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Poland syndrome: A proposed classification system and perspectives on diagnosis and treatment☆

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ABSTRACT

Poland Syndrome (PS) is a rare condition, with an estimated incidence of approximately 1 per 30,000 births and encompasses a wide range of severities of chest and upper arm anomalies. The etiology remains unknown, but genetic involvement is suspected. Few radiological investigations have proven useful in the study PS phenotypes and we propose a reference algorithm for guiding pediatricians. Our experience with 245 PS patients in the last 10 years stimulated a phenotypical classification of PS. The management of the different PS types and a therapeutic algorithm according to the phenotypical features of each PS patient are also proposed.

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Introduction

In 1841 during an autopsy as a Medical Student, Sir Alfred Poland, reported a case of pectoralis major and minor muscle agenesis associated with other muscle deficiencies and ipsilateral hand brachysyndactyly.[1] Since then, many reports of Poland syndrome (PS) (OMIM 173,800) were published. The incidence of PS was estimated between 1/30,000 and 1/32,000.[2,3] The etiology remains unclear, although a vascular injury of the subclavian artery has been hypothesized.[4] Familial cases have been described,[5,6] but the transmission mechanisms are still unknown and no genetic cause has been identified yet. PS phenotype can be extremely variable, including ipsilateral thoracic and upper limb anomalies, but, to date, the incidence of these anomalies has not been systematically studied in a large series of patients. Additionally, there is no specific guidelines to diagnose and manage patients with PS. In view of this, we present our experience with a large series of PS patient with the following main objectives:

1) To discuss genetic implications of PS.
2) To propose a PS classification according to the phenotype (minimal, partial, complete).
3) To consider the radiological and clinical investigations worthwhile for each type of PS.
4) To classify the thoracic defect based on the severity of different clinical parameters (TBN classification).
5) To propose an algorithm of treatment of the thoracic defect for each patient, based on previous classifications.

Genetics in PS

The pathogenic mechanisms underlying PS are still unknown. The hypothesis that PS defects could result from a vascular insult during early embryological stages[4] implies that environmental factors could contribute to PS phenotype. Alternatively, PS has been hypothesized to have a genetic origin secondary to deleterious mutations of genes regulating embryonic development, and particularly affecting pectoral girdle muscles and skeleton structures.[5,6] Further, PS has been proposed to represent a mosaic phenotype caused by a somatic mutation occurring during development, with the severity of the phenotype depending on the time of occurrence of the mutation during embryogenesis.[7]

Usually PS presents in an isolated form; however, there are also associations with other syndromes or sequences, i.e. Moebius, Klippel–Feil, and Pierre-Robin syndromes.[4,8] Though most cases of PS are sporadic, familial recurrence with higher prevalence in males has been observed, which suggests a genetic, hereditary ba-

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sis of this congenital anomaly. Familial recurrence was observed in about 10% of cases with different inheritance patterns including autosomal dominant with incomplete penetrance, autosomal recessive, and X-linked.[9]

Recently, monozygotic twin girls with PS were reported; phenotype concordance in monozygotic twins affected by a disease supports the hypothesis that this disease is under genetic control.[10] Even though most cases of PS appears to be sporadic, it seems essential, in the context of genetic counseling, to inform patients of the existence of familial cases and that the risk for an affected person to have children with PS is higher than that of the general population. Indeed, it should be discussed with the family that even in familial cases, the clinical presentation can be variable and, to date, unpredictable.

For the apparently sporadic cases, which constitute the majority of patients, an autosomal recessive model of transmission can be hypothesized according to which the affected individuals are homozygous for recessive alleles transmitted by heterozygous parents (healthy carriers). Alternatively, sporadic cases can be explained by the appearance of de novo mutations. Recent hypotheses seem to support the presence of different genes whose mutations may account for clinical differences among subgroups of patients and for the different inheritance patterns observed, together with environmental factors.

Two recently reported cases of de novo deletions contribute to support of the genetic origin of PS and suggest the involvement of the deleted regions in PS as the pathogenesis. The monozygotic twin patients described by Vaccari et al.[10] shared a heterozygous chromosome 11q12.3 deletion including genes involved in cellular growth, differentiation, and apoptosis through HRAS signaling pathways. As PS results from impaired development, genes controlling cell growth and differentiation may represent good candidate genes. The authors postulate that the deletion of one copy of these genes could be causative of the PS phenotype in the twin girls.[10] A large deletion of chromosome 6q21-q22.1 was also recently reported in a patient with a complex phenotype mainly characterized by mental disability and PS; haploinsufficiency of some of the genes overlapped by the CNV (Copy Number Variation) (in particular WISP3 and COL10A1) may act in the pathogenesis of the musculoskeletal defects reported in this patient.[11]

Recently Vaccari et al.[12] reported standard cytogenetic and array-CGH analyses performed in a cohort of 120 PS patients in order to elucidate the contribution of genomic imbalances in PS. No significant karyotype imbalance was found. The authors identified 14 CNVs that involved different genomic regions and different genes, which indicates that each identified CNV can account for single specific cases. Chromosome anomalies, duplications and deletions, are a rare cause of PS. Most of CNVs identified by the authors are inherited by unaffected parents, as expected on the basis of incomplete penetrance observed in familial cases[9] and suggesting they could act as modifiers and represent risk factors for PS phenotype.

Bioinformatic analyses showed significant enrichment of proteins involved in cell adhesion, blood coagulation, chondrogenesis, asymmetric development and skeletal muscle structure, suggesting these processes as playing a role in PS development. For example, one of genes discussed by Thyboll et al. is LAMA4; lack of this gene caused hemorrhages associated with capillary defects in mice,[13] suggesting that the deletion of LAMA4, by inducing hemorrhages during embryonic development, could cause a variety of defects, possibly including those observed in PS patients This would also be consistent with vascular hypothesis of PS.

Another attractive candidate gene is TRIO, whose complete absence in mice causes embryonic lethality associated with abnormal development of skeletal muscle and neural tissues. Indeed, TRIO deficiency caused a specific defect of myogenesis resulting in anomalies of skeletal muscle formation.[14] Vaccari et al. suggest the overlapped genes as candidates for further evaluation in functional studies or mutation screening in other patients by direct sequencing or whole exome sequencing (WES).[12] Preliminary data of WES performed by the same authors in selected sporadic and familial cases confirm the involvement of genes that regulate cell-cell and cell-matrix interaction in cell adhesion processes and a possible contribution of genes involved in vascular development (Vaccari et al., ESHG 2014 comm., unpublished data). At the moment, however, there is no data to support execution of the array-CGH genetic test or the standard karyotype as routine diagnostic investigations, which could be reserved for the most complex cases.

Phenotype and PS classification

We have studied the PS phenotype in 245 patients during the last ten years. The diagnostic criterion for the clinical diagnosis of PS was the absence (partial or complete) of the pectoralis major muscle. All patients followed the diagnostic protocol approved by the Scientific Committee of the Italian Association of Families with PS (AISP). The study was approved by the Institutional Board and all patients or parents gave written informed consent. The diagnostic protocol included multidisciplinary assessment (pediatric surgeon, plastic surgeon, hand and orthopedic surgeons, geneticist, and psychologist) and radiological investigations (pectoral region ultrasound, echocardiography, abdominal ultrasound, chest radiography; hand/upper arm radiography in case of evident anomalies; computerized tomography of the thorax or other investigations in selected cases only). This workup was aimed at defining PS phenotype and at studying its clinical variability. For upper limb anomalies, we adopted the classification published by Catena et al.[15] and currently in use in our Institute, representing a modification of the previously adopted Al Qattan classification.[16]

Proposal of classification

We propose a Poland syndrome classification based on the most frequent abnormalities associated with the pectoral muscle defects, namely the upper limb and rib cage. We thus identified three types of PS, according to the presence or absence of each:

- Type-1 or Minimal Form: Isolated pectoral muscle defect (without rib or upper limb anomaly)
- Type-2 or Partial Forms: Pectoral muscle defect associated with either rib or upper limb anomaly
- Type-2a or Upper Limb Variant: Upper limb anomalies without rib anomalies
- Type-2b or Thoracic Variant: Rib anomalies without upper limb anomalies
- Type-3 or Complete Form: Pectoral muscle defect associated both with upper limb and rib anomalies.

Statistical analysis

Data were described as means with standard deviation (SD), or medians with a range for continuous variables, while absolute and relative frequencies were used for categorical variables. Parameters of the study groups were compared using $\chi 2$ or Fisher's exact test for categorical variables. A p-value less than 0.05 was considered statistically significant, and all p-values were based upon two-tailed tests. Statistical analysis was performed using SPSS for Windows (SPSS Inc, Chicago, Illinois USA).

Results

Among the 245 PS patients, 155 (66.3%) were males and 90 (33.7%) females. The demographic and clinical features of this population are summarized in Table 1. PS was more frequent in males

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