Autism spectrum disorder today: not only genetics

Günümüzde otizm spektrum bozukluğu: tek başına genetik temelli değil

Cite this article as: Posar A, Visconti P. Autism spectrum disorder today: not only genetics. Turk Pediatri Ars 2019; 54(2): 137–8.

Dear Editor,

Today, a significant role of genetic factors is widely accepted also in non-syndromic autism spectrum disorder (ASD), that is ASD not secondary to a well-known genetic condition (e.g., fragile X syndrome) (1). Modern genetic techniques, such as microarray and whole-genome sequencing, showed the involvement of a large number of genes in ASD etiopathogenesis (2). However, the dramatic increase of ASD prevalence during the last decades, which in the United States of America reached 16.8 per 1000 children aged 8 years (3), suggests that environmental factors also play an important role. The pre-, peri-, and postnatal exposure to many heterogeneous environmental factors have been hypothesized to be involved, such as air pollutants (particularly heavy metals and particulate matter), pesticides, and other endocrine-disrupting chemicals (1). There would already be enough data to try to take appropriate preventive measures against these pollutants, although the research conducted so far showed an association between exposure to them and ASD, but not a clear causal link.

We absolutely do not want to minimize the importance of genetic factors, which is suggested also by the persisting prevalence of males compared with females in the ASD population (3). If ASD etiopathogenesis was related only (or mainly) to environmental factors, with which individuals of both sexes indifferently can come into contact, the persisting prevalence of males would not find an explanation (1). We think that environmental factors could amplify the effects of a genetic predisposition, so that the threshold corresponding to the occurrence of ASD would be overcome. Consequently, we believe that findings emerging from the modern genetic techniques should be interpreted taking into account environmental factors as well. For example, consider the microarray that showed copy number variants (CNVs) in a non-negligible percentage of individuals with ASD (2). A CNV is a DNA segment that differs in copy number compared with a reference genome. Copy number variants are usually classified as pathogenic, likely pathogenic, of uncertain significance, likely benign or benign, based also on comparisons with general population databases (4). We believe that the pathogenic significance of a CNV should be assessed while also taking into account the environmental context in which the individual lives. That is, a CNV could be pathogenic if the child, in a specific (usually early) period of his/her existence, comes into contact with an environmental factor (or with a certain amount of the environmental factor), otherwise the CNV remains silent. Perhaps this mechanism could also explain why sometimes a CNV is present in a healthy parent and at the same time in a child affected by ASD.

Further research is needed to understand the subtle interactions between genetic and environmental factors in the etiopathogenesis of ASD, considering also the concept of epigenetics, which is a very important gene regulation mechanism based on chemical modifications of DNA and histone proteins, without altering the DNA sequence (1). Moreover, an increasing amount of literature data suggest that epigenetic mechanisms could be the mediators of effects deriving from environmental factors both in ASD and in other neurodevelopmental disorders (5).

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Acknowledgment: The authors would like to thank Cecilia Baroncini for linguistic support.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.P., P.V.; Design - A.P.; Supervision - A.P., P.V.; Literature Review - A.P.; Writing - A.P.; Critical Review - A.P., P.V.

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Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Teşekkür: Yazarlar, dil desteği için Cecilia Baroncini'ye teşekkür eder.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - A.P., P.V.; Tasarım - A.P.; Denetleme - A.P., P.V; Literatür Taraması - A.P.; Yazıyı Yazan - A.P.; Eleştirel İnceleme - A.P., P.V.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için finansal destek almadığını belirtmiştir.

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Received / Geliş Tarihi: 09.08.2018
Accepted / Kabul Tarihi: 14.01.2019
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DOI: 10.14744/TurkPediatriArs.2019.98216