

**Research Letter****Unexpected Death due to Refractory Metabolic Acidosis and Massive Hemolysis in a Young Infant With Prader–Willi Syndrome****To the Editor:**

We read with interest the two research articles recently appeared in this *Journal*, about the causes of death in subjects with Prader–Willi syndrome (PWS) [Schrandt-Stumpel et al., 2004; Stevenson et al., 2004]. PWS is a genetic disorder, which may be difficult to diagnose at birth given the paucity of dysmorphic features. Beyond the well-known phenotype and the neurodevelopmental features, the recently described hypothalamic dysfunction appears to have a crucial role in the prognosis of infants with this syndrome. In particular, temperature dysregulation, adrenal insufficiency, and impaired ventilation control might be involved in unexpected death cases observed in the first few months of age.

We describe the clinical course of a 6-month-old female infant affected by PWS, who eventually died after a short history of acute febrile enteritis followed by generalized seizures, refractory metabolic acidosis, and massive hemolysis.

Parents originate from India and are not consanguineous. The mother is a 27-year-old at her first pregnancy no miscarriages were reported (G1 P0 A0). Pregnancy was entirely followed-up in Italy. Intrauterine asymmetric fetal growth restriction was detected by routine ultrasound examinations. Prophylaxis for lung maturity with steroids was administered. The patient was born at 34<sup>3/7</sup> weeks of gestational age by caesarian section because of fetal bradycardia.

Birth weight was 1,710 g (5–10th centile), length 43 cm (10th centile), and head circumference 31 cm (50th centile). Mild intrapartum asphyxia was recorded. Apgar score was 7, 8, and 9 at the 1st, 5th, and 10th minute, respectively. Free-flow oxygen supplementation was necessary during the first 12 hr of life. Soon after birth she was noted to be limp, poorly reactive, and responsive to tactile stimuli. Cry was very weak. No major physical anomalies were recorded. In the third day of life transient apnea episodes were recorded, with no evidence of infections.

In the first well-child visits at the newborn nursery she was noted to be hypotonic (particularly central and upper limbs) and primary neonatal reflexes were not elicitable. During her stay in the nursery, feeding and growth were poor, while persistent mild compensated respiratory acidosis was docu-

mented. Basic metabolic studies were normal. Due to her abnormal neurological pattern, further investigations were performed, and a methylation study led to the diagnosis of PWS ( $\alpha$ -exon, Prader–Willi–Angelman region; SNRPN 15q11/q13 and absence of paternally derived gene). Her feeding pattern gradually improved and the failure to thrive subsided. The patient was discharged home and no other relevant illnesses were reported in her past medical history. At 6 months of age she was referred to the pediatric emergency department of a district hospital for a few-hours history of non-productive cough and mild upper respiratory tract infections. Body weight was 5.5 kg (3rd centile); with a presumed weight loss of about 5%. She was subsequently admitted to the Pediatric ward and diagnosed with pneumonia. Topical bronchodilator therapy and parenteral broad-spectrum antibiotic therapy were commenced. Respiratory symptoms gradually subsided. After 24 hr since admission she developed watery diarrhea and high fever (39°C). The patient was hyponatremic and moderately dehydrated and intravenous fluids were then commenced. Physical examination was otherwise unremarkable. Stool culture revealed a Rotavirus infection. Gastroenteritis symptoms persisted for the subsequent 48 hr. At the sixth day of admission she presented a sudden episode of cardiorespiratory arrest. Cardiopulmonary support was immediately instituted, and return of spontaneous circulation was obtained after 12 min, soon followed by generalized seizures activity. The patient was treated with intravenous diazepam and subsequently referred to our PICU.

Upon admission the clinical conditions were critical, with ongoing seizure activity, high fever (40°C), tachycardia (heart rate > 200 bpm) and hypotension. Central venous pressure was 4–6 cm H<sub>2</sub>O. Venous blood gas analysis revealed severe metabolic acidosis (pH = 6.99, pCO<sub>2</sub> = 42 mmHg, pO<sub>2</sub> = 35 mmHg, HCO<sub>3</sub> = 7, BE = –25). No evidence of mucocutaneous petechiae or purpura was present. High ventilatory parameters as well as high oxygen concentration were required (Oxygenation Index ranged between 35 and 60). A chest radiograph showed right-sided patchy infiltrates consistent with aspiration.

Despite aggressive fluid resuscitation and bicarbonate infusion the acid–base status remained compromised (best pH value = 7.00), and the patient became oliguric. An echocardiographic evaluation documented a normal biventricular function. Poor peripheral perfusion prompted inotropic support with dopamine and epinephrine, which had to be raised to maximal level in the next few hours, with scarce response.

Continuous electroencephalographic recording showed persistent and diffuse seizure activity, which subsided only after repeated boluses of phenobarbital and phenytoin.

Blood chemistry showed elevated creatinine and urea nitrogen. Potassium was 5.3 mM/L.

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Upon admission hemoglobin level was 117 g/L. Platelets' count was slightly below normal limits. White cells count was within normal values, C-reactive protein was negative, while plasma procalcitonin (PCT) was extremely elevated (>500 µg/L). Coagulation parameters (activated PTT, antithrombin III, D-dimer, fibrinogen levels) were within normal limits, except for prothrombin time, which was moderately elevated.

Ongoing problems were refractory metabolic acidosis, high lactate (peak lactate level was 25 mM/L), and anuria unresponsive to loop diuretics. Four hours after admission hemoglobin level acutely dropped to 47 g/L; despite an abundant (30 ml/kg) packed red blood cells transfusion hemoglobin level raised just to 66 g/L. Platelets' count decreased down to 10,000/µl without any evidence of mucocutaneous hemorrhage.

Potassium levels rapidly rose up to 10 mM/L, with typical ECG trace alterations, and did not significantly decrease despite repeated administration of polystyrene sulfonate, sodium bicarbonate, calcium chloride, glucose, and insulin. Emergent hemodialysis was attempted but could not be performed because hemodynamic instability and poor vascular access.

Major intraventricular conduction disturbances (tachycardia and ventricular fibrillation) leading to recurrent cardiac arrest episodes were recorded. Maximal inotropic support (dopamine, epinephrine, and enoximone) was ineffective and all resuscitation efforts failed. The patient deceased 7 hr since admission.

On autopsy a well-defined cause of death could not be established. Weight was 5.8 kg (<5th centile), although subcutaneous adipose tissue was abundant for age. No major hemorrhagic signs were detected in the parenchymatous organs and serous cavities. Petechiae and purpura were found on the esophageal and gastric mucosa, respectively. Partially digested blood was present in the stomach. The lungs revealed the presence of a substantial intra-alveolar infiltrate and diffuse atelectasis, consistent with acute respiratory distress syndrome. Myocardium showed no markers of acute ischemia. Liver was congested and enlarged, most likely a terminal finding. Muscle tissues were pale. Brain appeared to be normal, with no sign of edema. Adrenal glands were described as "shrunk" by the pathologist, but weight was not recorded. Kidneys did not show evidence of cortical necrosis.

We have described a young infant affected by PWS who, following an episode of febrile gastroenteritis, unexpectedly died due to severe metabolic acidosis, acute massive hemolysis, and intractable hyperkalemia. Although the past medical history, the catastrophic clinical course during acute infections, and the autopsic findings observed in our patient are very similar to those described in the two recently published case series [Schrandt-Stumpel et al., 2004; Stevenson et al., 2004], there are some unresolved issues in this case which in our opinion need to be emphasized. Firstly, the possible cause of the unexpected cardiorespiratory arrest at the referring hospital remains unclear. Hypothalamic dysregulation (temperature and ventilation control), hemodynamic lability and failure of the stress response during an acute illness, well described in patients with PWS, may have been all causative factors.

On admission to PICU, our initial working diagnoses were acute dehydration, septic shock, and hemolytic uremic syndrome (HUS). The absence of response to fluid bolus and the normal central venous pressure values ruled out the acute dehydration state. Septic shock was suggested by the extremely compromised clinical status and lack of response to all therapeutic strategies, but was not supported by blood tests (acute phase reactants values, white blood cells count were within normal limits) and by the negativity of cultures. The high PCT values could have been artificially elevated because of the cardiac arrest episode [Fries et al., 2003].

Presence of diarrhea (although not bloody), thrombocytopenia, hemolysis, anuria, and extrarenal manifestations (seizure activity, heart failure) was suggestive of HUS, the most common cause of acute renal failure in infants and children [Corrigan and Boineau, 2001]. Though, no acute myocardial infarct was macroscopically found, and no schistocytes were documented on the peripheral blood smear.

Upon admission the hemoglobin level was normal; surprisingly, in few hours it dramatically fell by 60% with no clinical signs of acute hemorrhage. Aptoglobin level was low and lactic dehydrogenase was high.

Such episode of acute massive hemolysis might partially explain the refractory metabolic acidosis, as well as the acute hyperkalemia and the subsequent ventricular fatal arrhythmia. Massive intravascular hemolysis is a relatively uncommon phenomenon in children. It may be secondary to red blood cells' membrane defects or be immune-mediated. In our patient, erythrocytes' membrane defects were microscopically excluded.

Direct and indirect Coombs' test ruled out immune-mediated hemolysis (possibly triggered by infection).

We investigated other possible causes of hemolysis, such as congenital glucose-6-phosphate dehydrogenase deficiency. In fact, acute hemolysis could be secondary to an idiosyncratic response or hypersensitivity reaction to drugs, including anticonvulsant agents. Indeed, in our patient status epilepticus began shortly after the first cardiac arrest episode, and several drugs had to be used to keep seizures under control. In particular, phenobarbital and phenytoin boluses were administered on admission in PICU. Interestingly, less than 4 hr later, hemoglobin level markedly fell. No other drugs, except for dopamine, epinephrine, enoximone, and broad spectrum antibiotic (ceftriaxone) were given to the patient.

Neonatal screening test for glucose-6-phosphate dehydrogenase levels were normal (homozygosity for this genetic defect was therefore excluded). We are currently investigating by molecular biology techniques the heterozygosity for glucose-6-phosphate dehydrogenase deficiency, which can be missed by the neonatal screening in female subjects [Zaffanello et al., 2003; with permission of the authors] and it has been recently reported as a possible cause of hemolysis [Kaplan et al., 2001].

As recently suggested [Van Vliet et al., 2004], careful monitoring of population-based mortality data are urgent to better characterize the impaired stress-response observed in these patients.

To our knowledge, massive acute hemolysis has not yet reported among the catastrophic events related to the demise of patients with PWS. We believe that this phenomenon might have played a decisive role in the terminal course of our patient, even though the causative mechanism remains unclear. While further studies are needed in order to better clarify this issue, we suggest a close surveillance of these patients during acute diseases such as gastroenteritis and upper respiratory tract infections or when anticonvulsant treatment must be provided.

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