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Review

A review of the physical features of the fetal alcohol spectrum disorders

Miguel del Campo*, Kenneth Lyons Jones

Division of Dysmorphology and Teratology, Department of Pediatrics, University of California, San Diego, USA

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ABSTRACT

The fetal alcohol spectrum of disorders (FASD) includes four diagnostic categories for the clinical consequences of prenatal alcohol exposure (PAE) in the unborn child. Physical features are necessary for the diagnosis of the fetal alcohol syndrome (FAS) and partial pFAS. Moreover, these features are specific and a diagnosis of FAS can be made even in the absence of knowledge of PAE. Not only growth deficits, microcephaly and the 3 facial features (short palpebral fissures, smooth philtrum and narrow vermillion of the upper lip) are characteristic, since other dysmorphic features particularly in the hands are key to the recognition of FAS. Most features can be explained by the damage to the brain during pregnancy and can be replicated in animal models. Many different diagnostic guidelines are used for the diagnosis of FASD and the physical features are considered differently in each of them. There is a need for universal clinical criteria for the diagnosis of FASD if our goal is to favor universal recognition.

1. Introduction

The potential harmful effects of alcohol in pregnancy have been referred to on multiple occasions throughout History. Greek philosophers such as Aristotle suggested that alcohol should not be used in pregnancy with the following admonishment: "Foolish, drunken and hare-brained women most often bring forth children like unto themselves, morose and languid". The London Gin epidemic in the 1700s made the weakness and abnormal behavior of children born to alcoholic mothers quite evident, in addition to remarking on the marked increase in fetal and infant mortality (Calhoun & Warren, 2007). However, no specific diagnostic features were ever proposed nor medical recommendations suggested which might result in prevention of the deleterious effects of alcohol on fetal development.

Teratology refers to the study of birth defects due to environmental causes, the term was popularized by DW Smith in the 1960s. Dysmorphology refers to the study of structural differences for the identification and characterization of birth defects, in order to provide insight into their etiology. The characterization of major malformations and minor anomalies has proven particularly useful for the identification and delineation of genetic conditions as well as conditions caused by prenatal exposure to drugs, chemicals and environmental agents, and is certainly of prime importance for the diagnosis of the fetal alcohol syndrome (FAS). Syndromes can be defined as "patterns" of major malformations and minor anomalies in which several specific defects are repeatedly seen. Such patterns of malformations are indicative of a specific etiology even when, individually, none of them would lead to a specific diagnosis. Dysmorphology uses pattern recognition for syndrome identification and the knowledge of the molecular basis of genetic syndromes has most often proven to validate the clinical diagnosis.

Syndromes are often multidimensional in their manifestations and include, in addition to birth defects, features related to cognition, behavior, and functional impairment. Structural defects and functional manifestations of syndromes are sometimes very variable; therefore, minimum and discrete criteria need to be established in order to ensure their correct identification. The proposal of diagnostic criteria is key to identify populations of patients affected by the same condition.

Since its delineation, physical features have been the hallmark for the recognition of the Fetal Alcohol Syndrome (FAS). Moreover, the pattern of physical features of FAS is today considered specific enough that a diagnosis of FAS can be established in the absence of confirmation of prenatal alcohol exposure (PAE). Therefore, this pattern of malformation remains the only substitute for a specific "biomarker" of exposure, still unidentified. This is particularly

* Corresponding author.
E-mail addresses: migueldelcampocasanelles@gmail.com, midelcampo@ucsd.edu (M. del Campo).

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important because assessment of PAE is often times difficult, as mothers may not admit to a use or abuse that may have harmed their babies, and in other situations impossible, given that many of these children are placed in orphanages, foster care or adoption, without prior reliable information on exposure. Stigma is a fundamental component associated with the diagnosis of the Fetal Alcohol Syndrome (Zizzo et al., 2013), including personal, familial, social and medical stigma, and often precludes correct and routine assessment of drinking of alcohol beverages during pregnancy.

The physical features of FAS are not a major problem for affected children, although major birth defects and significant growth deficiencies can be relevant medical issues. Both cognitive impairment and behavioral manifestations including secondary disabilities are the major problems for the life of these children and their families. Most patients affected by PAE do not have physical features of FAS. The term fetal alcohol spectrum disorders (FASD) is an umbrella term which includes the full spectrum of defects resulting from PAE. This spectrum of defects was initially set forth by the Institute of Medicine of the National Academy of Scientists in 1996 to include all features seen in children affected by PAE. —years later it was clarified by Hoyme et al. (2015), and recently updated by the same author (Hoyme et al., 2016).

Assessing the neuropsychological characteristics of FASD requires very thorough neuropsychological testing, which is not always accessible. In addition, as of yet, the complex neurobehavioral pattern has not proven to be specific enough. The result is that the diagnosis of the effects of PAE on cognition and behavior, now called alcohol related neurodevelopmental disorders (ARND) in the IOM scheme, as well as neurobehavioral disorder associated with prenatal alcohol exposure (ND-PAE), a new diagnostic category included in the DSM-5, still require firm confirmation of minimal PAE. Therefore, physical features are, today, the most specific markers of prenatal alcohol exposure but are only found in a subset of patients with FASD. There are syndromes caused by genetic defects and exposures to other teratogens that share some features with FAS. The experience of a dysmorphologist, and sometimes genetic testing, will be necessary for the differential diagnosis with those conditions.

In this paper, we will describe the structural defects associated with PAE that will allow recognition of FAS, including dysmorphic features and growth deficits. We will provide a definition of the most relevant features, discuss their embryologic origin, their importance for the diagnosis of FAS and their consideration within the currently used diagnostic schemes.

2. The initial definition of FAS

The term FAS was set forth by Jones and Smith in 1973 (Jones and Smith, 1973). They identified a common pattern of growth deficits and dysmorphic features and proposed diagnostic criteria. In all cases there were abnormal neurological features as well as cognitive and behavioral deficits. This pattern included prenatal and postnatal growth deficiencies, microcephaly, short palpebral fissures, maxillary hypoplasia, epicanthal folds, joint limitations, altered palmar creases, and septal or ductal defects of the heart. A pattern emerged, and the authors proposed pathogenetic mechanisms for the teratogenic origin of the defects. This publication led to widespread recognition of the condition, and to a number of studies to further delineate the clinical phenotype and to better understand its developmental pathogenesis. It is important to recognize that Paul Lemoine, a French pediatrician had described in 1968 the potential effects of alcohol exposure in pregnancy in 127 children born to alcoholic mothers and published the description of his findings in the French literature (Lemoine et al., 1968). Lemoine pointed to a phenotype of microcephaly, a short anteverted nose, fine lips and midface hypoplasia. Both Jones and Lemoine recognized major ocular and cardiac defects occurring in these children. A broad range of less frequent defects were found in some of the cases.

3. Physical features of FASD: description, assessment and significance (Figs. 1–3)

3.1. Physical features included in the diagnostic criteria

3.1.1. Growth deficits

Growth deficits are frequent and part of the initial definition of FAS. Both height and weight can be abnormally low, and the presentation can be prenatal or postnatal. Maternal health, prenatal nutrition and placental function are important determinants of variation in prenatal growth, and can modify the effects of PAE. In the authors' experience growth deficits are most commonly found postnatally.

The cut-off point has been set at the 10th centile for both weight and height, instead of -2SD (2–3%), which is commonly used for the definition of endocrine and genetic causes of impaired growth. Inability to gain weight, low body mass index with decreased fat content leading to a slender muscular build have recurrently been reported. This is reflected in the fact that the Canadian criteria for FASD diagnosis include weight for length ratio below 10th centile as an indicator of abnormal growth in these patients (Chudley et al., 2005). Hyperactive behaviors, decreased cell mass and increased metabolic rates are most likely explanations for this body constitution. Growth deficits have also been noted in all animal models. Population specific curves for objective assessment of weight and height should be used when available, but validated curves are not available for all populations. Moreover, within specific populations, different ethnic origins and ethnic mixes are often not taken into consideration. Familial stature and weight should ideally be taken into account. When, in the absence of PAE, the parents and other family members show growth deficits or significantly tall stature, it can be difficult to interpret that the patient's growth status is determined by PAE, as opposed to genetic and environmental multifactorial determinants. However, none of the diagnostic criteria have yet taken into account these facts in an objective way.

3.1.2. Small head circumference (HC) and structural CNS defects

Similar to growth, HC $\leq$ 10% is considered in the diagnostic criteria for FAS. Microcephaly is caused by a global decrease in brain volume. HC of the parents should always be measured, since microcephaly can be a familial trait sometimes not associated with cognitive or behavioral deficits. Similarly, a genetic background of increased head size can make the absence of a decreased HC in a child with PAE difficult to interpret. Structural anomalies of the CNS have been recurrently reported, most frequently agenesis, partial agenesis or dysgenesis of the corpus callosum, as well as posterior fossa anomalies such as a hypoplastic cerebellum and the Dandy Walker malformation (Mattson et al., 1994; Astley et al., 2009). Other CNS defects have been reported, including reductions in brain volume in all areas but most significantly in certain regions such as the basal ganglia and the diencephalon (Roussotte et al., 2012).

3.1.3. Short palpebral fissures

The eyes are outpouchings of the brain, and appear to be selectively affected by the teratogenic consequences of PAE. Major malformations of the eyes occur in FAS including refraction errors and optic nerve hypoplasia and occasionally microphthalmia (Landgren et al., 2010). Reduced volume of the eye globes has been proven in animals and humans. Microcephaly is responsible for