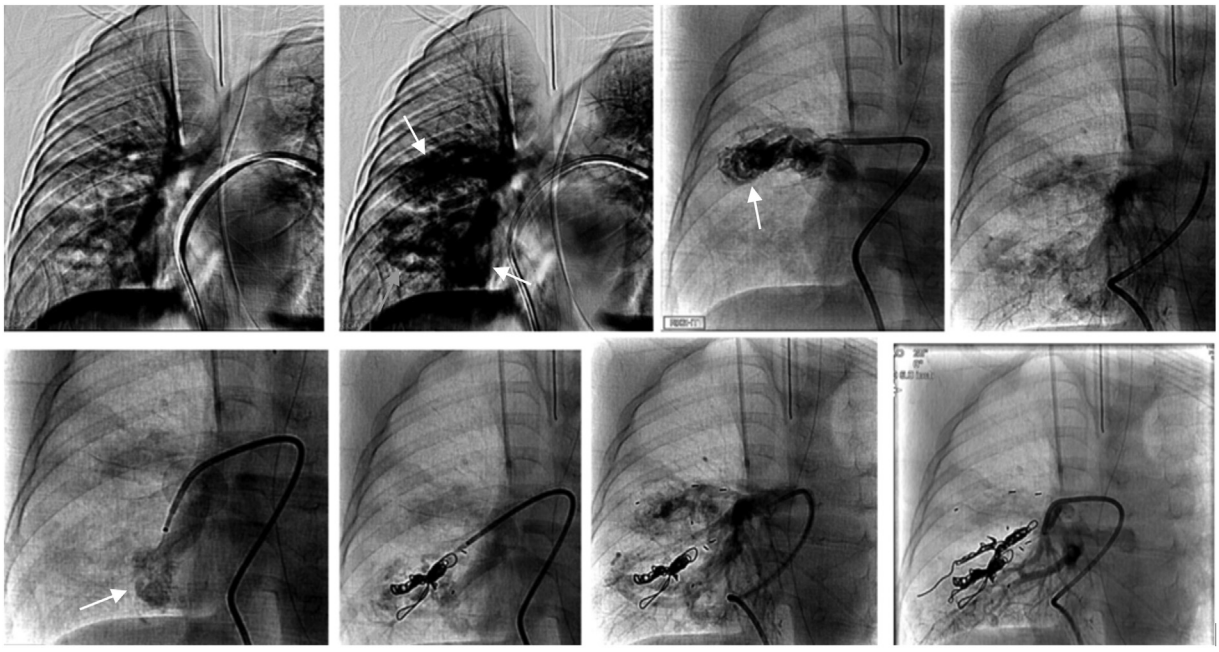

Figure 3. Angiography demonstrating multiple complex right middle lobe and right lower lobe pulmonary AVMs (*white arrows*) and subsequent embolization with vascular occluder plugs and detachable coils.

worsening opacification radiograph of the chest and right pleural effusion (Figure 4) that resolved with medical management. She was successfully extubated after embolization. Interventional neuroradiologists later attempted occlusion of the AVM of the brain; however, they were unsuccessful due to the size of the feeding artery and positioning.

From an injury perspective, her parents continued to state the cutaneous and oral injuries were from the simple fall from the bed. During the investigation, no other history was disclosed, either accidental or abusive. Follow-up skeletal survey was normal. There were no signs of healing and no CMLs, so the consensus between the CAPS team, pediatric radiology, and pediatric orthopedics was that these findings on the initial skeletal survey were normal variants or over-calls.

Despite the final opinion from the CAPS team and several discussions to explain the medical condition, CPS believed the medical condition complicated the diagnosis of abuse and that the abusive injuries were not serious enough to warrant removal. The law enforcement investigation was suspended. The patient was discharged home with the parents and offered intact family services.

Approximately 2 weeks after hospital discharge, she was readmitted to the hospital with unexplained bilateral distal femur fractures (Figure 5). She had no evidence of underlying bone disease or vitamin deficiencies that could predispose to pathologic fractures. The parents had no history initially to explain the fractures. CPS and law enforcement reports were made again. During the investigation, the mother reported that the legs possibly broke when she removed the child from a high-chair.

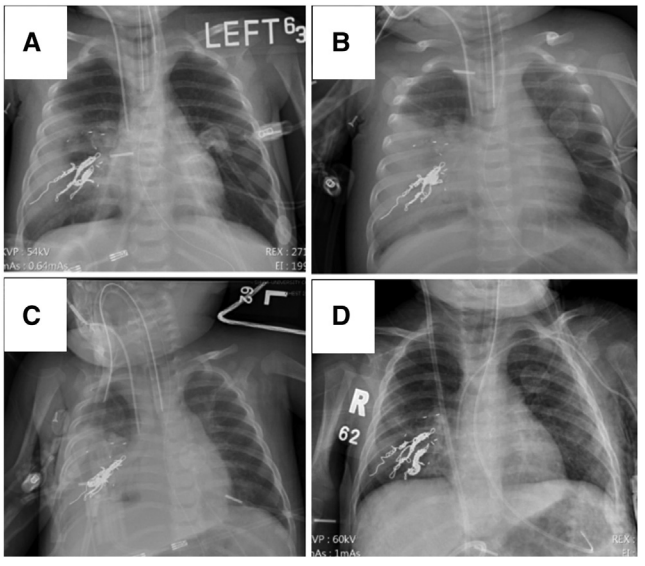

Figure 4. Radiograph of the chest demonstrating the evolution of right-side pulmonary hemorrhage at **A,** day 1; **B,** day 2; **C,** day 3; and **D,** day 16 showing improvement, postpulmonary AVM embolization with interventional radiology and cardiology.

The scene re-creation shared with the CAPS team by investigators did not demonstrate an adequate accidental mechanism for the fractures. In light of the previous abusive injuries and now more serious abusive injuries, CPS removed the child from the home and placed her in the custody of the state. Law enforcement again suspended their investigation, as they could not identify the specific perpetrator out of the 3 primary caregivers—mother, father, or maternal grandmother. The patient currently lives in a state residential facility, is thriving, and has had no further bruising or fractures.

Discussion

This case highlights a unique, severe presentation of HHT at a very young age, but it also showcases the challenges of diagnosing child abuse and advocating for safety in children with rare genetic and bleeding disorders. HHT is an autosomal-dominant disorder characterized by abnormal blood vessel formation with an incidence estimated between 1:5000 and 1:10 000.[1,8] It is historically diagnosed using the Curaçao criteria, which requires the presence of 3 of the following: recurrent epistaxis, multiple telangiectasias of skin, lip or tongue, AVMs of 1 or more internal organs (lung, brain, liver, gut), and family history of these manifestations.[9] Faughnan et al published that in 97% of patients with a clinical diagnosis of HHT, a causative mutation is identified in one of the following genes: *ENG, ACVRL1*, and *SMAD4*.[10] Because epistaxis and telangiectasias are disease manifestations that typically develop as one ages, this case demonstrates how clinching the diagnosis in pediatric patients often hinges heavily on genetic testing.

What makes HHT a challenging diagnosis to contend with in the setting of classic signs of abuse—subdural hematomas and bruising—is that the disease itself predisposes patients to bleeding as the result of high pressure vascular anomalies resulting in vascular wall fragility. Furthermore, the literature suggests HHT can be further complicated by the presence of a secondary bleeding disorder, the most prevalent being von Willebrand disease and hemophilia,[11] the co-occurrence of which could result in severe blood loss and anemia.[11] The list of congenital and acquired bleeding disorders that could potentially be confused with abusive injury is extensive including but not limited to disorders of fibrinogen, factor deficiencies, von Willebrand disease, thrombocytopenia, leukemia, aplastic anemia, and platelet function abnormalities.[12]

Although in our case there was sufficient clinical evidence with the discovery of AVMs to prompt genetic testing, it raises the question of whether extended genetic sequencing in the search for rare bleeding disorders should be performed for all patients suspected to be victims of child abuse. One study found that intracranial hemorrhage was the presenting event in 19.2% of patients with bleeding disorders.[13] The overall prevalence of AVMs of the brain in patients with HHT is ~10% and, of those, nearly 20% of patients will present with catastrophic hemorrhage.[8] However, no studies

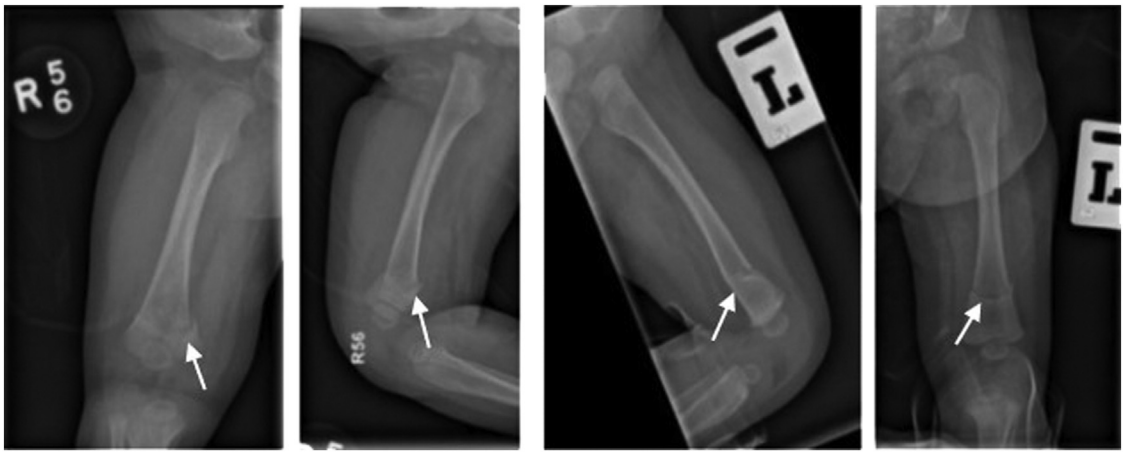

Figure 5. Radiographs of femurs demonstrating fractures of the bilateral distal femurs (*white arrows*).

have systematically compared the presentation, clinical findings, and patterns of intracranial hemorrhage or presence of retinal hemorrhages between children with bleeding disorders and or vascular anomalies and abusive head trauma.[12]

Finally, the diagnosis of child abuse in the setting of a medical condition is fraught with barriers. This often begins with the bias of medical providers that all the clinical findings must be related to the medical condition. There is often a level of denial or disbelief of abusive injury in the setting of an underlying medical condition. However, the literature demonstrates that children with chronic medical conditions and disabilities are at greater risk of abuse and neglect.[14] In addition to medical provider bias, the diagnosis of abuse is more difficult to distinguish when a medical condition can "mimic" abuse, ie, create findings that can be mistaken for unexplained trauma or can predispose to trauma with minor forces.[15] As in this case report, it was necessary to parse out which injuries can and should be labeled abusive, indeterminate, or ruled out to maintain medical and academic integrity, as that is what the child deserves. Even when the diagnosis of abuse is made by a CAPS team, CPS systems may be skeptical of the abuse diagnosis in the absence of a disclosure or confession of abuse. This approach by CPS makes it difficult to advocate for safety and protection of the child, as removal decisions are made by CPS and the courts, not by child abuse physicians. The opinion of the CAPS team may be weighted more heavily but is not the final determination of disposition.

This case illustrates the importance of validating the concerns surrounding sentinel injuries. When sentinel injuries are not addressed, children return reinjured. 27.5% of children who were definitely abused had a previous sentinel injury.[16] This case also illustrates the importance of recognizing that abuse can coexist with a complex medical condition. The inability to determine whether the head trauma was abusive or attributable to predisposition to bleeding does not negate the abusive etiology of other injuries. Jaudes and Mackey-Bilaver showed that in children aged 0-6 years, there was a slightly elevated risk of maltreatment with chronic physical conditions, no elevated risk with developmental delay, and twice the risk with behavioral/mental health problems.[14] The 2021 American Academy of Pediatrics Clinical Report summarizes the literature to date reporting 3%-10% rate of maltreatment in children with disabilities.

In conclusion, this is a unique and medically complex case of early infantile HHT with severe pulmonary and cerebral AVMs in combination with child abuse, posing challenges in diagnosis and management of this rare genetic disease. It is an important example of how a child with an underlying medical condition that may mimic abusive injuries also can be abused. In infants, child abuse is one of the most challenging diagnoses to make, and recurrent injury is often the foundation for definitive diagnosis. ■

CRediT authorship contribution statement

Brittany Tang: Writing – review & editing, Writing – original draft. **Stephen Pophal:** Writing – review & editing, Supervision, Conceptualization. **Madhusudan Ganigara:** Writing – review & editing, Data curation. **Brian Funaki:** Writing – review & editing, Data curation. **Mckenna Robinette:** Writing – review & editing. **Veena Ramaiah:** Writing – review & editing, Writing – original draft, Conceptualization. **Nancy Ghanayem:** Writing – review & editing. **Michael C. Hurley:** Writing – review & editing. **Umesh Dyamenahalli:** Writing – review & editing, Writing – original draft, Supervison, Conceptualization.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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