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CASE REPORT

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Sudden cardiac death in a child affected by Prader-Willi syndrome

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Abstract A case of sudden cardiac death in a 3-year-old young male affected by Prader-Willi syndrome, clinically diagnosed and confirmed by means of DNA methylation, is presented. The infant suddenly collapsed at home and was taken apparently unconsciousness by his mother to the emergency clinic where he was pronounced dead. A complete postmortem examination was performed and the histological findings led to the definition of cardiac death with a typical picture of contraction band necrosis. Pulmonary hypoxic alterations are frequently reported as the primary cause of death in PWS cases. In this fatal case according to the macroscopic and microscopic findings, the cause of death was most likely cardiac and possibly related to contraction band necrosis linked with ventricular fibrillation and sudden death.

Keywords Prader-Willi syndrome · Sudden cardiac death · Contraction band necrosis

Introduction

Prader-Willi syndrome (PWS) was first described in 1956 by Prader et al. who reported a series of patients with mental impairment, short stature, hypogonadism and obesity [1]. In 1981 Ledbetter et al. identified microdeletions within chromosome 15 as the site for PWS [2]. Actually, the diagnosis of PWS is based on genetic tests that confirm the clinical pattern characterized by muscle hypotonia, mental retardation, hyperphagia and obesity, hypogonadism and cryptorchidism. Disease prognosis in PWS is strictly connected to the control of obesity and its consequences. Exitus is an extremely rare event in the pediatric age group and has usually been ascribed to respiratory failure. However, the cause of death in these reports was typically based on clinical diagnosis without autopsy confirmation.

Our report concerns the sudden death of a 3-year-old male child affected by PWS who suddenly collapsed at home; the macroscopic and microscopic findings are discussed.

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Case report

VPC, a 3-year-old male infant affected by PWS clinically diagnosed and confirmed by genetic testing, suddenly collapsed while he was playing with his mother at home during a clinical phase of apparent good health. The child was taken to the local hospital by his mother and was apparently unconscious. In the emergency room the child exhibited pupillary rigidity and cardiac arrest. The vital parameters were monitored but the child was pronounced dead before cardiopulmonary resuscitation attempts could be carried out. A complete autopsy was performed 2 days later. The body was 107 cm long, 35 kg in weight, with a cranium circumference of about 96 cm (Fig. 1). External examination showed a severely hypotonic muscular body mass and an excessive accumulation of subcutaneous fat, penis hypoplasia, and an undescended scrotum. At internal examination the brain was edematous with reduced convolutions (microgyria) in the parietal and occipital lobes and revealed hypoplasia of the olivary complex in the medulla oblongata. The tracheo-bronchial tree and lungs were unremarkable except for the presence of a white fluid in the upper respiratory tract. Cardiac size was normal, with a conical shape; sections of the coronary arteries and main branches were unremarkable. Macroscopic examination of abdominal organs was unremarkable except for the liver, presenting a regular shape but enlarged volume and weight.

Cardiac histology findings were represented by spotty areas of fibrosis, observed in the myocardium of the anterior

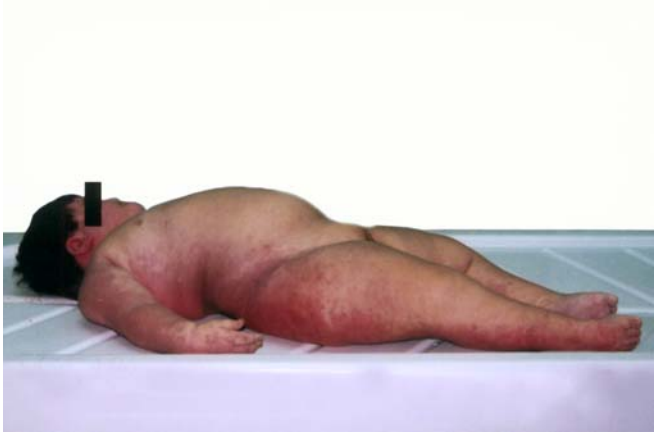

Fig. 1 The body with an excessive accumulation of subcutaneous fat

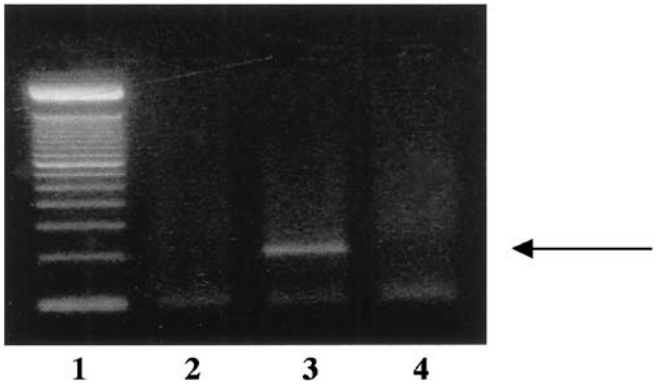

Fig. 3 DNA methylation test showing in *lane1* molecular weight ladder, *lane 2* patient, *lane 3* normal control, and *lane 4* DNA from Prader-Willi subject control. In the methylation test the DNA from our patient and from another patient affected by PW syndrome as control, clearly demonstrated the lack of paternal contribution in contrast with the normal control line (*lane 3*)

left ventricle with a size corresponding to 20% of the histologically examined area. Myocytes showed eosinophilic cross-bands ranging from segments of hypercontracted or coagulated sarcomeres to total disruption of myofibrils and cells with a granular aspect (Fig. 2). More specifically, the myocardial contraction band necrosis (CBN) was variably distributed in multiple foci, formed by a few myocells. The number of foci and myocells with non-haemorrhagic CBN were 219 and 272 in the anterior and 594 and 461 per 100 mm^2 in the posterior left ventricle, 19 and 36 in the interventricular septum and 6 and 22 in the right ventricle. There were no other findings except for mild brain and lung edema and generalized intraparenchymal acute haemostasis.

PWS diagnosis was based on body appearance and was confirmed by genetic testing. The karyotype of peripheral lymphocytes and FISH (fluorescence-in-situ hybridization) were performed using probes specific for the Prader-Willi/Angelman region which were normal. The DNA methylation test and the segregation analysis of the microsatellites located in the same region revealed a uniparental maternal disomy, lacking a paternal contribution (Figs. 3 and 4). The child had never been treated with growth hormone (GH).

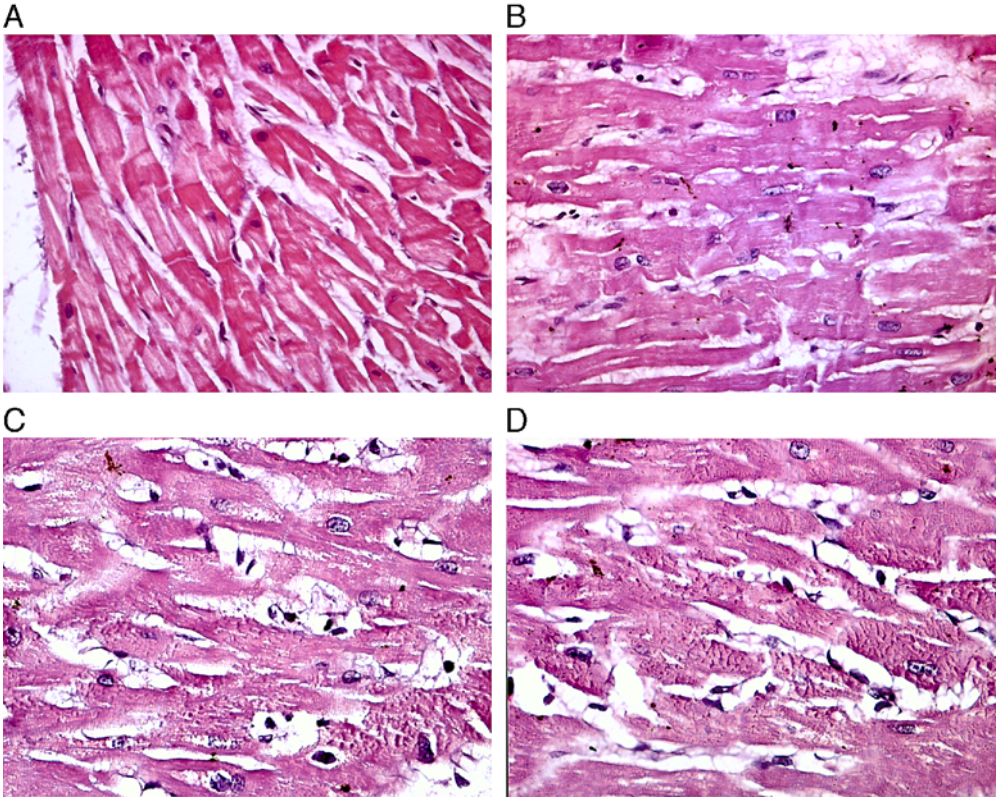

Fig. 2A contraction band necrosis: markedly thickened Z-lines and extremely shortened sarcomeres, **B** spotty fibrosis and multiple foci of hypercontracted sarcomeres (H&E×100), **C** granular destruction of myofibrils, associated with paradiscal lesion (H&E×250), **D** pancellular lesion with fragmentation of hypercontracted myofibrils and band formation of hypercontracted or coagulated sarcomeres (H&E×250)

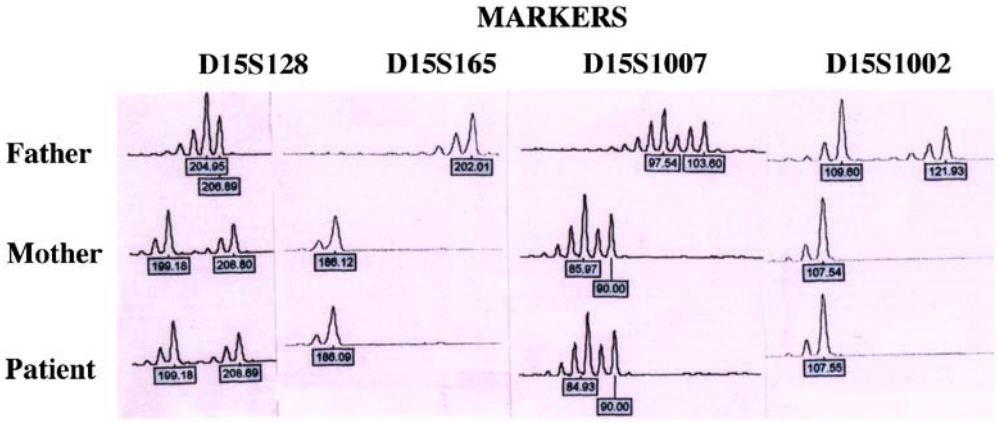

Fig. 4 Segregation analysis of four microsatellites located in the PW/A region: uniparental maternal disomy lacking paternal contribution

Discussion

In the case described PWS diagnosis was based on clinical criteria and was confirmed by genetic tests. According to macroscopic and microscopic findings, the cause of death was most likely cardiac and possibly related to CBN linked with ventricular fibrillation and sudden death.

Cases of sudden death due to rare diseases are a matter of forensic interest [3], especially in the pediatric age group. PWS is defined as a rare syndrome: several studies suggest a moderate frequency and a prevalence generally between 1:26,676 [4] or 1:22,000 [5, 6] and 1:16,062 [7–10], occurring in both sexes and in all ethnic groups.

PWS is a developmental disorder clinically characterized by severe hypotonia and feeding difficulties in early childhood, which often lead to an insatiable appetite (hyperphagia) in infancy thus developing morbid obesity, unless strict external control is imposed. A typical clinical aspect of PWS is hypogonadism and in particular, genital hypoplasia is evident at birth. More characteristic of the disease is a hypoplasic scrotum, that is small, poorly wrinkled and pigmented. Unilateral or bilateral cryptorchidism is present in 80–90% of patients. The hypogonadism which has a hypothalamic origin causes incomplete pubertal development and infertility in both sexes [11]. Diagnostic criteria for PWS have been collected and published in 1993 by Holm et al. distinguishing a major and a minor group [12] (Table 1).

Clinical suspicion needs to be confirmed by genetic tests. With the introduction of chromosomal banding it was noted that chromosome 15 was involved in the genesis of PWS [13–16]. Several studies regarding chromosome 15 in patients with PWS demonstrated a deletion of 15 q_{11}–q_{13} [2]; later it was observed that the deleted 15 q was paternal in all informative cases, and the exclusively paternal origin of the deletions was demonstrated by molecular analysis [17–19]. A maternal uniparental disomy of chromosome 15 (UPD 15) or an imprinting deficit (ID) could also be involved. UPD is present when both chromosomes in one pair are inherited from a single parent. Paternal deletions occur in 70–75% of cases, UPD 15 in about 20–25%, while ID is rare with a frequency of 2–5%. In less than 5%, there could also be an unbalanced translocation, i.e. an exchange of chromosomal material between two chromosomes [20, 21].

The methylation test is commonly used as a standard genetic test [22]; it detects all three of the abovementioned groups of molecular defects but does not distinguish between them, so further analysis is required. In particular, fluorescence-in-situ hybridization (FISH) detecting deletions, and analysis of polymorphic DNA markers to detect UPD; if both of these tests are negative, an imprinting defect is likely [23].

The region 15 q_{11}–q_{13} is believed to contain a specific gene or genes, which encode one or more important proteins for brain development and in particular for the hypothalamus [24].

Prognosis in PWS is strictly related to the control of pathological obesity and its consequences, such as hypoventilation, cardiac failure and diabetes. Death in the pediatric age group seems to be a rare event as suggested by the fact that only few cases of death in infants with PWS have been reported. In these previously described case reports, clinical features included coughing, fever and bronchopulmonitis, and death was attributed to respiratory failure. More often, the cause of death was based only on a clinical diagnosis, and was not confirmed by a complete autopsy [25–28]. This still represents a limiting factor in the study of Prader-Willi syndrome, and a multidisciplinary approach is called for by some authors, also by performing an autopsy in order to determine a possible underlying mechanism [28–31].

In contrast, in our case the autopsy confirmed the absence of acute pulmonary pathologies. The cardiac histopathological study revealed significant alterations consistent with CBN which can be used as a marker of sudden cardiac death [32]. Histologically, this form of myocardial necrosis is characterized by irreversible hypercontraction of the myocell with a breakdown of the whole contractile apparatus with markedly thickened Z-lines and extremely short sarcomeres. This breakdown varies from irregular, pathological and eosinophilic cross-bands consisting of segments of hypercontracted or coagulated sarcomeres, to a total disruption of myofibrils, the whole cell assuming a granular aspect without clear-cut pathological bands. The obvious need is to discriminate between CBN resulting from pre-terminal stimuli and its presence as a histological sign of adrenergic overdrive during the course of a disease. A significant variability of this lesion in different normal and

Table 1 Diagnostic criteria for Prader-Willi syndrome

Criteria	Diagnostic criteria for Prader-Willi syndrome
Major criteria	
1	Neonatal and infantile central hypotonia with poor sucking, gradually improving with age
2	Feeding problems in infancy with need for special feeding techniques and poor weight gain/ failure to thrive
3	Excessive or rapid weight gain on weight-for-length chart (excessive is defined as crossing two centile channels) after 12 months but before 6 years of age; central obesity in the absence of intervention
4	Characteristic facial features with dolichocephaly in infancy, narrow face or bifrontal diameter, almond-shaped eyes, small mouth with thin upper lip, downturned corners of the mouth (3 or more required)
5	Hypogonadism with any of the following, depending on age: Genital hypoplasia (male: scrotal hypoplasia, cryptorchidism, small penis and/or testes for age, <5th percentile; female: absence or severe hypoplasia or labia minora and/or clitoris Delayed or incomplete gonadal maturation with delayed pubertal signs in the absence of intervention after 16 years of age (male: small gonads, decreased facial and body hair, lack of voice change; female: amenorrhea or oligoamenorrhea after age 16)
6	Global developmental delay in a child younger than 6 years of age; mild to moderate mental retardation or learning problems in older children
7	Hyperphagia/food foraging/obsession with food
8	Deletion 15q11–q13 on high resolution (>650 band) or other cytogenetic/molecular abnormality of the Prader-Willi chromosome region, including maternal disomy
Minor criteria	
1	Decreased fetal movement, infantile lethargy or weak cry in infancy, improving with age
2	Characteristic behavior problems: temper tantrums, violent outbursts and obsessive/compulsive behavior; tendency to be argumentative, oppositional, rigid, manipulative, possesive, and stubborn; persevering, stealing, and lying (5 or more of these symptoms required)
3	Sleep disturbance or sleep apnea
4	Short stature for genetic background by age 15 (in the absence of growth hormone intervention)
5	Hypopigmentation (fair skin and hair compared to family)
6	Small hands (<25th percentile) and/or feet (<10th percentile) for height and age
7	Narrow hands with straight ulnar border
8	Eye abnormalities (esotropia, myopia)
9	Thick viscous saliva with crusting at corners of the mouth
10	Speech articulation defects
11	Skin picking
Supportive findings (increase the certainty of diagnosis but are not scored)	
1	High pain threshold, decreased vomiting, temperature instability in infancy or altered temperature sensitivity in older children and adults, scoliosis and/or kyphosis, early adrenarche, osteoporosis, unusual skill with jigsaw puzzles, and normal neuromuscular studies

Scoring: major criteria are weighted at one point each. Minor criteria are weighed at one half point. Children ≤3 years of age: five points are required for diagnosis, 4 of which should come from the major group. Children 3 years of age to adulthood: total score of 8 is necessary for the diagnosis. Major criteria must comprise 5 points of the total score (Holm et al. [12])

disease patterns exists. Beyond a histological threshold of 37±7 foci and 322±99 myocytes/100 mm^2, the lesion may indicate sympathetic overdrive in the natural history of a disease and associated arrhythmogenic supersensitivity [32].

In this case the number of foci and myocytes with non-hemorrhagic CBN was 219 and 272 in the anterior ventricle and 594 and 461×100 mm^2 in the posterior left ventricle, 19 and 36 in the interventricular septum and 6 and 22 in the right ventricle, respectively. Myocardial fibrosis was 10% in the anterior and posterior left ventricle, and absent in the right ventricle and the interventricular septum.

The finding of CBN is an important histological sign for interpreting the cause of death and the natural history of a disease in any single patient [32–34]. In particular, in rapid death CBN could be the marker explaining cardiac arrest as secondary to adrenergic stress [35–37]. Contrary to the general opinion that excess catecholamines produce cardiotoxicity mainly through binding to adrenoceptors, there is increasing evidence that catecholamine-induced deleterious actions may also occur through oxidative mechanisms. Recent studies have shown that oxidation of catecholamines results in the formation of highly toxic substances such as aminochromes (e.g. adrenochrome) and free radicals and by virtue of the latter's actions on different types of heart membranes, which cause intracellular Ca^{2+} overload and myocardial cell damage [38].

Few reports of sudden death in children with PWS have been described and in our opinion this report gives the first description of an extensive cardiac lesion (CBN) that is the

histological hallmark of an acute adrenergic stress which could trigger a malignant arrhythmia (ventricular fibrillation) [39, 40].

References

1. Prader A, Labhart A, Willi H (1956) Ein Syndrom von Adipositas, Kleinwuchs, Kryptorchismus and Oligophrenie nach myotonieartigem Zustand im Neugeborenenalter. Schweiz Med Wochenschr 86:1260–1261
2. Ledbetter DH, Riccardi VM, Airhart SD, Strobel RJ, Keenan BS, Crawford JD (1981) Deletions of chromosome 15 as a cause of Prader-Willi syndrome. N Engl J Med 304:325–329
3. Sperhake JP, Matschke J, Orth U, Gal A, Puschel K (2000) Sudden death due to cerebrotendinous xanthomatosis confirmed by mutation analysis. Int J Legal Med 113:110–113
4. Vogels A, Van Den Ende J, Keymolen K, Mortier G, Devriendt K, Legius E, Fryns JP (2004) Minimum prevalence, birth incidence and cause of death for Prader-Willi syndrome in Flanders. Eur J Hum Genet 12:238–240
5. Smith A, Egan J, Ridley G, Haan E, Montgomery P, Williams K, Elliott E (2003) Birth prevalence of Prader-Willi syndrome in Australia. Arch Dis Child 88:263–264
6. Butler JV, Whittington JE, Holland AJ, Boer H, Clarke D, Webb T (2002) Prevalence of, and risk factors for, physical ill-health in people with Prader-Willi syndrome: a population-based study. Dev Med Child Neurol 44:248–255
7. Vercesi AM, Carvalho MR, Aguiar MJ, Pena SD (1999) Prevalence of Prader-Willi and Angelman syndromes among mentally retarded boys in Brazil. J Med Genet 36:498
8. Ehara H, Ohno K, Takeshita K (1995) Frequency of Prader—Willi syndrome in the San-in district, Japan. Brain Dev 17:324–326
9. Akefeldt A, Gillberg C, Larsson C (1991) Prader-Willi syndrome in a Swedish rural county: epidemiological aspects. Dev Med Child Neurol 33:715–721
10. Burd L, Vesely B, Martsolf J, Kerbeshian J (1990) Prevalence study of Prader-Willi syndrome in North Dakota. Am J Med Genet 37:97–99
11. Burman P, Ritzen EM, Lindgren AC (2001) Endocrine dysfunction in Prader-Willi syndrome: a review with special reference to GH. Endocr Rev 22:787–799
12. Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenberg F (1993) Prader-Willi sindrome: consensus diagnostic criteria. Pediatrics 91:398–402
13. Hawkey CJ, Smithies A (1976) The Prader-Willi syndrome with a 15/15 translocation. Case report and review of the literature. J Med Genet 13:152–157
14. Fraccaro M, Zuffardi O, Buhler EM, Jurik LP (1977) 15/15 translocation in Prader-Willi syndrome. J Med Genet 14:275–276
15. Kucerova M, Strakova M, Polivkova Z (1979) The Prader-Willi syndrome with a 15/3 translocation. J Med Genet 16:234–235
16. Guanti G (1980) A new case of rearrangement of chromosome 15 associated with Prader-Willi syndrome. Clin Genet 17:423–427
17. Butler MG, Palmer CG (1983) Parental origin of chromosome 15 deletion in Prader-Willi syndrome. Lancet 1:1285–1286
18. Nicholls RD, Knoll JH, Butler MG, Karam S, Lalande M (1989) Genetic imprinting suggested by maternal heterodisomy in nondeletion Prader-Willi syndrome. Nature 342:281–285
19. Robinson WP, Bottani A, Xie YG et al. (1991) Molecular, cytogenetic, and clinical investigations of Prader-Willi syndrome patients. Am J Hum Genet 49:1219–1234
20. Buiting K, Dittrich B, Gross S et al (1998) Sporadic imprinting defects in Prader-Willi syndrome and Angelman syndrome: implications for imprint-switch models, genetic counseling, and prenatal diagnosis. Am J Hum Genet 63:170–180
21. Ohta T, Gray TA, Rogan PK et al. (1999) Imprinting—mutation mechanisms in Prader-Willi syndrome. Am J Hum Genet 64:397–413
22. Gillessen-Kaesbach G, Gross S, Kaya-Westerloh S, Passarge E, Horsthemke B (1995) DNA methylation based testing of 450 patients suspected of having Prader-Willi syndrome. J Med Genet 32:88–92
23. Delach JA, Rosengren SS, Kaplan L, Greenstein RM, Cassidy SB, Benn PA (1994) Comparison of high resolution chromosome banding and fluorescence-in-situ hybridisation (FISH) for the laboratory evaluation of Prader-Willi syndrome and Angelman syndrome. Am J Med Genet 52:85–91
24. Cassidy SB, Thuline HC, Holm VA (1984) Deletion of chromosome 15 (q11–13) in a Prader-Labhart-Willi syndrome clinic population. Am J Med Genet 17:485–495
25. Oiglane E, Ounap K, Bartsch O, Rein R, Talvik T (2002) Sudden death of a girl with Prader-Willi syndrome. Genet Couns 13:459–464
26. Eiholzer U, Nordmann Y, L'Allemand D (2002) Fatal outcome of sleep apnoea in PWS during the initial phase of growth hormone treatment. A case report. Horm Res 58 [Suppl 3]:24–26
27. Nordmann Y, Eiholzer U, L'Allemand D, Mirjanic S, Markwalder C (2002) Sudden death of an infant with Prader-Willi syndrome—not a unique case? Biol Neonate 82:139–141
28. Schrander-Stumpel C, Sijstermans H, Curfs L, Fryns JP (1998) Sudden death in children with Prader-Willi syndrome: a call for collaboration. Genet Couns 9:231–232
29. Vliet GV, Deal CL, Crock PA, Robitaille Y, Oligny LL (2004) Sudden death in growth hormone-treated children with Prader-Willi sindrome. J Pediatr 144:129–131
30. Stevenson DA, Anaya TM, Clayton-Smith J et al. (2004) Unexpected death and critical illness in Prader-Willi syndrome: report of ten individuals. Am J Med Genet 124A:158–164
31. Schrander-Stumpel CT, Curfs LM, Sastrowijoto P, Cassidy SB, Schrander JJ, Fryns JP (2004) Prader-Willi syndrome: causes of death in an international series of 27 cases. Am J Med Genet 124A:333–338
32. Baroldi G. Mittleman RE, Parolini M, Silver MD, Fineschi V (2001) Myocardial contraction bands. Definition, quantification and significance in forensic pathology. Int J Legal Med 115: 142–151
33. Oehmichen M, Pedal I, Hohmann P (1990) Diagnostic significance of myofibrillar degeneration of cardiocytes in forensic pathology. Forensic Sci Int 48:163–173
34. Virmani R, Farb A, Burke A (1996) Contraction-band necrosis: a new use for an old friend. Lancet 347:1710–1711
35. Nishida N, Ikeda N, Kudo K, Tsuji A, Kiyoshima A (2002) Forensic significance of conduction system abnormalities as a precise cause of accidental death. Int J Legal Med 116:344–349
36. Bajanowski T, Ortmann C, Teige K, Wedekind H, Zack F, Rase I, Brinkmann B (2003) Pathological changes of the heart in sudden infant death. Int J Legal Med 117:193–203
37. Edston E, Grontoft L, Johnssn J (2000) Tunel: a useful screening method in sudden cardiac death. Int J Legal Med 116:22–26
38. Fineschi V, Baroldi G, Centini F et al. (2001) Markers of cardiac oxidative stress and altered morphology after intraperitoneal cocaine injection in a rat model. Int J Legal Med 114: 323–330
39. Baroldi G, Silver MD, De Maria R, Parolini M, Turillazzi E, Fineschi V (2003) Frequency and extent of contraction band necrosis in orthotopically transplanted human hearts. a morphometric study. Int J Cardiol 88:267–718
40. Fineschi V, Neri M, Riezzo I, Turillazzi E (2004) Sudden cardiac death due to hypersensitivity myocarditis during clozapine treatment. Int J Legal Med 118:307–309