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Echocardiographic Follow-up in Aarskog-Scott Syndrome: Is It Useful? Report of AAS Twins with PFO

* Gasparini Paolo Alberto [1], Lodi Elisa [1, 2], Rodighiero Eleonora [1, 2], Rosero Morales Jonathan [1, 2], Fantini Giuseppe [2], Modena Maria Grazia [1, 2]

[1] University of Modena and Reggio Emilia, CHIMOMO Dept c/o Policlinico di Modena – Via del Pozzo, 71 – 41124 Modena (IT).

[2] Centro P.A.S.C.I.A. (Programma Assistenziale Scompenso cardiaco, Cardiopatie dell''Infanzia e A rischio) c/o AOU Policlinico di Modena – Via del Pozzo, 71 – 41124 Modena (IT).

Abstract

Background: Aarskog-Scott Syndrome (AAS), also known as facio-digital-genital dysplasia, is a rare syndrome mainly characterized by short stature, skeletal disorders and genitourinary dysmorphisms (1).

Case report: We present the case of two caucasian male twins affected by AAS and Patent Foramen Ovale (PFO). The AAS diagnosis was genetically confirmed by the homozygous mutation on the FGD1 gene on exon 6, variant c.1327 C>T p. (Arg443 Cys). Twins described in this report would have been at a higher risk of CHD because of three elements: they were affected by AAS, they were born after IVF, and they were twins. Despite having all these characteristics, only a PFO was detected. 2021 European position paper (22) asserts that after an incidental finding of a PFO, conventional flight or diving should not be denied. In professional divers and selected military pilots performing intensive high-altitude flight activities, a primary PFO percutaneous closure should be recommended.

Conclusion: A first echocardiography evaluation should be performed on a child presenting malformations because of possible involvement of the heart; nevertheless, we do not believe that AAS patients should undergo a mandatory cardiological follow-up. The larger PFOs or those with significant resting shunts should require a follow-up based on specific patient characteristics.

Key Words: Aarskog-Scott Syndrome (AAS), Echocardiographic Follow-up, Facio-digital-genital dysplasia, Patent Foramen Ovale (PFO).

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Corresponding Author:

Gasparini Paolo Alberto, University of Modena and Reggio Emilia, CHIMOMO Dept c/o Policlinico di Modena – Via del Pozzo, 71 – 41124 Modena (IT). Email: mariagrazia.modena@unimore.it

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1- INTRODUCTION

Aarskog-Scott Syndrome (AAS), also known as facio-digital-genital dysplasia, is a rare syndrome mainly characterized by short stature, skeletal disorders and genitourinary dysmorphisms (1).

This syndrome displays a wide spectrum of intellectual disability, with physical and neuropsychological (2-5) features, which include cranio-facial manifestations such as hypertelorism, anteverted nostrils, ptosis, widow's peak, dysplastic ears, downward slanting palpebral fissures, orthopedic findings such as short stature, brachydactyly and clinodactyly, and finally,and genitourinary disorders such as shawl scrotum and cryptorchidism.

This syndrome seems to be clinically prevalent only among males, because of the X-linked recessive pattern of inheritance. The genetic basis is represented by different heterogeneous mutations of the FGD1 gene on the Xp11.22 locus (6). Only few genetically confirmed cases1 (~60) have been described in literature since 1970-1971, when the syndrome was first described by Aarskog (7) and a year later reported by Scott (8). Nonetheless, the real estimated prevalence is more likely to be nearly 1/25000 or less (9).

2- CASE REPORT

We present the case of two caucasian male twins affected by AAS and Patent Foramen Ovale (PFO). The AAS diagnosis was genetically confirmed by the homozygous mutation on the FGD1 gene on exon 6, variant c.1327 C>T p. (Arg443 Cys).

The two dichorionic diamniotic twins were born via vaginal delivery, after In Vitro Fertilization (IVF), by parents both carrying a heterozygotic mutation of CFTR.

Propositus (P) number 1 had a fetal biometry < 5o p, weight at birth was 2640g (9o p). P. no 1 showed typical malformations consistent with AAS, i.e., "V-shaped" insertion of the hair on the median line of the forehead, hypertelorism, oblique downwards eyelid rims, broad nose root, low ear implant, right preauricular fistula, short hands and feet, shawl scrotum, while testicles in situ.

At 1 month (m) and 11 days (d) hip ultrasound (hus) was performed due to twinning and breech presentation at third trimester. Hus showed a good skeletal conformation, angled cotyloid eyelash, an alpha angle > 60o, while a beta angle was < 55o, resulting in 1a according to Graf (10) classification; 2 days later an abdomen ultrasound was performed, which resulted normal. The transfontanellar ultrasound was in range. Echocardiography showed a large PFO for which a follow-up was recommended. Auditory Evoked Potentials (AEPs) were in range.

At m 3, d 12 the auxological data collected was: 55 cm long (< 3o p), a weight of 4.7 kg (3o-15o p) and a cranial circumference of 38 cm (< 3o p).

At m 6, d 6 his auxological data was: 62 cm long (<3o p), 6.6 kg (3o p) and a cranial circumference of 41 cm (3o p). At this age, the toddler was able to play and interact; he could grasp and manipulate objects with both hands and sit by himself with minimum help. He had difficulty clenching his fist. Muscle tone and neurological development were in range for age.

Echocardiography at m 7, d 15 showed a residual PFO (Fig. 1) without any morpho-functional heart alterations.

P. no 2 weight at birth was 2500g (5o p) and after m 3, d 12 the auxological data collected was: 56.5 cm long (< 3o p), 4, 4 kg (< 3o p) and a cranial circumference of 38 cm (< 3o p). At birth and consequently at 26 d echocardiography showed an ample PFO with left to right shunt for which a

follow-up was recommended. Hip and abdomen ultrasound, together with AEPs, were normal. He displayed a spectrum of dysmorphisms similar to his twin brother and consistent with AAS, such as "V-shaped" insertion of the hair on the median line of the forehead, hypertelorism, oblique downwards eyelid rims, low ear implant, right preauricular fistula, sacral dimple, short hands, and feet and shawl scrotum; presenting the same mutation of his brother on the FGD1 gene; AAS was also diagnosed.

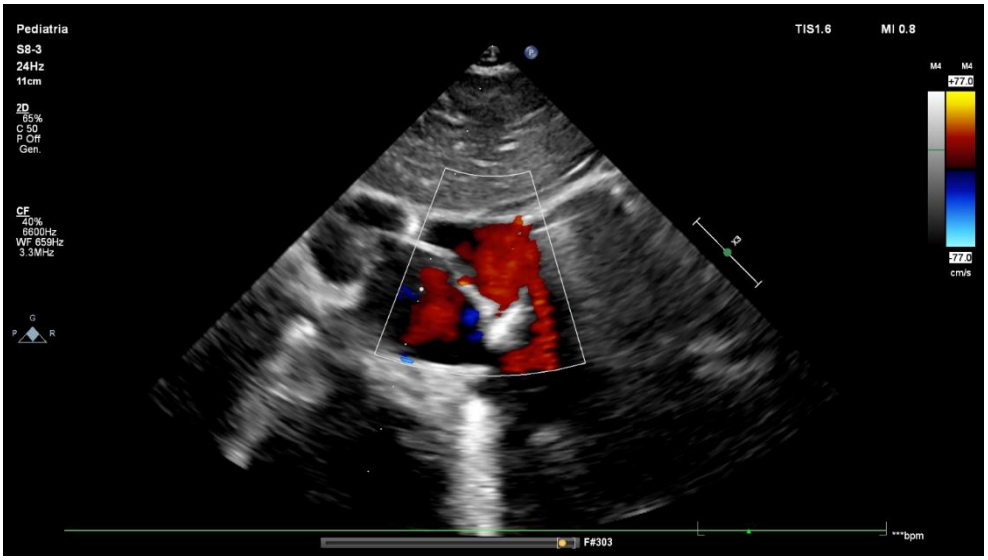

Fig. 1: subcostal long axis view, interatrial shunt (PFO).

As with P. no 1, muscle tone and neurological development were in range for age.

Echocardiography at m 4, d 27 showed a residual PFO as evident in Figure 2, while heart anatomy and function were normal.

At 10 months, no sign of intellectual disability was displayed in either P. no 1 or P. no 2.

3- DISCUSSION

It is reported that one Congenital Heart Disease (CHD) out of four might be associated with genetic syndromes accompanied by extra-cardiac anomalies (11).

According to a meta-analysis of 260 studies (12), the incidence of CHD among caucasians is nearly 8/1000 and rises to 20/1000 among dichorionic twins and even more (60-120/1000) among monochorionic twins (13). An increased risk of having CHD (~13/1000) can also be identified among babies born after IVF (14). It is not yet clarified if the risk of CHD associated to IVF may be attributed to the technique itself or to the fact that after IVF there is a higher and more cumulative probability of having twins or more rarely triplets (15); nevertheless, the fact that singleton-IVF-born seems to have an increased risk of presenting CHD could be consistent with the former hypothesis.

Fernandez et al. reported that AAS is probably associated with an increased risk of CHD and children affected by this syndrome should undergo cardiological evaluation (16). The only few AAS-related CHD were described in patients without

genetic diagnosis, represented by Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), mild pulmonary valve stenosis and aortic coarctation; these few CHD identified, especially among Japanese patients, were mainly described as mild, with spontaneous resolution and represent the most frequent CHD that can be found among general population. The absence of genetic diagnosis of AAS in the cases studied by Fernandez et al. could possibly imply that the patients studied were affected by other syndromes phenotypically similar to AAS but genotypically different; thus, the certain correlation between AAS and increased risk of CHD has not been identified. Based on similar clinical features, a differential diagnosis is needed between AAS and Noonan syndrome (NS) (1, 17). The estimated prevalence of NS is 1/1000-1/2500, at least ten times more frequent than AAS (18). Children affected by NS must perform a cardiological follow-up, because of a high prevalence of CHD and an early or late risk of developing hypertrophic cardiomyopathy (19, 20).

Twins described in this report would have been at a higher risk of CHD because of three elements: they were affected by AAS (16), they were born after IVF (14) and they were twins (13). Despite having all these characteristics, only a PFO was detected.

PFO is a physiological finding affecting about 25-30% of the population (21). 2021 European position paper (22) asserts that after an incidental finding of a PFO, conventional flight or diving should not be denied. In professional divers and selected military pilots performing intensive high-altitude flight activities, a primary PFO percutaneous closure should be recommended.

4- CONCLUSION

A first echocardiography evaluation should be performed on a child presenting malformations because of possible involvement of the heart; nevertheless, we do not believe that AAS patients should undergo a mandatory cardiological follow-up.

CHD has been reported in 0/60 AAS patients confirmed by genetics, including the twins in our study. Among the genetically confirmed AAS patients described in literature, the only candidates for an echocardiographic follow-up might be the children from our report under rare circumstances in rare specific conditions, because even if a PFO is an extremely frequent physiological finding among the population, a follow-up is sometimes needed. A PFO of small size without a significant resting right-to-left shunt is a common finding and is generally not associated with any abnormality of the patient's history, physical examination and electrocardiogram. In the absence of anamnestic or clinical signs, patients with a PFO should undergo a structural follow-up just in case of professional diving, and military and astronautical flights. The larger PFOs (approximately > or =4 mm size) or those with significant resting shunts appear to be potentially clinically significant and should require a follow-up based on specific patient characteristics. Overall we should consider that rare does not necessarily mean dangerous.

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