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 establish 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. 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 paternally 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 defects are determined by epimutations and are characterised by an exclusive maternal DNA methylation pattern regardless of both parental alleles being present).

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 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 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 defects  
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.  

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

MATERIALS AND METHODS  

We present the case of S.F.M., female infant, aged 6 months, transferred 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 °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 candidosis.  

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

Work-up revealed:  
- Normal blood count  
- Inflammation 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.
Prader-Willi syndrome diagnosed in infancy

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

- Negative tests for Hepatitis B and C, Human Immunodeficiency Virus, Cytomegalovirus and Syphilis
- Cardiac, thyroid and abdominal echography showed no modifications
- Normal aspect of the thoracic radiography
- Otorhinolaringology evaluation: acute rinopharyngitis, dental eruption, normal ear evaluation
- Ophthalmology evaluation: normal aspect on ophthalmoscopy.

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

Assessment 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 rehydration and symptomatic treatment for upper respiratory tract infection with initial favorable development. While waiting for the results of DNA methylation analysis the infant was transferred to the nutritional recovery department where she continues to present intermittent fever with no signs of acute infection (Figure 1). Weight gain during her long stay in the hospital was insignificant (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 deficit, particular facial features (thin upper vermillion, downturned 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. 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.

![Temperature curve evolution](image1.png)

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 vermilion and down-turned corners of the mouth.
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 inaccessible genetic tests such as DNA methylation analysis.

Children with Prader-Willi syndrome demand long time surveillance as they grow up. The only available treatment 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, hypothyrosis, 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 percent have scoliosis. They are also a challenge for the medical professionals since they have a high mortality rate.6

The prevalence rate of Prader-Willi syndrome varies a lot worldwide, from 1 per 8,000 populations in Sweden to 1 per 16,000 populations in Japan and 1 per 45,000 populations in the United Kingdom.7

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

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