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Review

Primary headache pathophysiology in children: The contribution of clinical neurophysiology

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HIGHLIGHTS

- Neurophysiologic abnormalities in pediatric headaches are different from adult ones.
- Brain maturation in children with migraine is different from that of healthy subjects.
- Future studies should investigate nociceptive and motor systems in migraine children.

ABSTRACT

Although primary headaches are very prevalent also in pediatric age, most neurophysiologic studies in these diseases concerned only the adulthood. The neurophysiologic investigation of the pathophysiological mechanisms subtending migraine and tension-type headache in children and adolescents could be particularly interesting, since during the developmental age the migrainous phenotype is scarcely influenced by many environmental factors that can typically act on adult headache patients. The neurophysiologic abnormality most frequently found in adult migraineurs, that is the reduced habituation of evoked potentials, was confirmed also in migraine children, although it was shown to involve also children with tension-type headache. Some studies showed abnormalities in the maturation of brain functions in migraine children and adolescents. While the visual system maturation seems slowed in young migraineurs, the psychophysiological mechanisms subtending somatosensory spatial attention in migraine children are more similar to those of healthy adults than to those of age-matched controls. There are some still unexplored fields that will have to be subjects of future studies. The nociceptive modality, which has been investigated in adult patients with primary headaches, should be studied also in pediatric migraine. Moreover, the technique of transcranial magnetic stimulation, not yet used in young migraineurs, will possibly provide further elements about brain excitability in migraine children.

Contents

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1. Introduction

Traditionally, primary headaches diagnosis is supported by anamnestic data and neurological examination (Hershey, 2010). Diagnostic techniques may be useful for the identification of secondary headache but do not help in distinguishing the different types of primary headaches (Lewis et al., 2002). However, in the last years, both neuroimaging and neurophysiologic advances were addressed to analyze the complexity of primary headache pathophysiology. While migraine, the most commonly studied primary headache, has been considered for a long time a disease of the head vascular structures, it has been more and more evident that the involvement of the cerebral cortex has a primary role in the cascade of events which trigger the migraine attacks (Silberstein, 1992). The functional neuroimaging techniques, such as the positron emission tomography (PET) and the functional magnetic resonance imaging (fMRI), have shown metabolic changes in several brain regions known to belong to the so-called "pain matrix" (Cohen and Goadsby, 2005). The anterior cingulate cortex (ACC) and the insula are the more frequently activated structures (Sánchez del Rio and Linera, 2004). However, these regions are linked to affective/emotional component of pain sensation and their involvement is very common also in both painful syndromes of body parts different from the head and experimental pain (see Peyron et al., 2000 for a review). Therefore, it is possible that the involvement of the cerebral cortex in the migraine attack, as demonstrated by PET and fMRI, represents an epiphenomenon of pain, rather than being important in pain generation. On the contrary, more interesting results seem the ones concerning the activation of different brainstem regions during the attack of migraine without aura (Sánchez del Rio and Linera, 2004). However, the inhomogeneous findings of different groups, which showed, in turn, the activity of the dorsal raphe nucleus, the periaqueductal grey and the locus coeruleus (Weiller et al., 1995), or of the dorsal rostral pons (Bahra et al., 2001), or of the red nucleus and substantia nigra (Cao et al., 2002), raise some questions about the real functional meaning of the brainstem involvement in migraine without aura. Although the functional neuroimaging techniques have the major advantage of a high spatial resolution, thus any metabolic changes can be accurately detected in the brain volume, they use the blood flow as a surrogate of the synaptic activity, thus they are limited by poor time resolution (Hobson and Aziz, 2004) and unlikely determine whether the underlying physiological event is related to increased or reduced excitability. In contrast, the use of electroencephalography (EEG) and evoked brain potentials (EPs), though having less spatial accuracy than imaging, has the advantage of excellent temporal resolution as these techniques measure the brain activity in real-time on a millisecond scale (Sharma et al., 2009). Moreover, the neurophyiologic techniques give us the possibility to explore the function of both the sensory and motor areas of the brain and to obtain a direct measure of their excitability (Valeriani et al., 2001; Valeriani, 2005).

Most neuroimaging and neurophysiologic studies on primary headache pathophysiology concerned the adults, while primary headaches in children have been far less studied. Neurophysiologic research should hopefully deal with primary headache pathophysiology in children for two main reasons: (1) some neurophysiologic studies produced contrasting results in children and adults with migraine, suggesting that the pathophysiological background of this disease may depend on central nervous system development; (2) childhood migraine is the best model for a pathophysiological investigation of the disease, because many factors occurring during the course of life, such as concomitant diseases, effects of drugs and environmental influences, can change the phenotypic expression of migraine (de Tommaso, 2005).

In this paper, we will review the clinical neurophysiologic studies on primary headache pathophysiology in children, considering the contribution provided by different techniques.

2. Abnormal excitability of the primary cortices in childhood migraine

Migraine is associated with abnormal central information processing and altered cerebral cortex excitability (Schoenen, 2006). Among the primary sensory cortices, the most frequently studied in children is the visual area. An early visual evoked potential (VEP) study showed higher amplitude to flash stimulation in migraine children than in healthy subjects (Brinciotti et al., 1986). This confirmed what had been previously found in adults (Lehtonen, 1974; Connolly et al., 1982). It is interesting that Lahat et al. (1999) proposed to use the VEP amplitude as a tool for diagnosing primary headache in very young children. In young migraineurs, increased VEP amplitude was found also by using the pattern-reversal stimulation (Aloisi et al., 1997; Lahat et al., 1997; Unay et al., 2008). Only one study found normal pattern-reversal VEP amplitude in migraine children (Rossi et al., 1996). It is conceivable that the increased VEP amplitude may represent the result of a reduced VEP habituation, which has been consistently demonstrated in adult migraineurs (see Ambrosini et al., 2003 for a review). Habituation means a physiological decrease of the response that the sensory cortices give to the arrival of repetitive inputs. From a neurophysiologic point of view, habituation entails the progressive reduction of the EPs to successive stimuli which is usually observed in healthy subjects. Habituation has probably a protective meaning by avoiding the accumulation of potentially toxic metabolic products within the brain. It is possible that in migraneous cortex the lack of habituation provokes meta-

Table 1
EP habituation in children.

	Brief description and generators	Evidence
Auditory MMN	Discriminable change in auditory stimulation without attention; bilateral auditory-cortex with the contribution of right frontal cortex	Valeriani et al. (2009): lower habituation in Ms-TTH than in Hs; no difference between Ms vs TTH
P300	Sensitive (auditory/visual) measure of the capacitiy to allocate attentional resources; multiple cortical-subcortical, relatively independent generators	Evers et al. (1998): lower habituation in Ms vs Hs; Buodo et al. (2004): habituation in Ms, but not in Hs; Zohsel et al. (2008): no difference between Ms Vs Hs; Valeriani et al. (2009): lower habituation in Ms-TTH than in Hs; no difference between Ms vs TTH
CNV	Preparation of a signaled movement and the simultaneous anticipatory attention for the imperative stimulus; generators in anterior cingulate cortex, the supplementary motor area and the prefrontal cortex	Kropp et al. (1999): no difference between Ms vs Hs
VEPs	Functional integrity of the visual pathways from retina via the optic nerves to the visual cortex of the brain; generators in the visual areas	Oelkers-Ax et al. (2005): no difference between Ms vs Hs

Ms (migraine subjects); TTH (tension type headache patients); Hs (healthy subjects).