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CASE REPORT

Multifocal cardiac Purkinje cell tumor in infancy

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Abstract Cot death is the commonest form of death among babies in the first year of life. The authors report the unusual case of a 2-month-old female infant dying suddenly and unexpectedly in whom a postmortem histological examination demonstrated a cardiac multifocal Purkinje cell tumor. Necroscopy studies of sudden infant death should always include an accurate histological examination of the cardiac conduction system and brainstem using serial sections.

''Pallida mors pulsat aequo pede alterno pauperum tabernas regumque turres'' (Horace, Carm., 1; 4: 13–14)

Introduction

Cot death is the commonest form of death among babies within the first year of life [1]. Cardiac Purkinje cell tumor, known also as histiocytoid cardiomyopathy, is extremely rare [2]. It occurs characteristically in infancy, although the literature consists mainly of reports of single cases [2,3–6].

We report an unusual case of multifocal Purkinje cell tumor located in the heart compressing the cardiac conduction system in a 2-month-old female infant dying suddenly and unexpectedly. Our investigations of the cardiac conduction system using serial sections uncovered important anatomo-pathological findings likely representing the morphological substrate of the sudden death. Preliminary findings have been reported in abstract form [7].

Case report

A 2-month-old female gypsy infant with no known history of medical problems became unresponsive. The baby was taken to an emergency department where resuscitation was attempted without success until she was pronounced dead 20 min after arrival. She was born at term, after an uncomplicated pregnancy. No previous ECG recordings were available. Little is known about her family history, since the baby was a gypsy, and her family moved to another country after her death.

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Postmortem examination was requested. Her death remained unexplained after a complete routine autopsy. The case was referred to the Institute of Pathology, University of Milan, to perform more specialized investigations, including the study of cardiac conduction system and brainstem using serial sections.

Materials and methods

A complete autopsy was performed, according to the autopsy protocol usually followed at our institute in cases of sudden death [8—10]. Multiple samples of all organs were fixed in 10% formalin buffer, processed and embedded in paraffin. Four-micrometer sections were stained with haematoxylin—eosin.

Histological observations were focussed on the cardiac specialized system and the cardio-respiratory centres in the brainstem involved in cardio-respiratory reflexes, as previously devised by the present authors [8—10]. To examine the cardiac conduction system, two blocks were prepared. The first contained the junction of superior vena cava and right atrium encompassing the entire area of the sino-atrial node, while the second contained the atrio-ventricular (AV) node, the His bundle to its bifurcation and the bundle branches, with 2 cm of attached septum above and below. The sino-atrial block was serially sectioned in a plane parallel to the crista terminalis. The AV junctional block was serially sectioned in a plane parallel to the two atrio-ventricular valve rings. All sections were cut serially at intervals of 40 μm. For these intervals, three sections were retained and mounted, and one of the mounted sections was stained alternately with haematoxylin—eosin and trichromic Heidenhain (azan). On selected fragments, histochemical reactions with periodic acid—Schiff (PAS), diastase—PAS, and alcian blue were applied. A section was stained with oil red O for fats.

Transversal 5 mm serial sections were made through the entire pons and medulla oblongata and were stained using alternately haematoxylin—eosin, Bielschowsky, and Klüver—Barrera stains. The pertinent nuclei were outlined, namely the parabrachial/Kölliker—Fuse complex in the pons, the arcuate nucleus, the nucleus hypoglossus, the dorsal vago-motor nucleus, the tractus solitarii nucleus, the ambiguus nucleus, the trigeminal tractus and nucleus, and the ventrolateral reticular formation in the medulla oblongata [8]. Plates in the atlas of Olszewski and Baxter were used for reference [11]. A morphometric analysis was performed with an Image-Pro Plus Image analyzer (Media Cybernetics, Silver Spring, MD) on both sides of the brainstem. The volume of the arcuate nucleus was measured by three-dimensional reconstruction.

Pathological findings

At autopsy the baby was described as a well-developed, well-nourished infant, with body length and weight at the 50th percentile. There were no marks of violence. The external and internal examinations were normal for the age and sex.

The heart weighed 46 g; the cardiac diameters were: transverse 4.5 cm, longitudinal 5 cm, antero-posterior 3.8 cm. Postmortem gross cardiac examination revealed cardiomegaly with irregularity of the epicardium (Fig. 1). Dissection showed a brownish and homogeneous appearance of the myocardium. The coronaries were normally patent.

Histological examination of the heart disclosed nodular aggregates of Purkinje cells throughout the left and the right endocardium, the interatrial septum and both the atrial walls. Histological examination of the cardiac conduction system showed the sino-atrial node and its adjacent ganglia to be normal. No abnormalities were detected along the internodal pathways. Islands of conduction tissue in the central fibrous body, known as persistent foetal dispersion [12], and areas of resorptive degeneration [9,12] in the atrio-ventricular node were observed. The complete examination of the cardiac conduction system using serial sections showed the presence of a Purkinje cell tumor, near the sino-atrial node, and another near the atrio-ventricular node (Fig. 2). The His bundle and bundle branches were unremarkable.

The multiple cardiac lesions proved to be small myocardial tumor nodules composed of large cells, characterized by a pale, granular and slightly acidophilic cytoplasm. Cytologic atypia was not observed (Fig. 3). The walls of the Purkinje cells varied in thickness and were more dense than the normal myocardial cells. In most groups the Purkinje cells were homogeneously distributed, but in some locations they contained a few intermingling other myocardial cells. There was no encasement or capsule around the Purkinje cell clusters. The Purkinje cells presented a moderate amount of strongly PAS and PAS—diastase-positive granular material, typical of glycogen. Fats, mostly phospholipids, were demonstrated in the cytoplasm by the oil red O reaction. Only occasional myofibrils were identified within these Purkinje cells.

All of the uninvolved myocardial cells were normal in appearance. There was no evidence of

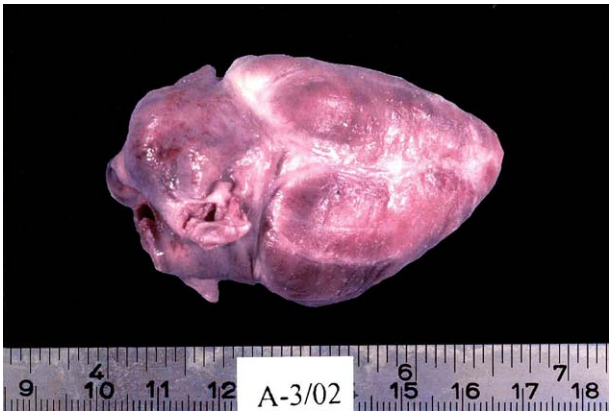

Figure 1 Postmortem gross cardiac examination revealing generalized cardiac hypertrophy with irregularity of the epicardium.

myocarditis. The histological examination of the pericardium disclosed a fibrinous pericarditis. The histological examination of the brainstem revealed a mild bilateral hypoplasia of the arcuate nucleus (Fig. 4). No other significant pathological changes were found.

Discussion

A multifocal Purkinje cell tumor of the heart is rare, mostly reported in female infants dying in the first two years of life due to intractable tachycardias [2—6]. Sudden cardiac death has occurred in some cases [2].

In the present case the histological examination of the heart and its cardiac conduction system using serial sections revealed a multifocal Purkinje cell tumor that diffusely compressed the cardiac conduction system.

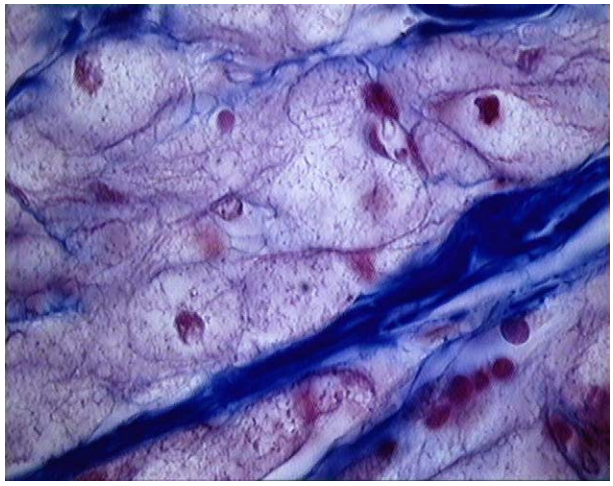

Figure 3 Detail of Purkinje cells at higher magnification. Trichromic Heidenhain, ×1000.

Rossi et al. [6] reported a case of multifocal cardiac Purkinje cell tumor in a 13-month-old boy. The infant was admitted to hospital because of difficulty in breathing, cough and transient cyanosis [6]. In the present case, instead, it is surprising that sudden and unexpected death was the initial manifestation of the multifocal tumor. Death could have been due to cardiac electrical instability caused by the diffuse compression of the cardiac conduction system. The case of this 2-month-old child is one of the youngest reported cases of this condition [2—6].

Distribution of Purkinje cells in the sheep heart includes some peculiar locations, such as numerous

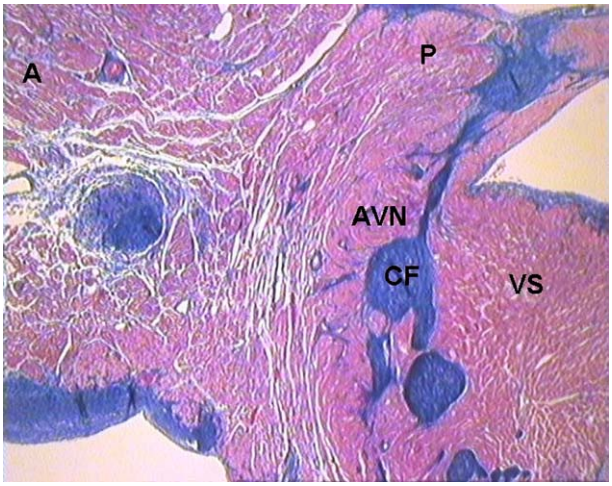

Figure 2 Cluster of Purkinje cells (P) are present among normal myocytes, close to the atrio-ventricular node (AVN). VS = interventricular septum; A = right atrium. Trichromic Heidenhain, ×25; CF = central fibrous body.

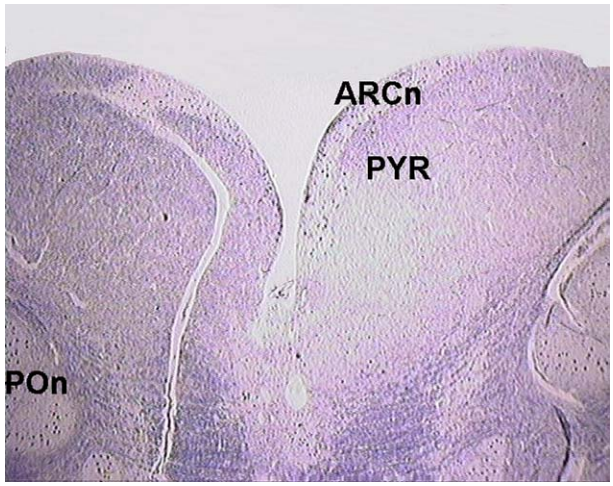

Figure 4 Transverse section of the medulla oblongata with mild hypoplasia of arcuate nucleus. Klüver—Barrera, ×25. ARCn = arcuate nucleus; POn = principal inferior olivary nucleus; PYR = pyramid.

focal clusters of Purkinje cells in the interventricular septum that are virtually identical to the Purkinje cell tumors in some human hearts [13]. We suggest that more research should be addressed to learn whether there is some genetic basis for the similarity between human Purkinje cell tumors and the classic normal Purkinje cell distribution seen in sheep hearts.

In the present case, the histological examination of the cardiac conduction system showed islands of conduction tissue in the central fibrous body and areas of resorptive degeneration in the atrioventricular node. These morphological findings have already been described in cases of cot death [9,12,14]. The histological examination of the brainstem on serial sections revealed bilateral hypoplasia of the arcuate nucleus (Fig. 4). The arcuate nucleus of the ventral surface of the human medulla is implicated in central chemoreception, cardiopulmonary coupling, and blood pressure responses. Arcuate nucleus hypoplasia characterizes a subset of cot deaths with a putative defect in brainstem chemoreception [8,15].

What makes this case unique is the combination of a multifocal nodular Purkinje tumor of the heart associated with a bilateral hypoplasia of the arcuate nucleus. The Purkinje cell tumor alone may or may not have accounted for the sudden death, but could have had a triggering role in this baby suffering from a hypoplastic arcuate nucleus. This case seems in part consistent with the triple-risk model of cot death, a hypothesis consisting of underlying biological vulnerability to exogenous stress or triggering factors in a critical developmental period [15,16]. Further studies on triggering factors and related mechanisms will lead to a better understanding of complex interactions involved in the pathophysiology of cot death.

These data confirm that an accurate examination of the cardiac conduction system and brainstem using serial sections [9,17] is essential in finding the morphological substrate responsible for sudden death in infancy.

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