Rom J Leg Med [28] 253-256 [2020]
DOI: 10.4323/rjlm.2020.253

NEVER UNDERESTIMATE MILD RESPIRATORY SYMPTOMS IN CHILDREN AFFECTED BY PRADER-WILLI SYNDROME - A CASE REPORT

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Abstract: Prader-Willi syndrome is a rare disease linked to chromosome 15, with morpho-functional features which place patients' lives at risk. We present the case of a 4-year-old boy affected by Prader-Willi syndrome, who died, in apparent good health, as reported by his mother, except for a common cold, diagnosed by a doctor few days before his death. Some months before, he was admitted to hospital with infectious pneumonia which was successfully treated. Forensic pathologist who performed the autopsy attributed the cause of death to respiratory insufficiency caused by acute inflammation on chronically impaired lungs. The reported case serves as a reminder to never underestimate the presence of mild respiratory and infectious symptoms in children affected by Prader-Willi Syndrome.

Keywords: Prader-Willi syndrome; respiratory failure; forensic pathology.

INTRODUCTION

Prader-Willi syndrome (PWS) is a genetic disorder that affects between 1:26000 and 1:16000 people, without differences in gender and ethnicity [1]. A rare DNA mutation is the source of the syndrome. In 1981 Ledbetter *et al*. identified a microdeletion on the long arm of chromosome 15, del (15) (q11-q13), as the cause of the syndrome described by Prader *et al*. in 1956 [2, 3].

Some of the syndrome's typical traits may be identified at birth, such as hypotonia, hypogonadism, feeding difficulties and several facial features such as narrow bifrontal diameter, almond-shaped eyes, small hands and feet, down-turned corners of the mouth, and dolichocephaly (abnormality of skull shape characterized by increased anterior-posterior diameter). Somatic and cognitive development delay appear in the first years of life [4], followed by hyperphagia and behavioral disorders. Other clinical findings are thalamic dysfunctions, which contribute, along with obesity and its complications, in reducing life expectancy of affected patients [2, 5]. In fact, disease prognosis in Prader-Willi syndrome is strictly connected to obesity control and prevention of its consequences [1] and the major cause of death in children is respiratory disease, particularly infections [6].

We report the case of a 4-year-old boy affected by Prader-Willi syndrome who was found dead at home.

CASE REPORT

A few months before his death, a 4 years old boy, affected by Prader Willi syndrome, diagnosed with molecular tests after birth, was admitted to the hospital because of respiratory distress. He was affected by Pneumococcal and Human Respiratory Syncytial Virus infections which were successfully treated.

A few days before his death he showed a productive cough, runny nose and several episodes of dyspnea. For these symptoms he was visited by a doctor who, detecting no other signs during physical examination, classified the disease as a common cold.

On the morning of the boy's death, the mother found her son asleep with wheezing not perceived as different from usual, but one hour later, called the local emergency number because her son was not breathing. The doctor found him without vital signs; after all

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attempts of resuscitation failed, the child was declared dead. A forensic pathologist was requested to perform the autopsy.

Autopsy findings

During external examination body length of 105 cm and weight of 30 kg were measured; body temperature was 37.6°C. Cervical lymphadenopathy, dolichocephaly, almond-shaped eyes, down-turned corners of the mouth, thin upper lip of the mouth, small hands and feet and penis hypoplasia, abundant subcutaneous fat (his body mass index was > 99th percentile) and mild skin-fold maceration were also observed. No injuries caused by other people were detected. Autopsy revealed cerebral edema with reduced convolutions (microgyria) in frontal and temporal lobes and hepatomegaly. Cervical and abdominal lymphadenopathy was also noted. The trachea had reduced consistency and a smaller diameter than normal; cardiac size was enlarged. Lungs appeared edematous with white material lining inside bronchi and bronchioles. Lungs' histopathological examination showed vessel congestion and focal alveolar hemorrhages; interstice appeared diffusely thickened with lymphocytic, monocytic and macrophages infiltration; multi-focal alveolar collapsed areas, alternating with expanded alveoli containing granular eosinophilic material mixed with lymphocytes, granulocytes and macrophages (Fig. 1). Histological examination of the remaining organ samples did not show other pathological elements.

Immunohistochemistry performed on lungs samples, detected a large number of macrophages, which were positive for cluster of differentiation 68 (CD-68) (Fig. 2, A and B). Inflammatory infiltrate was also positive for myeloperoxidase, indicating the presence of neutrophilic granulocytes and monocytes. (Fig. 2, C and D). The cause of death was attributed to respiratory insufficiency caused by acute inflammation on chronically impaired lungs.

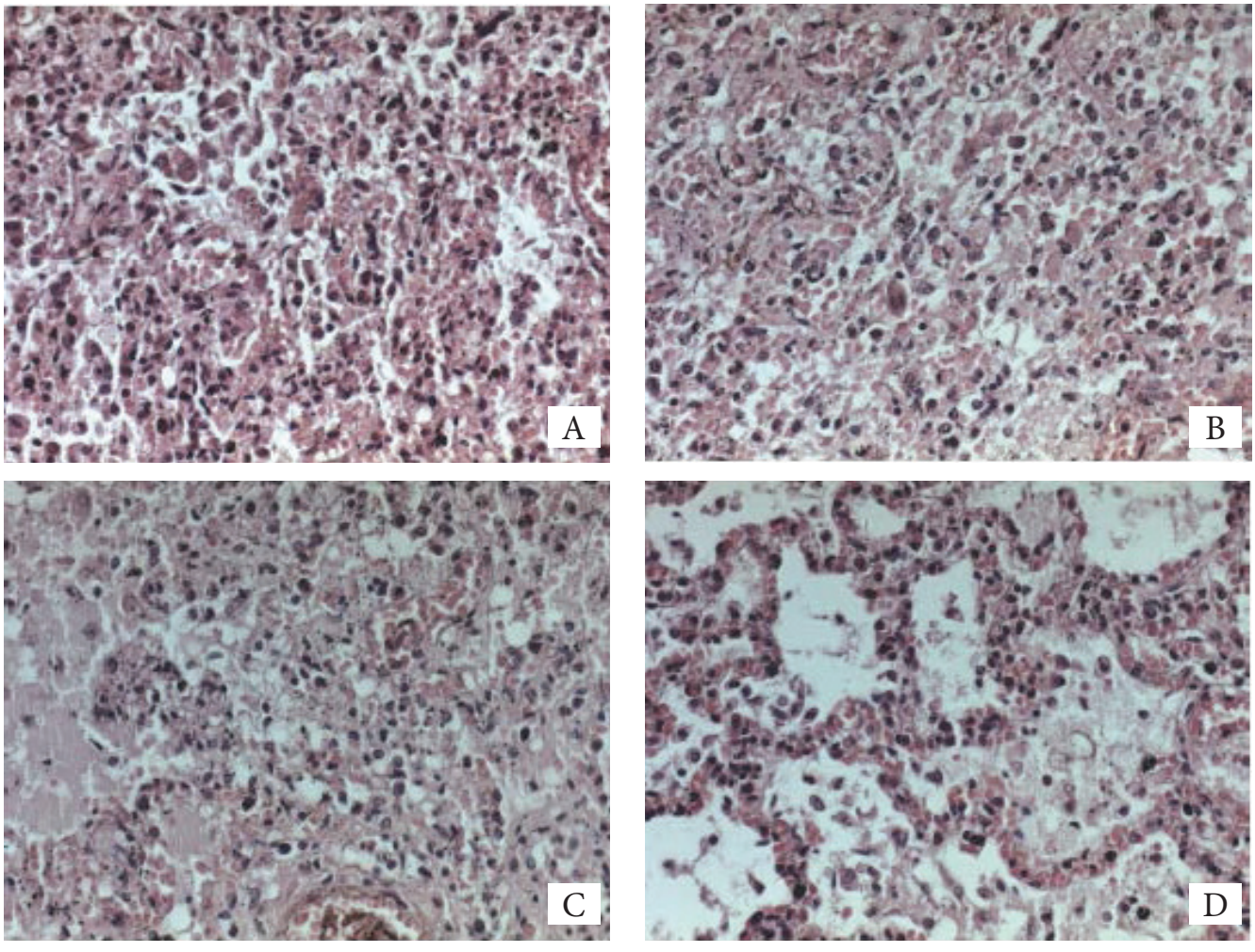

Figure 1. Histological images of the lungs. Hematoxylin and eosin staining. Inflammatory infiltration, especially into the alveolar septum; alveolar edema; alveolar collapsed areas.

DISCUSSION

PWS is a rare genetic disorder, often diagnosed in early childhood because of its nonspecific clinical findings and mild dysmorphisms in infants [7]. The main symptoms of the disorder at birth are hypotonia, poor sucking reflex, diminished or absent cry, and somnolence, which determine a global development delay in the first years of life. After one year of age, hyperphagia becomes a predominant sign that soon leads to obesity and related complications, if not controlled. Other common features are mild to moderate mental retardation and several hypothalamic dysfunctions, such as growth hormone deficit, body temperature dysregulation, high pain threshold, sleep disturbance and hypogonadism, that becomes more evident during adolescence [7].

In 1981, Holm *et al.* suggested some clinical criteria to identify this syndrome [1, 8] that reached a consensus in 1993 [9], at a time when genetic tests were not readily available in all laboratories [9]. Even now, these criteria, modified by Gunay-Aygun *et al.* [8] in 2011, who proposed a further selection criteria for patients to be tested for specific DNA investigations, are considered the first tools used in the diagnostic process, in order to identify early the syndrome and to establish satisfactory assistance, therapy and follow-up, thus improving life expectancy of affected patients. Moreover, the American Academy of Pediatrics established the molecular testing strategy for PWS [7].

Chromosome 15 is involved in the genesis of PWS: microdeletion of 15q11-q13, uniparental disomy (UPD) or imprinting errors lead to this syndrome. This region contain specific genes which encode one or more important proteins for brain development and in particular for the hypothalamus [1].

Many studies confirmed that infants affected by PWS have a shorter life expectancy than the overall population [2, 10, 11]. In fact, the syndrome is associated with an increased mortality and a higher rate of sudden

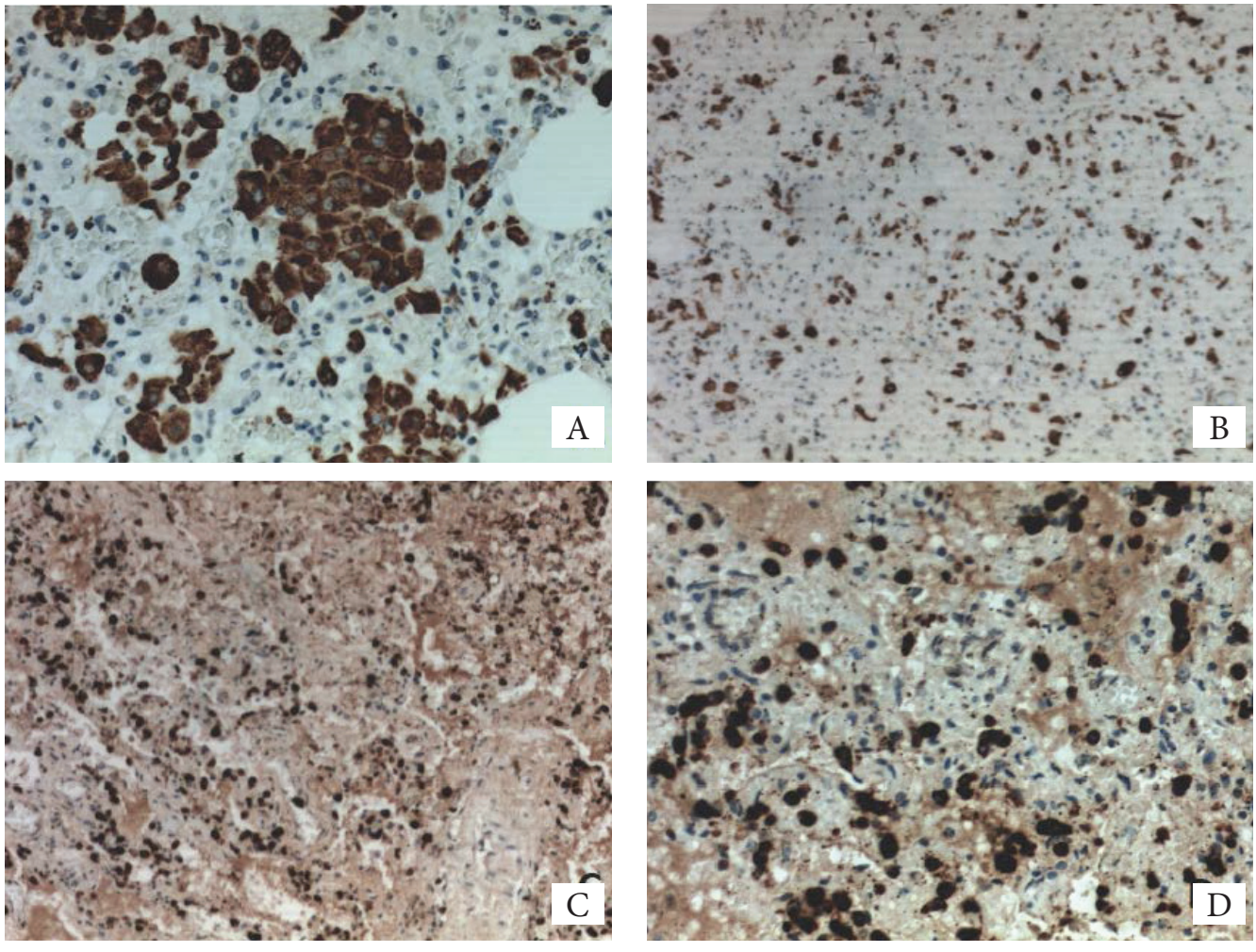

Figure 2. Histological images of the lungs. A and B Immunohistochemistry for CD68. C and D Immunohistochemistry for Myeloperoxidase.

death, both in childhood and in adulthood [2, 10].

In childhood most deaths are due to respiratory problems, particularly infections [7]; in young adults the main causes of death are related to obesity complications such as diabetes and respiratory insufficiency [2, 10]. The obesity that these patients develop in early childhood due to uncontrolled hyperphagia may lead to hypoventilation [8], facilitating the onset of respiratory failure. For this reason, great attention should be paid to monitor and control these conditions, and family education is recommended. Subjects with PWS also present an increased incidence of sleep apneas and a reduced response to hypercapnia during sleep, which partially explain the high number of deaths during sleep [12]. Respiratory dysfunction is further worsened by coexisting scoliosis or kyphosis and by residual hypotonia of the respiratory muscles [9, 12].

In the case we described, the diagnosis of PWS was formulated at birth, when clinical suspicion was confirmed by genetic tests. Macroscopic and microscopic autopsy findings demonstrated that the cause of death was related to extensive lung inflammation which caused a severe respiratory insufficiency on chronically impaired lungs. In fact, the forensic pathologist identified in the lungs both acute and chronic inflammation response signs, suggesting that acute inflammation developed on a existing chronic inflammation.

The reactive nature of the cervical and abdominal lymphadenopathy and increased body temperature, allowed to hypothesize an infectious origin of the disease. In the case we presented, during doctor's physical examination, carried out a few days before child's death, there was no hyperthermia which could have developed in the following days. Anyway, on this point it is worth highlighting that temperature instability is a common trait in PWS children and it is a consequence of a primitive hypothalamic dysfunction. Therefore, in these subjects, fever is not always an indication of a systemic inflammatory response, but it could be merely an expression of the syndrome. This characteristic of PWS represents a potentially dangerous condition as it may mask an infectious state that poses a risk to the patient's life. Moreover, hyperthermia had been proved a risk factor for sudden death in children affected by PWS, since it has a negative effect on the waking state and on the respiratory system [2, 13]. In these cases, the subject died unexpectedly in a very short time from the onset of signs and symptoms, which are often mild and underestimated [5, 13].

In conclusion, severe respiratory failure resulting from a widespread inflammatory lung process, caused the child's death.

With the presented case, we aim to highlight the importance of a knowledge of PWS and its characteristics. In cases of upper airway infection in patients affected by PWS, we suggest doctors to carry out very thorough clinical examinations and monitor symptoms evolution to exclude major illnesses that could lead these subjects to death.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgement

The authors would thank dr. George Rettagliata (NY) for his valuable contribution in the final revision of the article.

References

1. Pomara C, D'Errico S, Riezzo I, de Cillis GP, Fineschi V. Sudden cardiac death in a child affected by Prader-Willi syndrome. Int J Legal Med. 2005;119(3):153-157.
2. Dykens EM. Aging in rare intellectual disability syndromes. Dev Disabil Res Rev. 2013;18(1):75-83.
3. Ledbetter DH, Riccardi VM, Airhart SD, Strobel RJ, Keenan BS, Crawford JD. Deletions of chromosome 15 as a cause of Prader-Willi syndrome. N Engl J Med. 1981;304(6):325–329.
4. Hurren BJ, Flack NA. Prader-Willi Syndrome: A spectrum of anatomical and clinical features. Clin Anat. 2016;29(5):590-605.
5. Schrander-Stumpel CT, Curfs LM, Sastrowijoto P, Cassidy SB, Schrander JJ, Fryns JP. Prader-Willi syndrome: causes of death in an international series of 27 cases. Am J Med Genet A. 2004;124A(4):333-338.
6. Tauber M, Diene G, Molinas C, Hébert M. Review of 64 cases of death of children with Prader-Willi syndrome (PWS). Am J Med Genet Part A. 2008; 146A: 881-887.
7. Wattendorf DJ, Muenke M. Prader-Willi syndrome. Am Fam Physician. 2005;72(5):827-830.
8. McCandless SE, Committee on Genetics. Clinical report-health supervision for children with Prader-Willi syndrome. Pediatrics 2011;127(1):195-204.
9. Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenberg F. Prader-Willi syndrome: consensus diagnostic criteria. Pediatrics. 1993;91(2):398-402.
10. Nagai T, Obata K, Tonoki H, Temma S, Murakami N, Katada Y, Yoshino A, Sakazume S, Takahashi E, Sakuta R, Niikawa N. Cause of sudden, unexpected death of Prader-Willi syndrome patients with or without growth hormone treatment. Am J Med Genet A. 2005;136(1):45-48.
11. Lionti T, Reid SM, Rowell MM. Prader-Willi syndrome in Victoria: mortality and causes of death. J Paediatr Child Health. 2012;48(6):506-511.
12. Yee BJ, Buchanan PR, Mahadev S, Banerjee D, Liu PY, Phillips C, Loughnan G, Steinbeck K, Grunstein RR. Assessment of sleep and breathing in adults with prader-willi syndrome: a case control series. J Clin Sleep Med. 2007;3(7):713-718.
13. Stevenson DA, Anaya TM, Clayton-Smith J, Hall BD, Van Allen MI, Zori RT, Zackai EH, Frank G, Clericuzio CL. Unexpected death and critical illness in Prader-Willi syndrome: report of ten individuals. Am J Med Genet A. 2004;124A(2):158-164.