Psychiatric disorders: neurodevelopmental disorders, neurodegenerative disorders, or both?

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Abstract

Central nervous system disorders are traditionally dichotomized between early-onset neurodevelopmental and late-onset neurodegenerative diseases. Yet, there are commonalities in the mechanisms operating in both neurodevelopmental and neurodegenerative diseases.

Keywords: *neurodegenerative disorder; neurodevelopmental disorder; psychiatric disorder*

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Central nervous system disorders are traditionally dichotomized between early-onset neurodevelopmental and late-onset neurodegenerative diseases. Yet, significant cognitive symptoms observed in neurodegenerative diseases may appear early and subtle differences in higher cognitive functions can be identified in the presymptomatic phase. Furthermore, Ring et al[1] have shown that the first disease processes start during early embryonic development, prior to full neuronal maturation, in Huntington disease, which was typically considered as a neurodegenerative disorder. In fact, dysregulation of genes involved in neuronal development and formation of the dorsal striatum are involved. Similarly, Schwamborm et al[2] have made the assumption that Parkinson disease has a significant neurodevelopmental component which could be compensated for a long time. These developmental defects, on their own, might not cause the disease but may rather increase the susceptibility for disease onset after a "second hit": in a previously unbalanced system, one or more additional hits could disturb the entire system and lead to symptoms of Parkinson disease. If these hypotheses are later confirmed, this will expand the time window for putative preventive or curative treatment or, at worst, for treatment options which may postpone the onset of certain neurodegenerative diseases. Hadar and Gurwitz (in this issue, p 293) will review potential biomarkers which might be useful for early diagnosis of dementia.

Additionally, gender may be associated with various risk levels of psychiatric disorders. Examples of male-biased conditions mainly include early-onset neurodevelopmental disorders such as autism spectrum disorders, attention deficit-hyperactivity disorders (the hyperactive-impulsive subtype), language impairments, or even schizophrenia; whereas examples of female-biased conditions rather include emotional disorders such as anxiety, depressive or stress and trauma-related disorders, or even anorexia nervosa, which usually starts during puberty or later in life.[3] Interestingly, sex differences are also seen in neurodegenerative disorders: being male is a significant risk factor for Parkinson disease and motor neuron disease, whilst females are more susceptible to Alzheimer disease and multiple sclerosis. The organization of sexually differentiated brain circuits is based, among other factors, on sex hormones (mainly estradiol and androgens) and on genes located in the sex chromosomes including the Y chromosome gene Sry and others, as well as epigenetic mechanisms occurring at the DNA level. Neurosteroids may also influence DNA methylation and epigenetics.[4]

However, since the discovery of cell reprogramming technologies and the generation of induced pluripotent stem cells from somatic cells, the traditional dichotomy between early-onset neurodevelopmental and late-onset neurodegenerative diseases has been challenged. Taoufik et al[5] have reviewed commonalities in the molecular and cellular mechanisms operating at the synapse level in both conditions.

Even though clinical symptoms of neurological or psychiatric diseases can start in childhood or early or late adulthood, the precise time of initiation of the pathological cascades remains unknown in many cases. In the case of inborn errors of metabolism, clinical features are very diverse and may present as a neurodevelopmental disorder (antenatal or late-onset), as well as a progressive and late-onset neurodegenerative disorder (see Saudubray and Garcia-Cazorla in this issue, p 301).

In this issue, Guarnieri et al (p 255) have provided an overview of the molecular mechanisms that are implicated in the generation of genetic malformations

of cortical development associated with aberrations at various steps of neurogenesis and cortical development which may lead to neurological or even psychiatric disorders.

Finally, in this issue, Mott et al (p 283) have reviewed the importance of oligodendrocyte contribution to neurodegenerative diseases in which myelinated axons are lost, such as in Alzheimer disease, amyotrophic lateral sclerosis, and multiple system atrophy. ❑

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