Original Article

Characteristics of hyperthermia and its complications in patients with Prader Willi syndrome

ERDAL INCE,1 ERGIN ÇIFTÇI,1 MUSTAFA TEKIN,2 TANIL KENDIRLI,3 ERCAN TUTAR,4 NAZAN DALGIÇ,1 SELIM ÖNCEL1 AND ÜLKER DOGRU1

Divisions of 1Pediatric Infectious Disease, 2Genetics, and 3Intensive Care Unit, and 4Cardiology, Department of Pediatrics, Ankara University School of Medicine, Dikimevi, Ankara, Turkey

Abstract  Background: Thermoregulation problems, resulting in hypo- or hyperthermia, have been infrequently reported in children with Prader Willi syndrome (PWS), yet their clinical details remained unknown.

Methods: The clinical characteristics of three infants with PWS are reported.

Results: Etiologies of high fever could not be identified in three children with PWS. One of these children was also admitted to the intensive care unit with extremely high body temperature in a life-threatening condition, similar to septic shock, without a plausible explanation.

Conclusion: Hyperthermia may be a part of the clinical spectrum in young infants with PWS and should be carefully monitored, since it may cause life-threatening complications.

Key words  fever, hyperthermia, Prader-Willi syndrome, septic shock.

Prader Willi syndrome (PWS) is a well-known genetic disorder, which affects one in 10,000–15,000 live births. Its typical clinical features include central hypotonia, feeding difficulties during infancy, developmental delay, obesity usually starting after 1 year of age, hypogonadism, and distinctive physical appearance. The definitive diagnosis of PWS can be made with molecular and/or molecular cytogenetic investigations.1–3

Although it has long been believed that most of the typical findings of PWS can be explained with hypothalamic dysfunction, a structural defect in hypothalamus has not been demonstrated. Thermoregulation problems in patients with PWS have been mentioned in only few publications, for which a hypothalamic dysfunction has also been speculated.4–9 However, detailed characteristics of thermoregulation problems and their clinical presentations have remained unknown.

In this report, we present three infants with PWS, who were evaluated for fever of unknown origin starting in the early months of their lives. Our findings indicate that hyperthermia may be an internal feature of PWS and may result in life-threatening complications.

Patient 1

This boy was the third child of a 35-year-old mother and a 36-year-old father. He was born at term by normal vaginal delivery following an uncomplicated pregnancy. The mother noticed decreased fetal movements compared with her previous pregnancies. His birth weight and length were 3210 g (25th–50th centile) and 50 cm (25th–50th centile), respectively. He was admitted to the neonatal intensive care unit and observed for 2 days after delivery because the amniotic fluid was meconium-stained and onset of spontaneous respirations was delayed. Muscle hypotonia was noted during his hospital stay, which was the only pathological finding at discharge. He had decreased sweating and dermographism, which was also noted by the parents. He was readmitted to a regional hospital because of fever, presumed to be due to pneumonia, when he was 15 days old. His clinical findings quickly improved with intravenous antibiotics, although fever remained continuously high. He was admitted to the Department of Pediatrics, Ankara University School of Medicine, at 1 month of age, because of persistent high fever. His weight, length, and head circumference were 4300 g (50th–75th centile), 56 cm (75th centile), and 38.2 cm (75th centile), respectively. His rectal temperature was 38.8°C, heart rate was 146 b.p.m, respiratory rate was 42 breaths/min, and blood pressure was 68/42 mmHg upon admission. Marked hypotonia was noted with weak deep tendon reflexes and swallowing difficulties. A summary of the phenotypic

Correspondence: Erdal Ince, Hosdere caddesi 23/21 06550, Yukari-aiyranli, Ankara, Turkey. Email: ince@dialup.ankara.edu.tr
Received 30 October 2004; revised 25 January 2005; accepted 23 February 2005.
features observed in this patient is shown in Table 1. There was no identifiable origin for an infectious disease during clinical examination. Cultures for bacterial, fungal or viral pathogens remained negative.

His high fever persisted during his hospital stay. He was discharged with nasogastric feeding. His swallowing difficulty resolved at 2 months of age and oral feeding was successfully achieved. Due to his clinical findings, a presumptive diagnosis of PWS was entertained. A maternal only methylation pattern confirmed the clinical diagnosis, which was demonstrated by using a previously published PCR protocol with bisulfate modified genomic DNA and methylation specific primers. A routine FISH analysis was also consistent with the diagnosis. The high fever persisted during the outpatient follow-up period. These follow-up examinations included one episode of pneumonia, which was treated with intravenous antibiotics at the hospital. Although his clinical and radiological findings improved quickly with therapy, his high fever continued.

He was found unconscious by his mother in bed when he was 6 months old and rushed to the emergency department. On examination, his rectal temperature was 41.8°C, heart rate was 240 b.p.m., and respiratory rate was 58 breaths/min. His peripheral circulation was poor with absent radial and brachial pulses. Laboratory evaluation showed Hb 11.4 g/dL; WBC 8800/mm³ (lymphocyte 44%, neutrophils 38%, bands 10%, monocytes 8%); and platelets 88 000/mm³. The CRP level was 0.8 mg/dL and ESR was 8 mm/h. Urine analysis and posteroanterior chest X-ray were normal. Blood chemistry parameters included glucose 98 mg/dL; urea 43 mg/dL; Na 123 mEq/L; K 7.1 mEq/L; ALT 29 U/L; AST 32 U/L; Ca 5.8 mg/dL; CPK 196 U/L. Blood gas analysis showed metabolic acidosis. Hypocalcemia was considered to be due to metabolic acidosis and severe shock. PT and aPTT levels were not increased and the D-dimer level was normal. EKG revealed sinus rhythm and echocardiography showed tricuspid insufficiency with normal ventricular functions and no findings of pulmonary hypertension. Intravenous antibiotics were initiated with a possible diagnosis of septic shock. Intravenous fluid replacement and dopamine infusion were also started because of inadequate tissue perfusion. His perfusion and circulatory problems quickly improved with treatment. Bacterial, viral, and fungal cultures failed to identify a pathogenic organism. Despite his rapid clinical improvement, his fever persisted. Because of abrupt onset of these life-threatening problems associated with hyponatremia and hyperkalemia, his adrenal functions were evaluated after circulatory parameters returned to normal. His serum ACTH, cortisol, aldosterone, and plasma renin activities were all found to be within normal limits. He was re-hospitalized at 7 months of age due to increased defecation frequency and higher than his usual body temperature. Bacteriologic and viral investigations of the feces did not reveal a pathogenic organism. After his diarrhea resolved, his high body temperature continued. The patient is currently 8 months old and his high body temperature continues (Fig. 1).

Patient 2

This boy was born as the third child of 42-year-old parents. Polyhydramnios and presentation problems complicated the delivery and led to a Cesarean delivery. He was admitted to our infectious disease unit due to high fever, when he was 6 months old. His body temperature fluctuated between 37.6 and 39.6°C and was unresponsive to antipyretic medications. On physical examination, his weight was 6800 g (10th–25th centile), length

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of clinical characteristics of three infants with PWS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age/sex</td>
<td>1</td>
</tr>
<tr>
<td>8 months/male</td>
<td>24 months/male</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>Hypotonia</td>
</tr>
<tr>
<td>Feeding difficulty</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Narrow bitemporal diameter</td>
<td>Retrognathia</td>
</tr>
<tr>
<td>Almond shaped eyes</td>
<td>Almond shaped eyes</td>
</tr>
<tr>
<td>Retrognathia</td>
<td>Small hands and feet with tapering fingers</td>
</tr>
<tr>
<td>Small hands and feet with tapering fingers</td>
<td></td>
</tr>
<tr>
<td>Age at onset of fever</td>
<td>15 days</td>
</tr>
<tr>
<td>Observed range of rectal body temperature</td>
<td>37.2–39.6°C (41.8°C when admitted to the ICU)</td>
</tr>
</tbody>
</table>
67 cm (25th–50th centile), and head circumference 42 cm (25th–50th centile). His phenotypic features are summarized in Table 1. No focus for an infection was identified. Clinical suspicion for the diagnosis of PWS was confirmed with methylation analysis on molecular genetic studies. A FISH study demonstrated the deletion on the long arm of chromosome 15. All other investigations for an infectious cause of high fever failed. T4 and TSH levels were within normal limits. The patient has been followed up since his initial hospitalization and his high body temperature has persisted. No other episode resulting in hospitalization has occurred, although his body temperature is still high at 24 months of age (Fig. 1).

Patient 3

This girl was the second child of a 27-year-old mother and 32-year-old father. She was born at term by normal vaginal delivery. Her birth weight and length measured 3550 g (50th–75th centile) and 50 cm (50th centile), respectively. Hypotonia was noted just after birth. She had decreased sweating and dermographism, which was also noted by the parent. Increased body temperature was noted at 7 months of age. She was evaluated for the origin of high fever at 8 months of age. On physical examination, her weight, length, and head circumference were 9350 g (75th–90th centile), 71 cm (50th–75th centile), and 41 cm (3rd centile), respectively. Her rectal temperature was 39.1°C, pulse was 162 b.p.m., respiration rate was 39 breaths/min, and blood pressure was 86/44 mmHg upon admission. Marked hypotonia and retardation in gross motor skills were noted. Other phenotypic findings can be seen in Table 1. Definitive diagnosis was made with methylation studies followed by a FISH study demonstrating the deletion on chromosome 15. Her fever fluctuated between 38.5°C and 39.5°C during her hospital stay. All investigations remained negative for the etiology of the high body temperature. She is currently 10 months old and has had continuing fever without other accompanying findings since her discharge (Fig. 1).

The following investigations were performed in all three patients to identify infectious or inflammatory disorders: CBC, blood smears, CRP, ESR, blood chemistry, urinalysis, CSF examination, direct and stained feces microscopy, PA chest X-ray; throat swabs, blood, urine, CSF, fecal cultures; viral serological investigations and cultures; Salmonella, Brucella serologic investigations; immunoglobulin levels, CH50, PPD skin tests; ANA and anti DNA levels; thyroid function tests, urine output in 24 h, blood and urine osmoralties; abdominal ultrasound, thorax and head CT, bone scintigraphy, echocardiography, microscopical examination of blood films for malaria, blood and urine metabolic screening.

Discussion

All three patients presented here had typical phenotypic findings of PWS and were definitely diagnosed as having PWS by genetic studies. All three infants had high body temperatures starting from early months of their lives. It has been reported earlier that children with PWS might have thermoregulation problems, temperature instability and altered heat sensitivity during infancy. Stevenson et al. reported thermoregulation problems and unexpected death of 10 cases with PWS. Cassidy and McKillop have also reported that temperature instability, which is important at the clinical level, is not a frequent finding in PWS. Williams et al. have suggested that the temperature control problems and their clinical consequences do not necessarily reflect a hypothalamic disorder specific to PWS, but rather they are similar

![Fig. 1](Body temperature profiles of three patients with PWS. The highest temperature observed in each month is represented by '•' for patient 1, ‘–’ for patient 2, ‘■’ for patient 3.)
Hyperthermia in Prader Willi syndrome

Heat stroke is another clinical condition, which is the result of high body temperature, leading to high mortality and morbidity. Hemorrhagic shock and encephalopathy syndrome (HSES) is a condition similar to abrupt-onset septic shock with high mortality, observed especially in infants, which is again caused by high body temperature. The first case presented here was admitted to the intensive care unit due to sudden deterioration with an extremely high body temperature, which was thought to be the result of septic shock, for which all investigations remained negative. We therefore believe that extremely high body temperatures observed in children with PWS may result in life-threatening clinical consequences similar to heat stroke or HSES.

In conclusion, children with PWS may have long standing hyperthermia probably as a result of hypothalamic dysfunction. Extreme body temperatures in these patients may result in life-threatening complications.

References