THE PUBLISHING HOUSE
OF THE ROMANIAN ACADEMY

MEDICINE
Case report

PRADER-WILLI SYNDROME DIAGNOSED IN INFANCY

Mirela Silvia COVĂCESCU[1,2], Ioana Sonia ARDELEANU[1,2], Vasilica PLĂIAŞU[1], Lucica GHIŢĂ[1], Zoica MOLDOVAN[1], Andreea Teodora TOPOR[1], and Ioan GHERGHINA[1,2]

[1]"Alessandrescu-Rusescu" National Institute for the Health of Mother and Child, Pediatrics Department, Bucharest, Romania
[2]"Carol Davila" University of Medicine and Pharmacy, Pediatrics Department, Bucharest, Romania
Corresponding author: Mirela Silvia Covacescu,
E-mail: mirelacovacescu@yahoo.com

Accepted November 9, 2016

Prader-Willi syndrome is a rare disorder determined by the loss of function of genes in the proximal arm of chromosome 15. Clinical observations in infants are: feeding difficulties, need for special feeding techniques, hypotonia, hypogonadism, poor neuropsychological development, poor weight gain, distinctive facial features. Along with child growth excessive eating and obesity set in. Diagnosis is suspected on the clinical findings and it is confirmed by specific genetic testing such as DNA methylation analysis identifying abnormalities in segment 15q11-q13. We describe the case of a 6 months old infant admitted in our clinic for persistent fever. With a history of prematurity (birth weight 1800 g), perinatal hypoxia and a newborn Apgar score of 6, this infant continues to have feeding difficulties and unsatisfying weight gain along with hypotonia at the neurologic examination. Persistent fever determined the team to search for causes of prolonged febrile illness. Anorexia, severe hypotonia and dysmorphic facial features were evaluated by a neurologist and a geneticist and were considered suggestive for Prader-Willi syndrome. In the case of this 6 months old infant the reason for admission was persistent fever, a non-specific symptom that brought into discussion many possible causes demanding extended laboratory testing. Severe anorexia, malnutrition, severe hypotonia and specific facial features guided the diagnostic process towards a possible genetic cause. This case required genetic testing such as conventional karyotyping and FISH technique that were not able to establis the diagnosis. Further genetic evaluation such as DNA methylation analysis identified abnormalities in segment 15q11-q13 with specificity for Prader-Willi syndrome. As a conclusion even if initial laboratory tests were not able to support the diagnosis the suggestive clinical findings determined the team to use expensive and usually inaccessible lab tests that were compulsory for the diagnosis of the presented clinical case.

Key words: Prader-Willi, hypotonia, dysmorphic features, DNA methylation.

INTRODUCTION

Described for the first time in 1956 by Prader *et al*., Prader-Willi syndrome is a multisystemic complex genetic disorder characterized by severe hypotonia and feeding difficulties in early infancy. Later on, the child starts eating excessively and might, if not externally controlled, develop morbid obesity[1,2].

There are three types of genetic abnormalities that could determine Prader-Willi (PW) syndrome: chromosomal paternal deletion (65–75% of the individuals with PW, it is the outcome of an microdeletion of the parternally inherited 15q11.2-q13 segment), uniparental disomy (20–30% of the individuals with PW, there are two chromosomes 15 from the mother with no contribution from the father) and imprinting defects (1–3% of the individuals with PW, most of this kind of deffects are determined by epimutations and are characterised by an exclusive maternal DNA methylation pattern regardless of both parental alleles being present)[3–6].

The clinical suspicion of Prader-Willi syndrome includes evaluation of 6 major criteria (1 point for each) and 11 minor criteria (0,5 points each).

The major criteria[3] are:

1. Neonatal or infantile hypotonia and feeding difficulties such as poor suck
2. Feeding problems and failure to thrive (at infant age)

3. Weight gain at 1–6 years, obesity or hyperphagia
4. Characteristic dysmorphic facial features
5. Small genitalia and later on pubertal delay and genital insufficiency
6. Development delay or intellectual disability.

Minor criteria[3] are:

1. Decreased fetal movement and infantile lethargy
2. Typical behavior problems
3. Sleep apnea
4. Short stature for family by 15 years
5. Hypopigmentation for the family
6. Small hands and feet for height
7. Narrow hands, straight ulnar border
8. Esotropia, myopia
9. Thick, viscous saliva
10. Speech articulation deffects
11. Skin picking.

Clinical diagnosis requires five points of which at least four being major criteria at an age smaller than three years old and eight points for children older than three years, at least five being major criteria[3].

An article on comparrative molecular approaches in Prader-Willi syndrome diagnosis, published in 2015 mentions only 47 pacients (32 girls and 15 boys) registered with PW in our country[4].

MATERIALS AND METHODS

We present the case of S.F.M., female infant, aged 6 months, tranferred from a territorial hospital to our clinic ("Alessandrescu-Rusescu" National Institute for the Health of Mother and Child, Bucharest). She was admitted in the hospital for persistent fever.

Personal medical history of the infant revealed that she is born prematurely (gestational age 33–34 weeks) from an unfollowed pregnancy with a birth weight of 1800 g. At birth the amniotic fluid had meconial aspect. She suffered from perinatal hypoxia with an Apgar score of 6. During her stay in the maternity she was diagnosed and treated for neonatal sepsis. In the following period the infant suffered from premature anemia, retinopathy of prematurity, patent foramen ovale. As a newborn she was diagnosed with urinary tract infection (caused by Escherichia coli) and one episode of upper respiratory tract infection associated with bilateral otitis media. She is unvaccinated and did not receive rickets profilaxy. From birth the infant has feeding difficulties and she initially needed enteral feeding. Familial history reveals a mother diagnosed with intellectual disability who abandoned the newborn at the maternity hospital right after birth.

Two week before the transfer to our clinic the infant was admitted at the territorial hospital for rhinopharyngitis and otitis media where she was treated with Ceftriaxone, Hydrocortisone hemisuccinate and symptomatic treatment. She is transferred to our clinic because of persistent fever despite broad spectrum antibiotic therapy.

In which concerns clinical examination the infant presented with:

- Altered general status
- Fever (38.8 ^{o}C)
- Dysmorphic facial features (almond-shaped palpebral fissures, thin upper vermillion), hands and feet small for height
- Malnutrition
- Pale rose skin, dry oral mucosa with oral candidosis
- Pharyngitis
- Generalised enlarged lymph nodes
- Rickets sequelae (frontal bossing, right plagiocephaly, genu valgum, bilateral talipes calcaneovalgus)
- Hypotonia, delayed neuromotor development: does not support head and does not sit up, she does not follow moving objects with her eyes.

Taking all the above into consideration the infant was admitted with the following diagnosis:

1. Prolonged fever illness
2. Rinopharyngitis
3. Hypotonia
4. Mild malnutrition
5. Oral candisosis.

Laboratory testing was directed towards main causes of prolongued febrile illness, malnutrition and hypotonia.

Work-up revealed:

- Normal blood count
- Inflamation markers within normal range
- Normal thyroid function
- Digestion test within normal range
- Urinalysis with high lymphocyte count and presence of bacteria rises the suspicion of urinary tract infection but the urine culture shows growth of several types of bacteria

probably due to contamination. All the urine cultures performed afterwards were negative.

- Negative tests for Hepatitis B and C, Human Imunodefficience Virus, Cyto-megalovirus and Syphilis
- Cardiac, thyroid and abdominal echography showed no modifications
- Normal aspect of the thoracic radiography
- Otorhinolaringology evaluation: acute rinopharyingitis, dental eruption, normal ear evaluation
- Ophtalmology evaluation: normal aspect on ophtalmoscopy.

Following clinical examination and paraclinical work-up principal causes of fever were ruled out along with main causes of malnutrition. The only possible hypotesis at this point was a genetic cause.

Asessment of hypotonia included:

- Serum creatinfosfokinase and ammonia levels were evaluated and were found within normal range
- Neurological evaluation: severe hypotonia and severe psychological and motor development delay with no other suggestive findings
- Transfontanelar echography with normal aspect.

Genetic evaluation raised the suspicion of Prader-Willi syndrome. Conventional karyotyping is normal (46,XX) and FISH technique did not support the clinical suspicion. In this situation DNA methylation analysis was performed at an external private laboratory.

During her stay in our hospital the infant received symptomatic treatment for fever, local treatment for oral candidosis, intravenous rehydratation and symptomatic treatment for upper respiratory tract infection with initial favorable development. While waiting for the results of DNA methylation analysis the infant was tranferred to the nutritional recovery department where she continues to present intermitent fever with no signs of acute infection (Figure 1). Weight gain during her long stay in the hospital was insignifiant (Figure 2) as she continued to have feeding difficulties.

Final diagnosis is Prader-Willi syndrome and it is supported by clinical findings and DNA methylation analysis.

The clinical criteria considered as clues for Prader-Willi syndrome in this particular case were:

- Major criteria: hypotonia (Figure 3), feeding difficulties, poor weight gain, neuro-motor defficit, particular facial features (thin upper vermillion, down-turned corners of the mouth, almond-shaped palpebral fissures) (Figures 4 and 5)
- Minor criteria: weak cry/lethargy, hypopigmentation, small stature, hands and feet small for age and length (Figure 6).

Therefore we have 5 major criteria and 4 minor criteria. For clinical diagnosis of Prader-Willi syndrome we needed five points, four of which from major criteria[3]. Although fever is not a criteria we can consider this symptom as supportive finding.

DNA methylation study revealed an abnormal methylation profile in the region 15q11-q13, a specific finding for Prader-Willi syndrome.

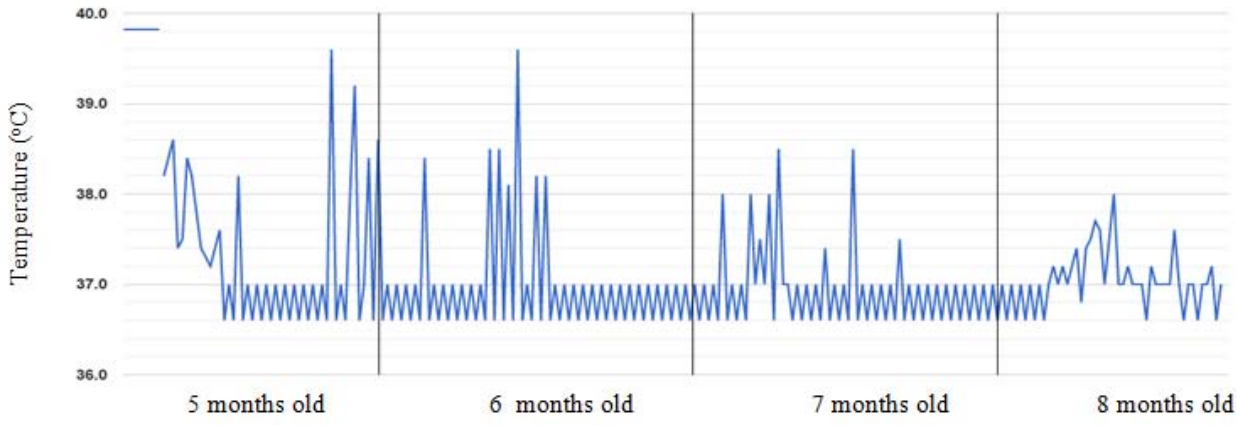

Fig. 1. S.F.M. 6 months old – temperature curve evolution.

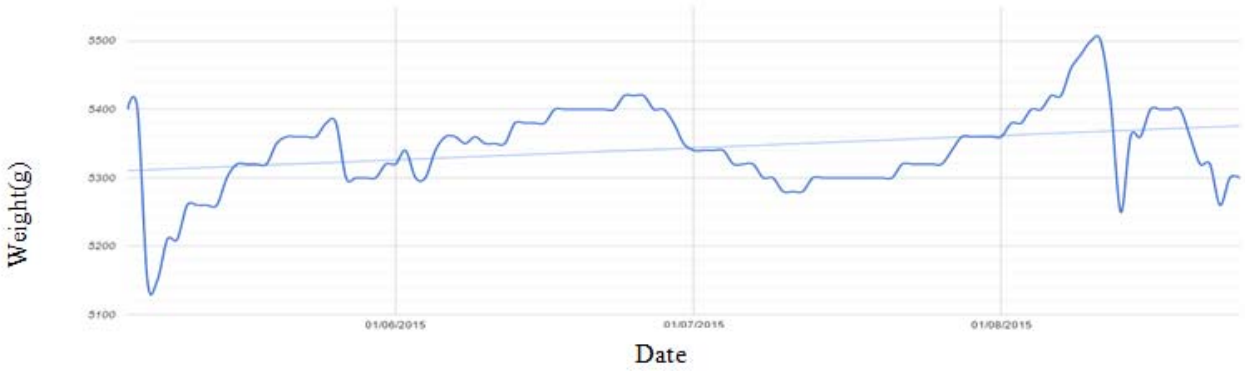

Fig. 2. S.F.M. 6 months – weight gain during her stay in our hospital.

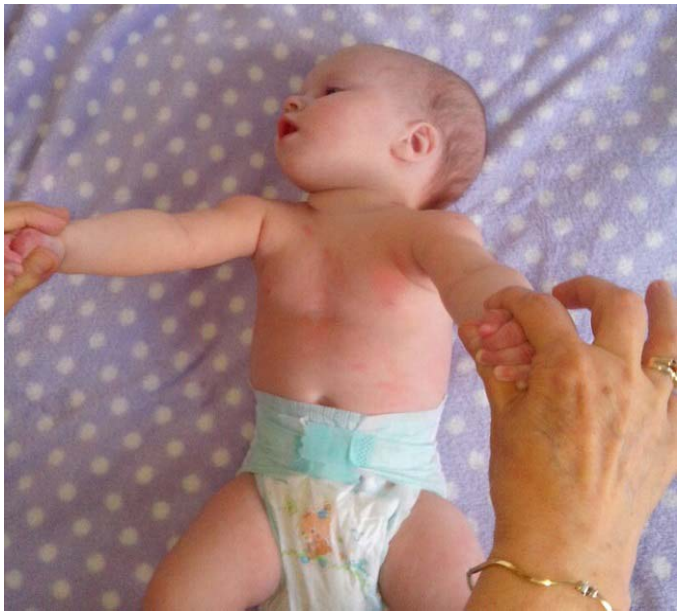

Fig. 3. S.F.M 6 months old, hypotonia.

Fig. 4. S.F.M. 6 months old, almond-shaped eyes.

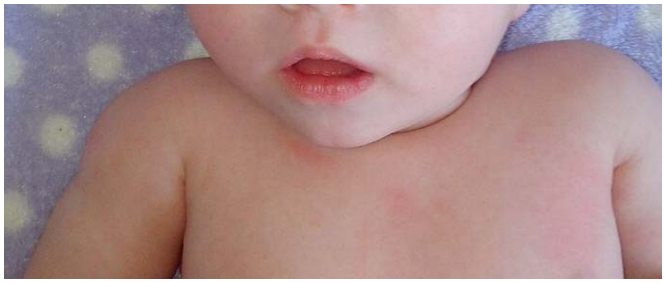

Fig. 5. S.F.M 6 months old, thin upper vermillion and down-turned corners of the mouth.

Fig. 6. S.F.M, 6 months old, small hands and feet for length and age.

RESULTS AND DISCUSSIONS

What makes this case interesting are its particularities such as the rarity of this disorder and the long and misleading diagnostic process. Persistent fever could have been linked with the suspicion of urinary tract infection while it was actually a supportive finding for the final diagnosis of Prader-Willi syndrome. Further more, the diagnostic process could have been interrupted when all the laboratory tests were within normal range and even genetic testing such as conventional karyotyping and FISH technique were not able to establish the diagnostic. High clinical suspicion for Prader-Willi syndrome kept the team going and made us decide to use expensive and usually inaccesible genetic tests such as DNA methylation analysis.

Children with Prader-Willi syndrome demand long time surveillance as they grow up. The only available tratment is supportive by dealing with natural evolution of the disease and fighting complications. There are multiple aspects to take into consideration such as behavioral and psychiatric disturbances (temper tantrums, stubborness, controlling and manipulative behavior, compulsivity and difficulty with change in routine), hypogonadism present in both sexes, growth hormone deficiency and other endocrine issues such as central adrenal insufficiency, hypothyrodis, impaired glucose intolerance and diabetes mellitus.

They also suffer from sleep abnormalities including reduced rapid eye movement latency, altered sleep architecture, oxygen desaturation and both central and obstructive apnea. 60–70% of children with Prader-Willi syndrome present with strabismus and a large procent have scoliosis. They are also a challenge for the medical professionals since they have a high mortality rate[3].

The prevalence rate of Prader-Willi syndrome varies a lot worldwide, from 1 per 8,000 populations in Sweeden to 1 per 16,000 populations in Japan and 1 per 45,000 populations in the United Kingdom[4].

In Romania there is an association (Romanian Prader-Willi Association) that aims to increase the quality of life for people affected by Prader Willi Syndrome. One of their objective is to stimulate early diagnosis. They report, for our country, 47 registered patients with PW (32 girls and 15 boys).

An important consideration regarding the diagnosis of Prader-Willi syndrome is the similarity with Angelman syndrome, a distinct neurogenic disorder cause by the absence of the maternal copy in the same chromosomal region as the one responsible for PW. In some cases comparative genomic hybridization or FISH technique might

reveal a deletion in the 15q11-q13 region but even so, DNA methylation study is neccesary if the child is younger than 2 years old since Angelman syndrome can present with similar clinical findings in the neonatal period (hypotonia, feeding difficulties and developmental delay)[5, 6].

CONCLUSIONS

As a conclusion, in what concerns this clinical case, prolonged fever has initialy mislead the diagnosis towards multiple possible diseases that required complex laboratory tests. The association of other clinical elements (such as severe anorexia, malnutrition, severe hypotonia and facial dysmorphia) guided the diagnosis process towards a genetic cause. Even if usual laboratory tests did not support the clinical diagnostic of Prader-Willi syndrome our team pursued their suspicion and used expensive and usually inaccessible lab tests that were compulsory for the diagnosis of the presented clinical case.

REFERENCES

1. Angulo M.A., Butler M.G., Cataletto M.E., *Prader-Willi syndrome: a review of clinical, genetic, and endocrine finding, J. Endocrinol. Invest.*, **2015**, 38, 1249.
2. Driscoll D.J., Miller J.L., Schwartz S. *et al*., "GeneReviews", Pagon R.A. Ed., University of Wasington, Seattle, 2013.
3. Cassidy S.B. et al. *Genet. Med*., **2012**, *Prader-Willi syndrome*, 1, 10.
4. Botezatu A., Puiu M. *et al*., *Elsevier Gene*, **2016**, Comparative molecular approaches in Prader-Willi syndrome diagnosis, 575, 353.
5. Glenn C.C. *et al*., *Genomic imprinting: potential function and mechanisms revealed by the Prader-Willi and Angleman Syndromes, Mol. Hum. Reprod*., **1997**, 4, 321.
6. Mann M.R.W, Bartolomei M.S., *Towards a molecular understanding of Prader-Willi and Angleman syndromes*, *Hum. Mol. Genet.*, **1999**, 8, 1867.