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Minor physical anomalies and schizophrenia: literature review

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Many authors view schizophrenia as a neurodevelopmental disorder. Knowledge of whether patients have morphologic variants that occur during the development of different anatomic areas of the brain and an understanding of the relation between such variants and brain development or prenatal exposure to possible noxae could provide clues about the events that lead to schizophrenia. Nonspecific morphologic variants that occur during the first and second trimesters of gestation, which are known as minor physical anomalies (MPA) and can be used as disease risk markers in susceptible persons, have been related with schizophrenia, independently of the anatomic region where they occur. The importance of these anomalies in relation to schizophrenia is that they may reflect a substrate (schizotaxia) that is either inherited or acquired as a consequence of injury(ies) that would result in the disease in susceptible persons. This idea is also supported by indirect evidence provided by family studies, among others. On the other hand, the role of MPA in other neurodevelopmental orders is similar to the role proposed in schizophrenia.

Key words:
Schizophrenia. Morphogenesis. Biological markers. Etiology. Phenotype.

Actas Esp Psiquiatr 2010;38(6):365-71

Anomalías físicas menores y esquizofrenia: revisión de la literatura

La esquizofrenia es considerada una enfermedad del neurodesarrollo por muchos autores. Saber si en los pacientes hay variantes morfológicas producidas durante el desarrollo de áreas anatómicas diferentes al cerebro y entender la relación de esas variantes con el desarrollo

cerebral o con la exposición prenatal a posibles noxas, podría dar pistas sobre los eventos que llevan al trastorno. Variantes morfológicas inespecíficas producidas durante el primer y segundo trimestre de gestación denominadas anomalías físicas menores (AFM) que pueden ser usadas como marcadores de riesgo de una enfermedad en personas susceptibles se vienen relacionando con la esquizofrenia, independientemente de la región anatómica en la que se presenten. La importancia de estas anomalías en relación con la esquizofrenia estaría dada porque podrían ser el reflejo de un sustrato (esquizotaxia) heredado o adquirido como consecuencia de alguna injuria(s) que resultaría en la enfermedad en personas susceptibles. Esta idea se apoya además en evidencia indirecta proporcionada por estudios con familias, entre otros. Por otro lado, el rol de las AFM en otros trastornos del neurodesarrollo es similar al propuesto en la esquizofrenia.

Palabras clave:
Esquizofrenia. Morfogénesis. Marcadores biológicos. Etiología. Fenotipo.

INTRODUCTION

Although there are various theories about the etiology of schizophrenia, in one of the most accepted models, schizophrenia is considered a neurodevelopmental disease.¹ This hypothesis is based on evidence of the greater frequency of a history of problems during gestation or in the first months of life: pregnancy-induced hypertension,² low birth weight,³ prenatal exposure to influenza,^{4,5} or intrauterine or early postnatal exposure to toxoplasma,⁶ among other factors.⁷⁻¹¹ In addition, it has not been possible to consistently demonstrate signs of neurodegeneration^{12,13} or neurotoxicity in this psychosis.¹⁴ An important piece of evidence that weighs against the hypothesis of degeneration and in favor of a neurodevelopmental disorder is the absence of gliosis (a dense fibrotic network of neuroglia that occurs in an area of a degenerative injury) or any other conclusive proof of neuronal degeneration in post mortem studies of the neuronal tissue of persons with schizophrenia.¹⁵⁻¹⁷

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Knowledge of whether a morphologic anomaly occurs during the genesis of structures other than the brain, the identity of these structures, and the relation between these morphologic anomalies and possible prenatal exposure to noxae or with cerebral development could provide more clues about the events that eventually lead up to schizophrenia. This article is a review of the most recent scientific literature on a specific type of morphologic alterations, minor physical anomalies (MPA), and their relation with schizophrenia.

CONCEPT OF MPA

More than 100 years ago, Thomas Clouston (1891) observed that some subjects with psychosis ("*adolescent insanity*") had certain physical peculiarities like anomalies of the palate. Kraepelin also described "... signs of degeneration ... smaller size or deformity of the skull ... ear deformities" in people with dementia praecox.^{18, 19} In recent decades, the presence of physical anomalies has been studied in schizophrenia and in diseases related to neurodevelopment, such as autism. MPAs are morphologic variants that appear during the first and second trimesters of gestation, are not specific to any disorder, and are more or less subtle, without any important functional or cosmetic impact that could be used as a marker of disease risk in susceptible people. This is particularly true when several MPAs coincide in individuals with a known risk factor for a disease.²⁰

MPAs are due to genetic causes (not necessarily a genetic disorder, also variants of normality), environmental causes or a combination of the two.²¹ A family pattern exists in some cases and in others, such as Down syndrome, MPAs are associated with chromosomal defects in which the trisomy allows more variance in genetic expression and the resulting associated phenotype.²² MPAs also have been associated with a large variety of environmental injuries (teratogenesis) during gestation, including maternal infections, bleeding, exposure to toxins and fetal anoxia, which would act on genetically programmed development.²³

Evaluation of the MPAs

Waldrop et al.²⁴ evaluated the relation between MPAs and the behavior of preschool children and designed a scale for this purpose. Green et al.²⁵ prepared a revised version of the Waldrop scale to assess MPAs and this version was adapted to Spanish by Anguiano et al.²⁶ The score of this adapted scale is obtained by the evaluation of 6 anatomic zones: head, eyes, ears, mouth, hands, and feet. Each of these parts of the body has several items (resulting in a total of 14 for all the zones, and a range of scores from 0 to 22 for the entire scale). The instrument offers drawings of the items in

the different zones and a page for scoring. Briefly, the most important features sought in each anatomic area are:

Head: hair (quality of the hair fibers on the scalp, e.g.: thinness or charged with static electricity), microcephaly or macrocephaly.

- Eyes: palpebral fold, hypertelorism.
- Ears: low ear implantation, anomalous lobe direction and ear malformations.
- Mouth: form of the palate (vaulted or flat), presence of deep tongue furrows.
- Hands: curved fifth finger, presence of a single transverse palmar crease.
- Feet: third toe longer than the second toe, syndactyly, wide space between the first and second toes.

This scale, which evaluates a heterogeneous group of physical features that do not necessarily have specific etiological importance, has been used in most studies of MPA in schizophrenia (see Epidemiology), although the heterogeneity of the scale has been criticized.^{27, 28} This has led to the development of other instruments, such as the one proposed by Trilex et al.,²⁹ to differentiate MPAs that derive specifically from morphogenesis and thus, according to these authors, are relevant to the study of schizophrenia, from MPAs that could be phenogenetic (variants that arise during development). Trilex et al. proposed a differentiated list to assess the presence or absence of 31 morphogenetic malformations and 26 phenogenetic variants, but in 50 patients with schizophrenia who were specifically evaluated using these lists, they found both morphogenetic malformations (specifically, prominent lingual furrows, multiple buccal frenula and hemangiomas) and phenogenetic malformations (specifically, prominent pinnae and a large tongue).

A more recent approach to the measurement of MPAs, which has been used to evaluate persons with schizophrenia, proposes the use of a three-dimensional evaluation by means of laser holograms. Using this technique, Buckley et al.³⁰ found that patients with schizophrenia in which specific points of the face were evaluated had supero-inferior elongation of the face compared to healthy controls.

Lloyd et al.³¹ called attention to the possible impact of the age of the subjects studied using tools to evaluate MPA. Subjects over 60 years old have higher scores on the scale due to normal aging (alopecia, changes in the jaw and ears) compared to subjects under 60.

MORPHOGENESIS, MPA AND SCHIZOPHRENIA

The cerebral dysfunction in schizophrenia involves alterations in the prefrontal/cingulo-striato-pallido-

thalamo-cortical/fronto-temporal tracts that affect the afferent and efferent connections to and from the midline.³² In studies of brains (post mortem), cytoarchitectural anomalies that are consistent with early/intermediate neurodevelopmental disorders in the midline regions of the temporal lobe and frontal lobe have been reported.^{33, 34}

During early fetal development, cerebral and craniofacial morphogenesis are closely related and share a common ectodermic origin. Morphologic anomalies can range from very severe (which are probably produced in earlier stages of development) to MPAs. These anomalies are markers of abnormalities in organogenesis at the end of the first trimester and beginning of the second trimester of gestation.^{34, 35} In neuroimaging studies, MPAs have been associated with an increase in the size of the third ventricle (midline) but not with changes in the lateral ventricles.³⁶⁻³⁸

The palate, which is considered typical of the structures in which schizophrenia-related MPAs may exist, originates between weeks 6 and 9 of gestation and continues developing until it reaches its postnatal form between weeks 16 and 17. The palate is related to the vertical growth of the middle face and to frontonasal widening. The morphologic alterations associated with schizophrenia probably reflect lesions that occur in this period of embryological development.³⁸ The hippocampal formation (hippocampus-parahippocampal gyrus/cortex) differentiates in weeks 9 to 10 of gestation. The parahippocampal and entorhinal cortex has afferent and efferent connections not only with the hippocampus but also with the associative areas of the frontal, parietal and temporal lobes. All these structures are related to the defects observed in patients with schizophrenia. The reduction in volume of the hippocampal formation in association with schizophrenia has been confirmed by meta-analysis.³⁹ The period between weeks 9.5 and 13.5 is important because differentiation of the entorhinal cortex takes place in this period. In addition, there is proximity with the development of structures that have been reported to be altered in schizophrenia, such as the thalami.³⁸

Understanding the cellular and molecular mechanisms involved in the development of craniofacial and other structures in which MPAs have been identified in association with schizophrenia could help in the search for genes and developmental injuries related with schizophrenia.³⁸ However, the anomalies should not be interpreted as a necessary or characteristic feature of schizophrenia nor should it be thought that the only MPAs that can serve as markers of schizophrenia are cranial. On the one hand, the MPAs associated with schizophrenia may be located in other anatomic areas (see Epidemiology) and, on the other hand, the model of schizophrenia as a neurodevelopmental disease is dynamic and implies a progressive unfolding of a series of events that determine the trajectory of the psychosis from apparently pre-morbid stages to an established clinical

picture.^{28, 40} The true importance of MPAs in the context of schizophrenia is that they may reflect a substrate (not of the disease but a trait –schizotaxia) that is inherited or acquired as a result of injury and would result in disease in susceptible subjects.^{41, 42}

EPIDEMIOLOGY

Weinberg et al.,⁴³ in their meta-analysis of MPAs in schizophrenia, published in 2007, report more MPAs evaluated using the Waldrop scale or a modification of this scale in persons with schizophrenia compared to controls in 11 different studies (effect size 1.131, $p < 0.001$). They did not find evidence of any influence on results of the year of publication, use of diverse diagnostic criteria of schizophrenia (DSM III, DSM IIR, or DSM IV), study of populations from different countries, study heterogeneity, or possible publication bias. According to the 7 studies in which these authors assessed the frequency of MPA by anatomic region, patients present more MPAs than controls in all of the areas evaluated: head, eyes, ears, mouth, hands and feet (effect size > 1 , $P < 0.05$). The mouth had the largest effect size (2.65), followed by the head (effect size: 2.55), eyes (effect size: 2.47), hands (effect size: 2.14), feet (effect size: 2.15) and ears, with the smallest effect size (1.42).

The effect of gender on neurodevelopment and mental disease is highly relevant.⁴⁴ Akabaliev and Sivkov⁴⁵ evaluated the presence of differences in the Waldrop scale score in relation to gender in patients with schizophrenia, in addition to comparing their sample of persons with schizophrenia to a healthy control group. They found that both men and women have MPAs with more frequency than in controls, but when the frequency of MPA was compared by genders within the group of cases of schizophrenia, men had a statistically higher score on the scale (more frequent MPAs) only for the head zone (characteristics of hair, microcephaly or macrocephaly). Another aspect studied in relation to the etiology of schizophrenia is race.⁴⁶ Donovan-Lepore et al.⁴⁷ studied the existence of differences in the prevalence of MPAs, specifically malformations of the head and face, in a group of 32 whites compared to 20 Afro-Americans. Both groups had a specific diagnosis of schizophrenia or schizoaffective disorder and no differences were found in the distribution of these anthropometric variables. Dean et al.⁴⁸ did not find any differences in the frequency of MPAs in 42 Afro-Caribbean immigrants, 10 black Africans and 12 Asians with these anomalies compared to a group of 188 whites in the United Kingdom who consulted for an index psychotic episode. Elisarrarás-Rivas et al.⁴⁹ also reported the presence of MPAs in a group of 20 people of mixed race of Mexican origin with a diagnosis of schizophrenia. Overall, these findings support the hypothesis that neurodevelopmental anomalies are just as important in the etiology of schizophrenia in these ethnic groups as in whites.

FAMILY AND OTHER STUDIES

In the study of families by Maudsley,⁵⁰ this author divided patients with a diagnosis of schizophrenia into two groups, one of people with nonfamilial schizophrenia (sporadic) and the other of patients with familial schizophrenia (first-degree family members diagnosed of schizophrenia). They found, using the Waldrop scale, a higher rate of MPAs in subjects with sporadic schizophrenia and attributed this finding to the likelihood that these anomalies are markers of an injury sustained during development that would be related to the subsequent appearance of schizophrenia.

Shiffman et al.⁵¹ studied the MPA index (evaluated in subjects age 11 to 13 years) in a group of 81 people with a genetic risk of schizophrenia (a parent diagnosed of schizophrenia) to determine if it was higher in subjects who developed a disorder of the schizophrenia spectrum (schizophrenia, schizoid personality disorder, paranoid personality disorder) after 20 years of follow-up than in the subjects who did not. They found that MPAs were associated more frequently with disorders of the schizophrenia spectrum in subjects who presented any of these diagnoses than in subjects who did not (OR 3.53, 95%CI 1.34-9.27). These authors speculate that, in addition to genetic predisposition, some injury takes place during neurodevelopment that leads to the appearance of disorders of the schizophrenia spectrum and that MPAs are a marker in this group.

Gourion et al.⁵² explored the relation between soft neurological signs (including the assessment of functional integration and motor coordination) and MPA in the nuclear families of probands with schizophrenia (18 trios consisting of two healthy parents and a healthy offspring with schizophrenia or schizoaffective disorder and 42 healthy controls with no personal or family history of mental disease). They report that the probands had soft neurological signs and MPAs more frequently than the rest of the sample. However, there was an intrafamilial correlation in relation to the soft neurological signs (both patients and their parents had these signs more frequently), whereas there was no family correlation for the MPAs. According to the findings of these authors and those of other studies,⁵³ soft neurological signs are related to genetic aspects and MPAs are related to environmental injuries. On the other hand, an association was observed between soft neurological signs and the predominance of negative and disorganized characteristics in the schizophrenia, but no clear association between MPA and a specific symptomatic pattern.⁵⁴

Hata et al.⁵⁵ postulated the hypothesis that early onset schizophrenia (before 18 years) is determined more by epigenetic injuries than schizophrenia of later onset. They

report that in a group of patients divided by age of onset, the patients with early onset schizophrenia more frequently presented abnormalities of the cephalic perimeter, hypertelorism, low-set ears, vaulted palate, deeply furrowed tongue, curved fifth finger, single transverse palmar crease and wide space between the first and second toe in comparison with patients in which schizophrenia was at a later age.

Mednick et al.⁵⁶ suggest that the interaction between genetic predisposition and environmental stress (injury *in utero*) could increase the risk of schizophrenia. Green et al.⁵⁷ consider MPAs to be a marker of the occurrence of intrauterine stress in vulnerable individuals.

MPAS IN OTHER DISORDERS

Since MPAs are markers of embryological development in general, they have been studied in other disorders in which abnormalities of morphogenesis during early gestation are sought. Knowledge of the role of MPAs in these disorders could be useful for understanding the relation between MPAs and schizophrenia. In the case of bipolar affective disorder (BAD), Green et al.⁵⁷ could not demonstrate a greater frequency of MPAs. Trixler et al.⁵⁸ studied 30 patients with schizophrenia, 30 with BAD and 30 healthy subjects matched for age, gender and ethnic origin. They found that in the group of people with schizophrenia, 6 had more than 5 MPAs, 19 had 1 to 5 MPAs, and 5 did not have any. In the BAD group, none had more than 5 MPAs, 20 patients had 1 to 5 MPAs, and 10 had none. Among the healthy controls, none had more than 5 MPAs, 14 had 1 to 5 MPAs, and 16 had none. The group of patients with schizophrenia differed statistically from the other two whereas the BAD group did not differ statistically from healthy controls. Although these findings are consistent with a model of BAD distinct from the model of schizophrenia, it is important to consider that there have been few studies of MPAs in affective disorders and the sample sizes are small and in many cases not differentiated by BAD subtypes or even between unipolar and bipolar conditions.⁵⁹

Several studies, the majority using the Waldrop scale, have reported a higher frequency of MPAs in persons with autism, specifically: more hypertelorism, syndactyly and anomalies of the mouth and ears in comparison with healthy controls or siblings without autism. The authors of these studies propose that the greater frequency of MPAs in patients with autism supports the hypothesis that autism is produced by some injury that affects embryological development during the first trimester of gestation.^{60, 61} Strömland et al.⁶² report the case of children exposed *in utero* to thalidomide during the first trimester of gestation who presented autism and malformations ranging from the absence of the pinnae (anotia) in severe cases to moderate

anomalies and hearing defects. One of the weaknesses of the studies in autism is the lack of suitable controls to pair with the cases because autism is associated with mental retardation with a certain frequency. Since mental retardation is accompanied by a greater prevalence of MPAs,⁶³ it is difficult to determine whether the MPAs are associated with the autism or with the mental retardation. In this sense, Rodier et al.⁶⁴ used data from the Nova Scotia Epidemiological Study to control for the effect of intellectual quotient on MPA and found that the children with autism but not mental retardation had an alteration in the rotation of the ears. These authors point out the fact that the otic disc appears in week 4 of development, which could mean that the causes of autism must be sought in early development. More recently, Hardan et al.⁶⁵ evaluated the interorbital distance by means of magnetic resonance in a group of 40 individuals with autism and without mental retardation compared to 40 healthy controls. They found that the interorbital distance and the interorbital/orbital radius were smaller in the group of persons with autism.

CONCLUSIONS

MPAs are nonspecific morphologic variants that are produced during first and the second trimesters of gestation and can be used as markers of risk of disease in susceptible people. They are due to genetic causes (but not necessarily a genetic disorder), environmental causes, or a combination of both. MPAs have been associated to a large variety of environmental injuries (teratogenesis) that occur during gestation, including maternal infections, bleeding, exposure to toxins and fetal anoxia, which act on genetically programmed development.

Patients with schizophrenia have more MPAs in all of the anatomic zones evaluated with the Waldrop scale (the instrument most used in the study of MPAs), head, eyes, ears, mouth, hands and feet, in comparison with healthy controls. This should not be taken to mean that MPAs are a necessary requirement for the development of schizophrenia. The true importance of these anomalies in relation to schizophrenia is that they may reflect the existence of a substrate that is inherited or acquired as a result of injury(ies) that leads to disease in susceptible subjects. This idea is also supported by indirect evidence from diverse types of studies, such as family studies, that suggest that the interaction between genetic predisposition and environmental stress (*in utero*) may increase the risk of schizophrenia and that MPAs are a marker of the occurrence of this stress in vulnerable individuals.

On the other hand, a high frequency of MPAs has been reported in autism (also considered a neurodevelopmental disease), which supports the notion that an injury that affects development during the first trimester of gestation

could be involved in its etiology. This also provides indirect support for the hypothetical relation between MPAs and schizophrenia.

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