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Suspected Syndrome of Chromosome 22 Deletion in a Fetal Autopsy

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Abstract: Malformation syndrome caused by genetic mutation of chromosome 22 was described in 1965 by Angelo DiGeorge, an italo-american doctor. He observed a common clinical picture in a group of children characterized by cardiac malformation, recurrent infection due to absence of thymus and a typical fenotipic aspect of these children. Only in 1992 the chromosomal anomaly was found as a result of studies based on Fluorescence In Situ Hybridation technique (F.I.S.H.). In this report it is described a case of a stillbirth during the second gestational trimester with multiple malformations that are suspected for syndrome of chromosome 22 deletion. The present case is an example of what careful macroscopic and microscopic examinations can be able to identify syndromic defects attributable to chromosome 22 mutations.

Keywords: DiGeorge Syndrome, Chromosomal Deletion, Fetal Autopsy

1. Introduction

DiGeorge Syndrome is caused by a defect in the embryological development of the third, the fourth gill pocket and fourth gill arch. It is characterized by abnormalities of the heart, thymus, parathyroid and specific facial dysmorphic features.

The incidence is estimated to be 1/5000 live births. Males and females are affected in equal proportion.

It is caused by a partial deletion of the long arm of chromosome 22. The deletion can occur random in the affected individual (80/85% of cases) or transmitted by a parent, which in turn can be affected in a nuanced form (15/20% of cases). In these last cases the risk of recurrence of the disease in future pregnancies is 50% at each conception, regardless of the sex of the infant [1].

We reported a case of female fetal autopsy with peculiar malformations that can be attributable to DiGeorge Syndrome.

2. Case Presentation

In this report a fetal autopsy on a female dead at 15 week of gestation for placental failure is described.

At macroscopic reply, we didn't find thymus, in absence of other salient reports. Organs were taken as a whole, paraffin embedded and Alcian-hematoxilyn coloured.

Microscopic examination revealed the presence of a hypoplastic residual thymic on atrial pericardium (figure 1). Also, we have observed abnormal dilatation of the brain lateral hemispherical ventricles, with diffuse cortical atrophy (figure 2), and papillary hyperplasia of the choroid plexus. No alterations were detected at cardio-pulmonary or gastroenteric level, except for pancreas, that presented a partial parenchymal atrophy with decreased both of Langerhans islands than of exocrine portion (figure 3). Remarkable bilateral cortical atrophy was found in the kidneys with dilation of the caliceal spaces facilities from possible clogging downstream (figure 4). As regards the reproductive system, there were female gonads with aspects of uterine hypoplasia.

Placental microscopic evaluation revealed acute decidual infection identified as the cause of stillbirth. We also have noticed the presence of many including stromal syncytiotrophoblast in staminal chorionic villi (figure 5).

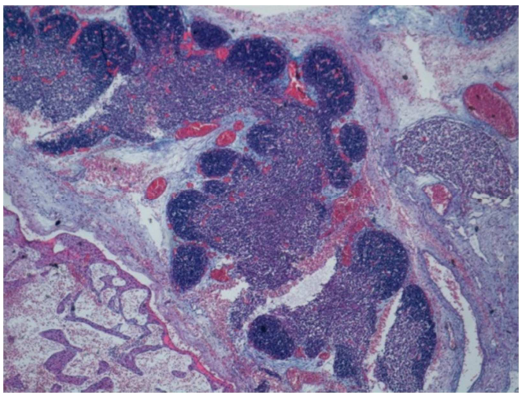

Figure 1. *Hypoplastic residual thymic on atrial pericardium (10X).*

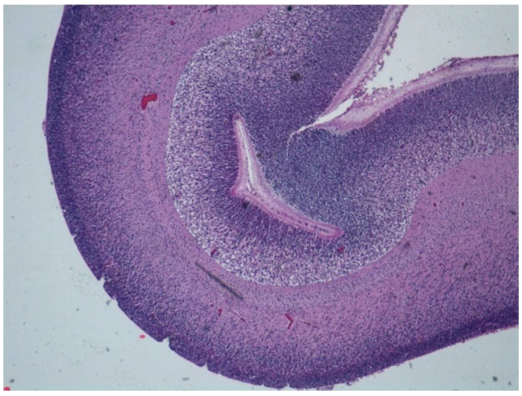

Figure 2. *Abnormal dilatation of the brain lateral hemispherical ventricles (4X).*

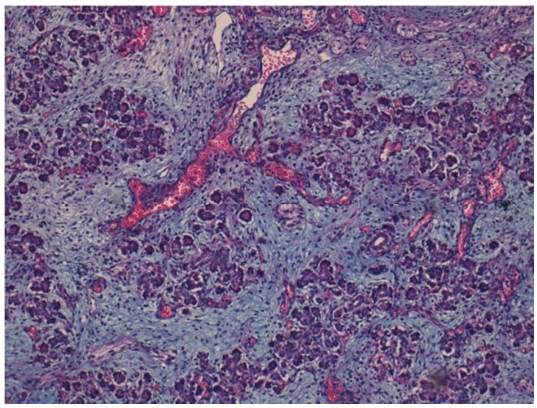

Figure 3. *Partial parenchymal atrophy of pancreas. (10X).*

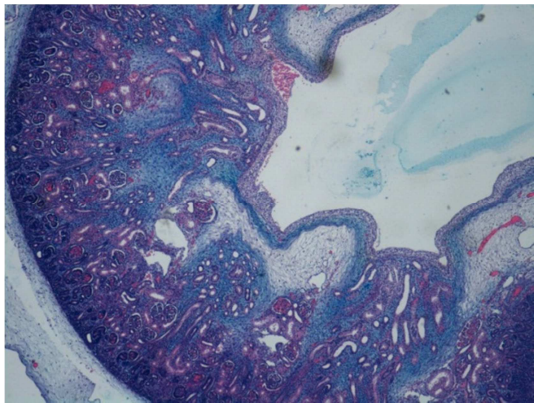

Figure 4. *Dilation of the caliceal spaces in kidney.(10X).*

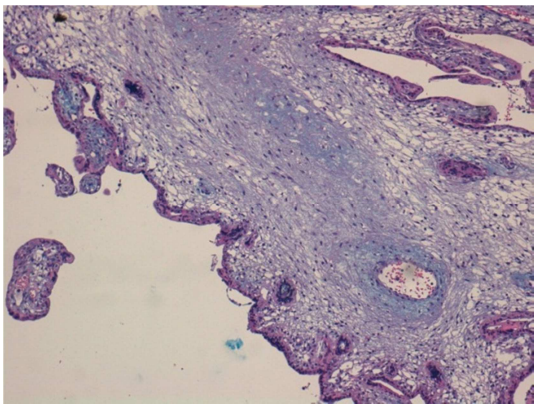

Figure 5. *Stromal syncytiotrophoblast inclusions in staminal chorionic villi (10X).*

3. Discussion

In cases of diagnosis or diagnostic suspect of stillbirth for 22q11 delection, it would be important a cytogenetic and molecular analysis of the parents to rule out a possible vertical transmission of the disease.

The survey is carried out using the F.I.S.H. method to detect and locate the absence of specific DNA sequences in chromosomes. Chromosomal microarray is also increasingly utilized for genetic testing of individuals with unexplained developmental intellectual disability, autism spectrum disorders, or multiple congenital anomalies. The International Standard Cytogenomic Array

Consortium held two international workshops and conducted a literature review of 33 studies, including 21.698 patients tested by microarrays. They agreed on an international consensus statement about low cost and clinical utility in using chromosomal microarrays to detect genetic anomaly in suspected cases [1].

The symptoms and signs of 22q11.2 deletion configure a wide range of clinical conditions. So they have been described as many syndromes. These include the velo-cardio-facial syndrome (also called Shprintzen syndrome), the DiGeorge Syndrome and other [2]. The acronym CATCH-22 is what best summarizes the anomalies found, where C means cardiac defects, A means abnormal facies, T is for thymic hypoplasia, C is for cleft palate and H means hypocalcemia. The syndrome is caused by deletion of many thousands of bases on the long arm of chromosome 22. For this reason, the term "22q11.2 deletion syndrome" is the most frequently used today.

Microdeletions in 22q11 region are described too. They are associated with a risk 30 times higher than normal for developing schizophrenia. [3, 4].

The syndrome is caused by a new mutation, however it can also be an autosomal dominant familial transmission in a minority of cases. Sometimes the syndromic phenotype described is due to partial deletion on the short arm of chromosome 10. The deletion regards about 30 genes, not well known.

The key gene for the onset of the symptoms of the

chromosome 22 syndrome is TBX1, a transcription factor that induces the activation of other transcription factor [5]. Genes in the T-box family play important roles in the formation of tissues and organs during embryonic development [6]. These genes are expressed in gill pockets III and IV, during embryonic life. This explains tissue alterations of the cranial organs, such as thymus, hearth, face and parathyroid. The T-box 1 protein appears to be necessary for the normal development of large arteries that carry blood out of the hearth, muscles and bones of the face and neck, and neck glands such as the thymus and parathyroid. Although the T-box 1 protein acts as a transcription factor, it is not yet known which genes are regulated by the protein. T-box protein early expression explains the wide phenotypic spectrum (more than 180 clinical features both physical and behavioral) exhibited by patients with the syndrome. Clinical penetrance of mutations on the long arm of chromosome 22 is extremely variable, so there are no reported cases of the syndrome that has all or even most of the clinical findings. The prognosis for 22q11.2 deletion syndromd varies widely, depending largely on the nature and degree of involvement of different organs. Many adults live long and productive lives. They present characteristic facies (micrognathia, long face, high and broad nasal bridge, narrow palpebral fissures, small teeth, asymmetrical crying face, downturned mouth, short philtrum, low-set, malformed ears, hypertelorism), hearth defects, cleft palate and immunodeficiences. Children and adults with 22q11.2 deletion syndrome have high rates of behavioral, psychiatric, and communication disorders. In children, these include attention-deficit/hyperactivity disorder, anxiety, autism, and affective disorders. Adults have a high rate of psychotic disorders, particularly schizophrenia [3].

The prevalence of 22q11.2 deletion syndrome is estimated at one case per 4000 live births. 80% of these newborns present cardiac defects. In 80% of cases the deletion occurs de novo by a pair of healthy parents, while the 18-28% cases however are familial segregation. Despite all these statistical findings on malformed children, no data are avaible on the intrauterine death of fetus with 22q11.2 deletion syndrome. Only a forensic report of a neonatal autopsy finding was described, as a possible omicide of an infant with a cleft palate apparently died during feeding [8].

It's often difficult to reliably intrauterine fetal diagnosis without a clinical and anamnestic suspect on the parents. Many laboratory test and imaging studies of the baby can help for a correct individuation of the syndrome, but only genetic determinations on the product of conception can be considered decisive for diagnosis [1, 9, 10].

The peculiarity of our described case consists in having made a presumptive diagnosis in the first instance with the finding at autopsy on the second trimester stillbirth, in absence of clinical or ultrasonographic reply.

4. Conclusion

Somatic alterations detected in this reported stillbirth female fetus (thymic and uterine hypoplasia, cerebral cortical atrophia, atrophic involution of the pancreatic parenchyma, cortical renal atrophy with dilatation of calico peliche structures) are suggestive for a malformative syndrome. The presence of syncytiotrophoblast in the stroma of the staminal chorionic villi can be considered an indirect sign of chromosomal genetic mutations. Than, severe thymic hypoplasia together with pancreatic parenchimal involution are very suspect for chromosome 22 deletion syndrome. In our case, for the early gestational date of death it hasn't been possible to detect cardiac failure. In fact, in the most of the cases cardiac defects can be valuable during the last trimester of intrauterine life only.

In the described case, there wasn't any contact with the parents, because the report of the autopsy finding wasn't delivered to the mother. Furthermore there were no genetic investigations on parents and brothers of the fetus.

The reason must be sought to the precarious economic and social conditions of the family.

For these grounds and because the fetus was formalin-fixed, it was not possible to obtain a genetic and molecular confirmation to our morphologic response.

Furthermore the heterogeneity of morphologic and clinical manifestations does not allow to carry out follow-up strategies apply to all patients. In the complexed malformative syndrome, medical equipe favors the personalization of interventions with close links between neonatologists, pediatricians, geneticists, otolaryngologists, cardiologists, psychiatrists [7].

Even if chromosome 22 deletion syndrome is detected through molecular studies, we think that a through diagnostic perinatal examination can be useful for obstetrics to improve the reliability of ultrasound examination during intrauterine morphological assessment of fetal wellbeing. The detailed description of the pathologist should, in fact, be compared with the ultrasound intrauterine images aimed to instrumental recognition of specific fetal somatic alterations.

Furthermore a complete autopsy finding including full examination of all organs must be considered necessary in the event of stillbirth, especially in the absence of clinical or obstetric reasons. It would ultimately be desirable that all the cases of perinatal death were treated in a multidisciplinary context, especially when a malformative phenotypes is detected.

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