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Seminars in
Pediatric
Neurology

# Migraine and Puberty: Potential Susceptible Brain Sites

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**Puberty is a sensitive and critical period for brain development. The relationship between developmental processes in the brain during puberty and the onset of migraine disease in relation to the potential sites of susceptibility in the brain remains largely unknown. There are few data on how such processes interact with each other in influencing the migraine onset during puberty or even later in adulthood. Focusing on the migraine brain during pubertal development may provide us with a "window of opportunity" both to better understand the mechanisms of the disease and, also more importantly, to effectively intervene.**

**Semin Pediatr Neurol 23:53-59 © 2016 Elsevier Inc. All rights reserved.**

## Introduction

Migraine is one of the top 5 most frequent childhood diseases.[1,2] It occurs in up to 10.6% of children between the ages of 5 and 15 years, and in up to 28% of children between 15 and 19 years of age.[3,4] Compared to adults, migraine attacks in children are of shorter duration and may be bilateral or unilateral. Episodes are associated with photophobia, phonophobia, and nausea and less commonly with auras. Migraines can be seriously disabling to pediatric sufferers by impairing their quality of life, school attendance, or participation in various activities. They may also develop comorbidities such as anxiety, depression, sleep disorders, and a variety of other pain conditions.

Multiple population-based epidemiologic studies have observed that the prevalence of migraine increases with age during adolescence. However, there is a notable sex difference in the age-related presentation. Prepubertal youth males have a slightly higher prevalence of migraine compared to females, whereas after puberty, prevalence increases sharply among females and remains low in males. This pattern suggests that changes involved in pubertal development among females are critical in their having migraine. The increase in incidence among females starts during the earlier stages of pubertal development and increases rapidly,[5] reaching its peak between the ages of 14 and 16 years. Incidence then gradually declines with age in females. Headache disorders can persist for a long time, and the prevalence of migraine peaks between ages 35 and 45 years, affecting 2-3 times more women than men.[6-9]

Sex differences in the time of hormonal changes that occur during puberty and their associations with brain development may lead to the previously described differences in the risk of sex-influenced diseases, such as migraine.[9] The mechanisms through which the hormonal changes during puberty may influence the phenotypic expression of migraine are not well understood, and the identification of potential sensitive or susceptible regions in the brain remains largely unknown. Moreover, there are few data concerning how such processes interact with or influence brain development during puberty.[10] Understanding the underlying mechanisms of such interactions in the brain during puberty may provide a "window of opportunity" to better explain the mechanisms of the

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http://dx.doi.org/10.1016/j.spen.2016.01.011

disease and also better understand how to effectively intervene. Changes in the brain during pubertal development may play a significant role in the onset of the disease, not only in childhood but also later in adulthood.

## The Activation of Neuroendocrinal Pathways

Because hormones influence brain structure and function and because hormone secretion is governed by the brain, applied molecular neuroscience techniques can begin to reveal the role of hormones in brain-related disorders and the treatment of these diseases.[11]

Pubertal development is a process that is initiated by hormonal signals from the brain to the gonads. Gonadotropin-releasing hormone (GnRH) pulse generating neurons located in the arcuate region of the mediobasal hypothalamus are reactivated by the onset of puberty.[12-14] GnRH pulsatile secretion through these neurons triggers gonadotropic cells within the anterior pituitary to stimulate the synthesis and secretion of the gonadotropin hormones, follicle-stimulating hormone, and luteinizing hormone into the systemic circulation. Luteinizing hormone and follicle-stimulating hormone stimulate the secretion of steroidal hormones: estrogens and progesterone from the ovaries, which are then released into systemic circulation and regulate hypothalamic GnRH and pituitary gonadotropin secretion through positive and negative feedback mechanisms.[13,15]

Results from basic science, epidemiologic, and clinical studies strongly suggest changes in estrogen levels to be an important influence on the development and phenotypic expression of migraine among adults.[16-18] Migraines can be triggered by decline in estrogen levels that occurs during the drop in levels immediately before menstruation, during the pill-free week in women who are on contraceptives, or in women with bilateral oophorectomy.[19] There is evidence for different age-related changes in the hypothalamic-pituitary-gonadal axis on estrogen negative and positive feedback.[20]

## Brain Reorganization During Puberty

Converging lines of evidence indicate that puberty is a sensitive period for brain reorganization.[9,21-25] This process involves both genomic as well as hormonal regulation of signaling pathways that influence reproductive behaviors and structures and also interact with the brain in determining its organization.[9,26,27] The brain grows by developing synapses between the neuronal cells and subsequent pruning of the connections to get rid of unnecessary connections. During puberty, the brain undergoes a second round of reorganization through synapse formation, pruning, and myelination (the first round is completed early in childhood during the approximately the first 2 years). Changes in the brain's electrical activity during sleep[28] and reduction in the cerebral metabolic rate[28,29] that occur during puberty may be surrogates for changes in the number and connectivity of neuronal networks and be an indicator of significant reorganization in the brain. The reorganizational changes of the brain during puberty contribute to emotional, behavioral, intellectual, and social development during adolescence, all of which require remodeling of cortical and limbic circuits in the form of the regional neuroanatomical changes or the connectivity among them[9,30] or changes in the neuronal excitability, metabolism, and survival.[11] Errors in the reorganization of the brain during this sensitive period could potentially lead to the formation of malfunctioning of structures, connections, or networks, causing mental or neurological disorders.

## Separation of the Effects of Pubertal Maturation From the Effect of Chronological Age on Brain Development

There are interindividual differences in different aspects of pubertal maturation such as age of puberty onset, length of puberty period (from onset to completion), and the amount of growth happening during this period. Therefore, when studying the brain during this period of life, chronological age is an inefficient variable, as there is a wide range of maturational states or levels for children of the same chronological age. Given the reorganizational changes in the brain during puberty, it is important to take both age and the pubertal maturation state into account in studying the brain. Separation of the effects of pubertal maturation from the effect of chronological age is particularly crucial in studying pediatric migraine, as it is a disease with the highest incidence during puberty. Unfortunately, there are no studies in the field that have accounted for both factors, and such research is needed to better differentiate the role of these 2 important factors. Recent advances in neuroimaging techniques can help address this gap by allowing collection of an array of data on functional, morphometric, and chemical brain changes combined with data on pubertal status and hormonal levels in a pediatric population to define the effects of the disease vs maturation, vs the growth of brain structure and function.

## Potential Sites of Susceptibility During Pubertal Brain Development

Multiple studies have shown that cortical gray matter changes during puberty are region specific and happen predominantly nonlinearly[31-33] with the peak ages for increase in the frontal and parietal lobes corresponding to the ages of puberty onset.[34] The increase in white matter volume seems to be more linear.[35] Age-related increases in