Gender, migraine and affective disorders in the course of the life cycle

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Summary

The relationships existing between migraine and affective disorders are still far from clear. Despite the evidence of a high prevalence, in association, of both conditions, many questions remain unanswered. To what extent is the coexistence of migraine and affective disorders, in particular depression, genetically determined? How important a role is played by pregnancy? What interactions occur between genetic and epigenetic factors?
The authors analyse all these open questions and review the state of the art on this intriguing topic.

KEY WORDS: depression, gender, hormones, life cycle, migraine, temperament.

Introduction

It is well known that migraine is a multifactorial disorder in which biological, genetic and epigenetic aspects are closely interwoven. Remembering the riddle that the sphinx set Oedipus, our aim in this paper is to trace the evolution of migraine and affective disorders throughout the life cycle.

The concept of the family, in particular the psychosomatic family, seems to constitute a good starting point for our discussion, and fertile ground on which to identify the main dynamics that, during the developmental period, lead a child to express conflicts and distress through his or her body. The relationship between the environment and hormones is already evident during pregnancy, when maternal stress can lead to increased levels of placental corticotrophin-releasing hormone (CRH) which can interfere with the development of the foetus and, later on, be related to impairments of temperament, learning and behaviour.

Although migraine shows no gender differences in pre-pubertal children, occurring equally in boys and girls, in adults it is more frequent in women; the same is true of depressive disorders.

Rates of significant depression roughly double in boys and more than quadruple in girls after puberty. The presence of significant levels of somatic symptoms also increases with increasing maturity in girls, whereas in boys levels remain almost unchanged.

Furthermore, depression and somatic symptoms in girls increase the prevalence of pain syndromes in a multivariate model.

While the association between depressed mood and hormonal changes during the transition to menopause is controversial (1), it is worth noting that after the menopause the prevalence of migraine is comparable in the two sexes; in other words, there is a return to the pattern seen in childhood and, we might suppose, a closing of the cycle (2).

Why psychosomatic?

Minuchin et al. (3), introducing the concept of the "psychosomatic family model", proposed three necessary conditions for the development of psychosomatic illness in children.

First, the child possesses physiological vulnerability to a chronic illness.

Second, the family engages in four specific dysfunctional patterns of interaction: i) enmeshment or overinvolvement among family members; ii) overprotectiveness or excessive concern for each other's wellbeing; iii) rigid or redundant interaction patterns that stifle change; iv) lack of conflict resolution or failure to resolve problems by avoiding or detouring conflict.

Third, parents involve the sick child in potentially contentious marital discussions. This triangulation is likely to be detrimental to the child's wellbeing, given that it has been reported that recruiting children in disputes in this way results in increased symptom manifestation (4-6). Minuchin et al. (3) concluded that the rigid, overprotective and enmeshed interactional patterns that characterise psychosomatic families reflect a low threshold for conflict. Some individuals, when confronted with stress, develop physical rather than neurotic or psychotic complaints and/or symptoms; to diagnose these patients as psychosomatic constitutes a rather broad application of the term "psychosomatic" (7). Psychosomatic refers to an increase in general susceptibility to physical illness. On the other hand, it is no longer possible to classify a patient as psychosomatic solely on the basis of a medical diagnosis (e.g. asthma, ulcers, colitis). The psychosomatic aspect of the diagnosis must be established in each single case on the basis of positive psychosocial

criteria, since the same illnesses can be brought about by different causes and psychological factors may carry different weights in each case.

As specified by Wirsching, most psychosomatic complaints contain common elements (8): i) patients consciously suppress stressful or threatening feelings and fantasies; ii) they give the impression of composed rationality and appear particularly oriented to "thing-like", concrete objects; iii) they avoid conflict as much as possible, as demonstrated by excessive conformity to the expectations and wishes of their environment; iv) they give the impression of normal, if not pseudonormal, social behaviour, and strongly comply with dominant sex-, age-, or class-specific role expectations; v) in stressful situations, restraint is significantly apparent.

Weakland (9) created a concept of "family somatics" referring to a type of family that denies conflicts and is, apparently, particularly harmonious. The only problem is that diseases such as ulcerative colitis, anorexia nervosa, bronchial asthma, headache, etc., are present in one, or several, members of such families. Could it be hypothesised that this is often the basic background of the migrainous child? (10-12).

Hormones and the foetus

The development of an individual is determined by the interaction of influences, external and internal.

The overall process of ontogenesis is not simply a battle between nature and culture, but rather a dynamic intersecting of processes occurring within a system shaped by the indissoluble link between the body and its environment. Genes and hormones are the factors that determine the biological differences between the sexes in the brain. However, while the presence of a pair of XX or XY genes causes the release of specific sex hormones which lead to the phenotypical differentiation of the gonads as male or female, it has not yet been possible to demonstrate that a similar process also acts on the brain. It is indeed unlikely that the brain develops in the same way as the gonads, given that these glands are relatively simple bodies, whereas the brain is the most complex organ in the whole body. Compared to those of the gonads, the cells that make up the brain show much greater differentiation. That said, at a very early stage in ontogenesis, and even before birth, the ovaries and testes begin to secrete sex hormones that may affect the development of the brain. In the early '60s, Geoffrey Harris and Seymour Levine's studies on rats showed that, in order for the brain to develop in a typical male direction, testosterone must be present in the blood during the first five days after birth. This interval is the sensitive phase in which testosterone determines the diversification of the brain as male as opposed to female. For the record, it must be pointed out that this diversification involves only the hypothalamus and, in particular, the pre-optical area controlling luteinising hormone secretion and the development of sexual behaviour. Thus, the action of testosterone during the first days of life may lead to sexual differentiation, determining a switch from female to male. We must take into account that although the brain structures start to develop in the first part of pregnancy, their development is a process that continues until late adolescence. Since the

male secretes, both in intrauterine life and later, a greater amount of testosterone than females, it seems likely that any effect, due to testosterone, on the development of the brain could occur after birth. Research conducted in the '80s, however, suggested that the exposure of the female human foetus to high levels of androgens results in a masculinisation of behaviour later in life. During the different stages of development there are periods of increased sensitivity in which the effect of sex hormones could determine phenotypical gender differences.

In girls, after menarche, the situation is more complex than it is in males, because the levels of oestrogen and progesterone change during the menstrual cycle. The brain is the organ that controls the concentration of sex hormones secreted and released into the blood: most of the time, the concentrations of these hormones in the blood remain constant, although they may vary in the course of the day and, in women, in the course of the month.

Neonatal hyperactivity, temperament and migraine

Maternal stress during pregnancy has been studied as a risk factor that may have developmental and health consequences persisting throughout the lifespan. Animal and human studies have demonstrated that maternal stress during pregnancy has consequences on cognition and learning (13,14), stress reactivity (15), behavioural responses to novelty (16,17), and can contribute to emotional and behavioural disturbances (17-20) in the offspring. The hypothalamic-pituitary-adrenal (HPA) axis appears to be a primary pathway by which stress affects the foetus (21,22). The activity of the HPA axis is regulated by the release of hypothalamic CRH. Foetal and maternal levels of CRH are correlated because the active peptide is released into both the maternal and the foetal circulation (23-26).

Plasma CRH is of placental origin (27). CRH has been proposed as one mechanism by which prenatal stress influences foetal and infant development (28,29). While placental CRH has a direct effect on the foetus and plays a role in foetal development and maturation (30), the effects of placental CRH on human postnatal development have not been investigated. Research in humans and in non-human primates has demonstrated that an important consequence of prenatal exposure to stress and stress hormones is an increase in fearful or reactive behaviour (16,17,22). Significantly increased levels of CRH are associated with preterm delivery (31-36). An early rise in CRH may signify a hostile environment (37) and precipitate a cascade of events that influences the foetal nervous system.

It has thus been suggested that exposure of the human foetus to CRH affects infant temperament. Indeed, foetuses exposed to lower levels of maternal CRH at 25 weeks of gestation were rated by their mothers as exhibiting less fear and distress behaviour in infancy. CRH levels at 19 and 33 weeks were not significantly associated with infant temperament, indicating that there may be a critical period in which programming influences of CRH on infant temperament can be observed (38). These data indicate that CRH may influence foetal central nervous system (CNS) development and are consis-

tent with the few existing studies showing that elevated CRH during the prenatal period is related to impairments in learning and behavior (29,39).

Postnatal maternal anxiety and depression were also associated with reports of infant fear and distress behaviour. However, after controlling for postpartum maternal psychological state the relation between placental CRH and infant temperament was not altered, supporting the conclusion that prenatal experiences were responsible for this association (37). The mechanisms underlying the association between placental CRH and fear and distress behaviours in infancy are unknown. One possible explanation is that CRH acts directly on regions of the brain that underlie temperament characteristics. Associations were found between CRH and infant temperament at 25 weeks' gestation, but not at 19 or 33 weeks' gestation, suggesting that the end of the second trimester may be a period of vulnerability to exposure to elevated levels of CRH.

Several studies in humans and in non-human primates have suggested that the foetus is more susceptible to the effects of stress during the second trimester of pregnancy (17,40).

In an interesting study that examined behaviour and cognition before birth, Wadhwa et al. (34) found that the foetuses of mothers with elevated CRH levels did less well in *in vivo* studies of learning in foetuses. Susman et al. (41), for example, established a relation between low levels of maternal hormones (cortisol among others) at three months' gestation and greater aggressiveness in the same children at 3 years of age, which is in line with earlier findings on the HPA axis and antisocial behaviour. O'Connor et al. (18) found prenatal maternal anxiety to predict behavioural/emotional problems in a very large sample of children at 4 years of age. Also, Huizink et al. (42) found prenatal maternal stress, psychosocially and endocrinologically measured in a prospective study, to be related to poorer mental and motor development of the infant. Graham et al. (43) showed the infants of depressed mothers to be more irritable, and to have growth delays, higher neonatal levels of cortisol, and poorer motor and cognitive development, with the effect persisting until at least the age of 3 years.

In a study by De Weerth et al. (44), higher cortisol levels at the end of pregnancy were related to more crying, fussing and negative facial expressions in the infant during a series of routine mother-infant interactions. Supporting these observations, the mothers' reports confirmed that these infants displayed more difficult behaviour: they had higher scores on emotion and activity.

The differences between the infants were strongest in the neonatal period. At 4/5 months of age, most significant differences had disappeared, although the infants born of mothers with higher cortisol levels still fussed more during the interactions and also had a tendency to spend more time displaying negative facial expressions. At 18 weeks postnatally, the maternal reports on temperament in the two groups of mothers grew more similar to each other, leading to disappearance of the earlier significant differences.

Developmental processes related to children's pain, although not well understood, are of critical interest to practitioners involved in the assessment and management of children's pain (44). Both biologically-based individual difference variables and environmental context have been suggested to play a role in infant pain response. Accordingly, Sweet et al. (45) attempted to assess their relative contributions to pain behaviour in early versus late infancy.

Children's biologically-based reactional styles may be related to their reactions to pain. Vagal tone, defined as "the amount of inhibitory influence on the heart by the parasympathetic nervous system", indicating the amount of autonomic arousal at rest (46), has been proposed as a physiological indicator of biologically-based reactivity; instead, temperament has been proposed as a behavioural indicator of biologically-based reactivity. It is widely viewed as a psychobiological construct in which differences in physiological processes are reflected in differences in behaviour (47). Temperamental difficulty has been found to be positively related to pain in 3- to 7-year-olds undergoing venipuncture (48), 5-year-olds undergoing immunisation (49), and 6-year-olds with abdominal pain (50). However, in younger children, relations have been less consistent.

Various prodromes identifiable as components of the periodic syndrome (PS), in particular recurrent abdominal pain, cyclical vomiting, growing pain and benign paroxysmal vertigo, can be detected as early as the second year of life in the history of children suffering from recurrent, non-organic headache.

In a retrospective study (51) of healthy children, we found that subjects who eventually developed PS frequently presented a number of behavioural and physical peculiarities characteristic of "hyperreactive" children during the first six months of life. Of the 102 subjects considered "hyperreactive", 54 (52.9%) suffered from common migraine and in 55.5% of cases had a family history of headache in first- and second-degree relatives. Sixty-six children (64.5%) in the "hyperreactive" group had suffered from one or more components of PS. Hyperreactivity is known to be a frequent feature among otherwise healthy neonates and infants and seems to be a pattern of response to the inputs a neonate typically receives; hyperreactive subjects constantly show "amplified" responses compared to a control group. It can be assumed that these subjects show early altered adaptability of the CNS. This might express itself as a congenital dysfunction of the nocioceptive system and of the sensorial system, in other words, as an amplification of inputs with a general repercussion on a number of behavioural and physical parameters. Hyperreactive infants might therefore be typical "amplifiers".

This tendency to amplification finds different modes of expression at different ages and different levels of functional development.

Various components of PS, plus common migraine, may thus emerge as different expressions of a common predisposition identifiable with the marker "amplification". According to others, this tendency may extend to a predisposition to psychosomatic disorders in general. From this perspective, both the neurobehavioural basic equipment and the characteristics of the environment would play an important role (51).

Higher responsiveness and/or a lack of habituation to sensory stimuli of various modalities including aversive and painful stimuli (52-55) suggest that migraine may be characterised by cortical hypersensitivity and/or a lack of cortical inhibition (56,57). Hypersensitivity to aversive or noxious stimuli could also be related to sensitisation

of pain pathways resulting from repeated intense nociceptive stimulation during migraine attacks (58,59). Hence, higher responsiveness to noxious stimuli, in the context of the hypothesised crossmodal hypersensitivity in migraine, may represent a useful index of vulnerability to migraine (60). Migraine has been shown to be strongly familial with substantial evidence of vertical transmission (61), suggesting a maternal pattern of inheritance (62,63). One approach aiming to identify sources of heterogeneity in the familial transmission of migraine has been the investigation of vulnerability markers in the relatives of migraine probands. Indeed, alterations in sensory and cognitive-evoked potentials (64-66) as well as hypersensitivity to aversive stimuli (60) have been reported to aggregate in the families of people who have migraine and have been suggested to represent an index of vulnerability to migraine. However, none of these studies tried to evaluate the specificity of these findings in relation to anxiety and mood disorders which have been shown to co-occur in individuals from families with migraine.

Although a comorbidity of migraine with mood and anxiety disorders is well-established (67), there is a lack of prospective research focusing on specific subtypes of these conditions and on their patterns of onset in relation to migraine. In young adults, the onset of anxiety disorders tends to precede that of migraine and to be followed by the onset of depression (68). In order to examine this question prospectively, the offspring of parents with these conditions have been examined in order to identify vulnerability factors and early forms of expression of the anxiety disorders and migraine. The offspring of parents with anxiety disorders were found to display increased startle responsiveness (69,70). This finding indicates that in addition to the possible trigeminal hyperresponsiveness resulting from repeated intense nociceptive stimulation during migraine attacks (54,58), migraine may also be associated with greater responsivity to aversive stimuli, as here reflected in the acoustic startle reflex. The finding of increased reactivity among children who have not yet developed migraine suggests that increased physiological reactivity may be an index of vulnerability to migraine.

These findings support previous studies that documented an increased responsivity to visual, acoustic, somatosensory and nociceptive stimuli in migraineurs (71-73) and strengthens the hypothesis of crossmodal hypersensitivity in migraine.

Since the core neural pathway underlying the acoustic startle reflex is formed by cochlear nuclei (74), startle reflex hypersensitivity could be present at brain stem level or be caused by a top-down modulation. One possible neurobiological mechanism for a top-down modulation could be related to altered central serotonergic transmission. The central serotonergic system is known to modulate acoustic startle (75,76), and altered serotonergic function is believed to be responsible for some of the electrophysiological abnormalities observed in migraine (77).

The startle reflex is also very sensitive to fear and anxiety. In Wang's study (77), startle was potentiated by fear in the threat condition. Baseline startle reactivity is also increased by contextual threat (e.g., participation in an experiment in which aversive stimuli are anticipated) (78). It is therefore possible that the increased intertrial interval (ITI) startle was caused by anticipatory anxiety, suggesting increased sensitivity to contextual threat in children of migraineurs compared to those of non-migraineurs. Similar results have been reported in children of parents with an anxiety disorder (70). In addition to increased ITI startle, Duncko's analysis revealed that children at risk of migraine had "higher responses during the threat condition and the threat-safe difference" (79). These findings seem to point to the existence of an impairment of both the "anxiety system" and the "fear system" in the children of migraineurs (78-80).

The significant effect of both maternal anxiety and maternal migraine on ITI startle was shown by Grillon et al. (69,70), and indicates that these two diagnostic entities might in part share common pathophysiological mechanisms. Although maternal inheritance of migraine has been reported in several studies (62,63,81,82), the evidence is inconclusive. Maternal inheritance could be attributable to mitochondrial transmission, pre- or perinatal complications and/or endocrine factors, or a lower threshold for the expression of migraine among women (68). The strong predictive value of maternal history of migraine on startle observed in this study might indicate that increased startle responsiveness is one of several vulnerability factors involved in the pathogenesis of migraine (79).

The significant interaction observed between a maternal history of anxiety and age of offspring showing increased ITI startle responsiveness was attributed to increased amplitude of the startle response in older youth (Grillon et al., unpublished data), a finding consistent with the results of a parallel study that demonstrated an increased potentiated startle after puberty (Grillon et al., unpublished data). This finding might be related to the behavioural sensitisation observed in puberty (83), and might represent a marker of vulnerability to the development of anxiety disorder. No significant association was found between maternal history of anxiety and "startle during the threat condition or the threat-safe difference", suggesting that children at risk of anxiety exhibit impairment in the "anxiety" but not in the "fear system" (79). In another study (84), although the lack of an association between lifetime migraine and baseline startle among the children investigated was an unexpected finding (see 52-55), it can probably be attributed to the fact that a large proportion of the sample had not yet progressed through the period of risk for migraine (84).

These results are consistent with the current understanding of migraine as a genetically complex disorder (85) and suggest that, in combination with other tests, the startle paradigm could be used as a marker of vulnerability to the onset of migraine. Duncko's study (79) reports higher acoustic startle responsiveness in children at high risk of developing migraine and anxiety disorder, and thus highlights the importance of assessing migraine and anxiety comorbidity when investigating the pathophysiology of these disorders, since acoustic startle may be a possible marker of vulnerability to developing them.

As regards temperament, the interest of authors has focused particularly on reactivity as one aspect of temperament. According to Zimmermann and Stansbury (86), reactivity (i.e. threshold and intensity of emotional experience) and regulation of emotions (i.e. the control or modulation of this reactivity) are two dimensions of

temperament that interact to become behavioural patterns and that can create different developmental trajectories for the child's personality and life. According to Rothbart (87), the neonatal temperament is defined by individual differences in motor and emotional reactivity, and the "attention ability to support the auto-regulation." Recent studies report that early negative emotionality may be a sign of heightened sensitivity or an amplification of bodily reactions to inner and outer stimuli; moreover, it could be a factor related to the development of psychosomatic problems, in particular recurrent headache and abdominal pain.

Studies of visual and auditory evoked potentials and event-related responses have suggested that lack of habituation is the main abnormality of sensory processing in migraneurs. It also seems that the children of migraneurs are more "stress-reactive" than others, having lower physiological reaction thresholds.

One study, assessing the incidence of primary headache and of some components of PS (recurrent abdominal pain, cyclical vomiting, benign paroxysmal vertigo and growing pains) in hyperreactive newborns, found after an 18-year follow up that these newborns suffered from migraine and PS (mainly recurrent abdominal pain) more frequently than the control group (p<0.001) (88).

Hormones and migraine

Epidemiological studies confirm the clinical impression that migraine is mainly a disorder affecting women. Although no gender difference is apparent before puberty, with migraine occurring equally in boys and girls (89), in adults it occurs more frequently in women (18%) than in men (6%) (89). This difference between the sexes becomes greater with age, peaking early in the fifth decade of life and then declining thereafter (89).

Cyclical ovarian sex steroid production may affect the clinical expression of migraine, as demonstrated by a wide variety of clinical, epidemiological, and basic science observations. Clinical observations include the fact that migraine attacks in some women correlate with the menstrual cycle and improve when hormonal cycling ceases during pregnancy or after the menopause. Epidemiological evidence includes the fact that migraine is more common in women than in men, with incidence peaking in the year of menarche.

It is important to distinguish between menstrually-related migraine (MM), premenstrual syndrome (PMS) and attacks that occur mostly at the time of menstruation in women who also have attacks at other times of the cycle.

Somerville (90) did several studies in a small group of women who had a history of pure menstrual migraine in the preceding six menstrual cycles. He noted that oestrogen "priming", i.e. several days of exposure to high oestrogen concentrations, is necessary in order for migraine attacks to result from oestrogen withdrawal, such as that which occurs in the late luteal phase of the menstrual cycle. This effect would explain why migraine attacks are not associated with ovulation (91). Several other studies support Somerville's oestrogen withdrawal theory and conclude that changing hormonal activity might be an important factor in all women with migraine;

other factors in addition to the hormonal environment could account for the development of menstrual attacks (89). In contrast to the association between oestrogen withdrawal and attacks of migraine without aura, high plasma concentrations of oestrogen seem to be associated with attacks of migraine with aura (92). High oestrogen levels have also been reported in women with migraine with aura during the normal menstrual cycle.

Whether women diagnosed with migraine with aura also had attacks without aura was not clear. Whereas the use of combined oral contraceptives commonly improves migraine without aura, by contrast, migraine with aura becomes worse, or attacks with aura occur for the first time. Granella et al. (93) found that worsening of migraine was more likely to occur with use of combined oral contraceptives in women with pre-existing migraine with aura. These women were also more likely to continue having attacks during pregnancy. Women with pre-existing migraine without aura may develop aura for the first time during pregnancy. Oestrogen concentrations fluctuate throughout the menstrual cycle, showing large interindividual and intraindividual variations in serum concentration and exposing susceptible women to this additional migraine trigger. Ovarian hormones could potentially modulate these structures/pathways to increase or decrease the frequency, severity or duration of migraine headache. While ovarian hormones could potentially affect numerous loci within the trigeminal vascular pain pathways, it is their effect on the trigeminal nucleus caudalis (TNC) that has been best studied. Modulation of neurotransmission within the TNC by ovarian hormones could play an important role in the pathophysiology of migraine headache. Progesterone may also affect neurotransmission within the TNC as well as decrease plasma extravasations in an animal model of migraine headache. The predominant effect of oestrogen appears to be facilitation of the glutamatergic and serotonergic systems as well as inhibition of the sympathetic nervous system. It has both facilitory and inhibitory effects on the opiatergic, GABAergic and noradrenergic systems. The main effect of progesterone and/or its metabolites seems to be activation of GABAergic systems as well as modulation of the actions of oestrogen on the CNS. In addition, oestrogen and progesterone influence the pain processing networks and vascular endothelium, which are believed to be involved in the pathophysiology of migraine headache.

Migraine may worsen during the first trimester of pregnancy and although many women become headache-free during the last two trimesters, 25% experience no change in their migraine. MM typically improves with pregnancy, perhaps due to sustained high oestrogen levels. Hormone replacement therapy with oestrogens can exacerbate migraine and oral contraceptives can change its character and frequency (89). On the basis of quasi-experimental observations in a small number of women with menstrually triggered migraine, Somerville (90) proposed that the late luteal phase drop in oestrogen levels could trigger migraine. A study by Lichten et al. (94) supports oestrogen withdrawal as a migraine trigger in postmenopausal women. However, women with migraine who had undergone surgical menopause had a much less favourable course and the authors concluded that abrupt surgical menopause appeared to worsen migraine. In line with the view that oe-

strogen withdrawal is an important headache trigger, the majority of women with hormonally influenced migraine report significant headache improvement after the menopause. Although one might expect oestrogen levels in premenopausal women to decline smoothly and gradually during this transition phase, oestradiol levels are in fact increased during the perimenopause, and are often higher than those of the premenstrual years. These factors probably explain the amply documented worsening of headaches during the perimenopausal transition, and the fact that the women in most headache clinics and clinical trials are, on average, in their early 40s. Oestrogen levels decline markedly in the first year after the last menstrual period and then remain low and stable. The oestrogen withdrawal theory of migraine suggests that women may be vulnerable to an exacerbation of their migraine in the perimenopausal years, when the orderly cycling of oestrogen and progesterone secretion becomes more erratic, but that physiological menopause, once it is established, is likely to result in an improvement in migraine. Unfortunately, many studies of headache and migraine in the menopause actually include both perimenopausal and postmenopausal women. There are no reports of women without migraine experiencing migraine headache during oestrogen withdrawal. The most plausible explanation for oestrogen withdrawal as a trigger for migraine is the hypothesis put forward by Welch et al. of a "mismatch" between the timing of oestrogen's effects on gene regulation in the CNS and its effects on cell membranes (95). He suggests that under ordinary circumstances oestrogen-mediated gene regulation "modulates inhibitory peptide function in the trigeminal nerve." This counterbalances oestrogen-mediated increases in neuronal membrane excitability. When oestrogen levels fall, their down-regulating effect on inflammatory genes is removed and compensatory mechanisms cannot always be invoked quickly enough to avoid the possibility of headache in women who have "the neuronal excitability that is an inherent feature of the migraine-prone brain." It is thus not surprising that some women with migraine are particularly vulnerable to attacks during the late luteal phase of the natural menstrual cycle, the pill-free week of combined hormonal contraceptive regimens, or the perimenopause, to name just a few situations that may be characterised by periods of oestrogen decline after sustained high levels.

Comorbidity

Migraine reduces quality of life; part of the burden of migraine is produced by the psychiatric conditions that are associated with it. When one disorder occurs with another with greater-than-chance frequency, the disorders are said to be comorbid. Studies in both clinic and community-based settings have demonstrated an association between migraine and a number of specific psychiatric disorders. While the association between migraine and depression is most widely reported, there are also strong associations with other psychiatric disorders. Understanding the nature of the association between migraine and these psychiatric disorders has implications for diagnosis and treatment. The occurrence of comorbidity may also provide clues as to the aetiology of each disorder. Merikangas et al. (61) studied the association between psychiatric syndromes, including depression, and migraine headache. Migraine was found to be strongly associated with major depression. This (61) was the first study to demonstrate a strong association between migraine and major depression in an unselected sample. Breslau et al. (96) conducted a population-based study of people aged 25 to 55 years with migraine or other severe headaches to examine the relationship between migraine and major depression. This study used Cox proportional hazards models to estimate the risk of first occurrence of migraine associated with prior major depression and the risk of depression associated with prior migraine. Migraine was found to be strongly associated with major depression.

There is a considerable overlap between migraine and depression incidence, and both conditions may be associated with low levels of 5-hydroxytryptamine (5-HT). During a migraine attack there is evidence of low levels of platelet 5-HT and possibly also low Vmax for 5-HT uptake; these two findings are also associated with the depressed state. Both conditions can be treated by tricyclic and monoamine oxidase-inhibiting antidepressants. Migraine may form part of a family of brief recurrent self-limiting disorders, which involve disturbances of both mood and monoamines; during the "headache phase of the migraine attack, the links with depression are most apparent" (97).

Breslau suggests the existence of a "bi-directional" influence between migraine and depression, with each disorder increasing the risk of first onset of the other (98).

Unfortunately we do not know of any studies exploring the relationship between migraine and depression after the menopause. With regard to the comorbidity of menopause and depression, we can say woman more often suffer from depression than men, particularly in the perimenopausal stage, indicating that low oestrogen levels might be involved in the aetiology of this disease. Several studies have supported this hypothesis (1,99). On the other hand, other studies found no correlation between menopause and depression (100-102).

In a prospective, population-based study, Swartz et al. (103) examined the relationship between specific psychiatric disorders and migraine. In cross-sectional analyses, major depression was found to be strongly associated with migraine.

These results, in combination with those reported by Breslau et al. in 2000 (96), suggest that the bidirectional relationship is specific to migraine, and does not extend to all severe headaches. Anxiety disorders are also associated with migraine. This relationship has been observed in both clinic and community-based populations. These two studies have demonstrated a cross-sectional relationship between migraine and various anxiety disorders.

Breslau's study (96) reported that the association between migraine and anxiety disorders was even stronger than that for other affective disorders. Although phobias were generally associated with migraine, agoraphobia did not show this relationship, a fact that may be explained by the rarity of this condition. An association between migraine and panic disorder has also been reported, but the temporal relationship between the two disorders has not been thoroughly explored.

Many studies indicate that panic disorder is comorbid not only with migraine, but also with other headache types. Investigation of the temporal relationship between these disorders suggests that the influence is exerted in the headache-to-panic disorder direction, rather than the reverse.

Merikangas et al. (61) also reported the results of a logistic regression analysis conducted to examine the diagnostic overlap between the psychiatric disorders most strongly associated with migraine. The model controlled for sex and risk group while assessing the effects of major depression, bipolar spectrum, general anxiety disorder, and social phobia. The best fitting model included only general anxiety disorder. Migraine and anxiety disorders are comorbid conditions and in some studies, the relationship is even stronger than that between migraine and depression.

In addition, most people with depression also have anxiety disorders, but many people with anxiety disorders do not have depression. For this reason, it is important to screen for both depression and anxiety in individuals with migraine. Several studies (104,105) have reported high levels of depression, anxiety and somatisation symptoms in children and adolescents with migraine. The results of a prospective longitudinal cohort study of young adults revealed that the onset of anxiety disorders tended to precede that of migraine in about 80% of the cases of migraine with comorbid anxiety and depression, and that the onset of depression followed that of migraine in 75% of the comorbid cases (68). LeResche (106) found that significant levels of depression were roughly twice as frequent in boys and more than four times as frequent in girls who had already gone through puberty compared with those who had not begun pubertal development. These results are similar to those of a recent large cross-sectional study (107) which found an association between a trichomised measure of pubertal development and physical symptoms, including headache. In a study of adolescents girls, Sillanpää and Aro (108) found a higher frequency of headache and depression among those with a younger age at menarche.

Environmental risk

Aromää and coworkers (105) investigated the predictors of headache in children at school entry. Frequent headache in the mother prior to pregnancy was found to be strongly predictive of headache in the child before school entry. The mother's assessment of her infant's poor health status and feeding problems at the age of 9 months was significantly predictive of preschool headache. Nocturnal confusion seizures and suspected headache in the child or in his or her family members at the follow up at the age of 3 years were significantly associated with later headache in the child. At the same age, the presence of recurrent difficulties in falling asleep was also predictive of later headache. At 5 years of age, the presence of long-term disease, nocturnal enuresis, and travel sickness were headache predictors. Headache occurring in attacks and tension headache were predictive of headache at school entry.

As regards psychological factors, concentration difficul-

ties, behavioural problems, and unusual tiredness at the age of 5 years were strong predictors of headache. High sociability was also predictive; instead, up to the age of 5 years, parents' divorce, being in a one-parent family, and number of siblings were not predictive of headache occurring before school age, nor were several relocations, hours of television watching, or other parenthood variables.

Messinger et al. (109) found that the prevalence of headache sufferers rose from 64% when neither parent was a headache sufferer to 85% when one parent had headache episodes and to 98% when both parents reported headache episodes. In that study, the "heredity" of headache was also recognisable; again, it was observed that having a mother with frequent prepregnancy headache was strongly predictive of headache at preschool age.

In addition (62), a history of maternal depression occurred 1.5 times more often in headache and migraine groups than in controls. The mother's assessment of her infant's poor health at 9 months was predictive of preschool headache. The mother's tendency towards depression and her sensitivity to the somatic complaints of her infant are aspects worthy of consideration (62).

Merikangas et al. (61) found that migraine combined with anxiety and depression may constitute a distinct clinical syndrome, often manifesting in early childhood. Conversely, some "positive characteristics" in a child can be predictive of headache, for example high sociability at the age of 5 years has been found to be a strong predictor of headache. In a study by Borge and Nordhagen (110), children complaining of headache showed good conduct as preschoolers and a tendency towards high achievement motivation at school. This tendency may explain their sociability, although their efforts to excel may cause exhaustion and tiredness leading to concentration difficulties. When relations between predictor variables were analysed in this study (110), an association emerged between high sociability and concentration difficulties. Such analyses have helped to clarify the profile of child headache sufferers and their families. The presence of concentration difficulties seems to be a very strong predictor of headache.

A number of other studies (e.g. 111-113) have also reported a relationship between low socioeconomic status and pain in children and/or adolescents. However, there are also studies in which no such relationship was found (e.g. 114,115). If low social class is a risk indicator for pain in adolescents, a number of possible mechanisms (e.g. levels of family and economic stress, living conditions, patterns of health care utilisation) might be involved. This finding suggests that biological development (over and above growing older, i.e. the simple passage of time, and age-related exposures) plays an important role in this adolescent population.

LeReche et al. (106) confirm that the prevalence of pain conditions in adolescents, particularly adolescent girls, is substantial. In addition, we have found that physical development as well as gender is associated with the experience of pain in adolescents. These findings suggest that the process of pubertal development may initiate biological changes that predispose women, in particular, to experience symptoms, including pain (106).

Gender differences, prevalence and pain perception

Although chronic/recurrent pain is generally considered a problem of adults, the rates of some pain conditions – particularly back pain and headache – are substantial in adolescents, ranging from 20 to 50% of the teenage population (116-118). Moreover, many adults with persistent pain report that their pain condition had onset during adolescence.

Many epidemiological studies of pain in adolescents consider age as a risk factor. However, few (104,107, 119,120) have examined the relationship of pain to pubertal development. The sequence of hormonal and anatomical changes occurring during puberty is similar in individuals of a given sex, but the age at onset of puberty and rates of change can vary widely. At a given age, adolescents of the same sex may be in very different stages of puberty, with some yet to begin pubertal development and others who have completed it. Thus, while older adolescents are generally further along in pubertal development than younger ones, age is not a robust indicator of biological/hormonal status in adolescents. In addition to the physical changes associated with puberty, adolescence is a time of rapid cognitive and social development (121). Although the stereotype of adolescence as a turbulent and emotionally troubled period is an exaggeration, some adolescents do experience great emotional distress (122). In adults, psychological distress, notably depression (123), is commonly associated with chronic pain conditions. Depression is more likely among persons with multiple pain conditions as opposed to a single pain condition (124). In addition, the presence of multiple pain conditions may predict onset (125) and persistence (126,127) of chronic pain in other body sites.

LeResche et al. (106) hypothesised that the prevalence of all pain conditions, as well as rates of other symptoms, increases with the progression of puberty in females, but not males. In both sexes, pubertal development was found to be a better predictor of pain than age, and it was found that pain, other somatic symptoms and depression increase systematically with pubertal development in girls. Accordingly, the prevalence of headache pain was similar for boys at all stages of puberty, the prevalence of back pain and facial pain increased with increasing levels of pubertal development, and the prevalence of stomach pain declined as boys became more mature. In girls, the prevalence of each pain condition increased with increasing levels of pubertal development, although the increase in stomach pain was not statistically significant. In both boys and girls, the probability of experiencing at least one pain condition and of experiencing two or more pain conditions increased with increasing physical maturity.

Because this was a cross-sectional study, it is not possible to determine cause and effect relationships between the variables measured. However, it appears more logical to assume that pubertal status influences the rates of pain and symptoms than to infer that the presence of pain and symptoms alters rates of pubertal development.

Angold et al.'s findings of dramatic increases in depression with pubertal development in girls (128) are similar to those of longitudinal studies. Because both psychological distress and pain prevalence are associated with pubertal status, especially in girls, depression and somatic symptoms added little to the prediction of pain in multivariate models.

Children with recurrent headaches have a risk of developing additional physical and mental problems, such as anxiety and depression, in adulthood. In addition, recurrent abdominal pain among children and adolescents not only affects physical and psychosocial aspects of daily family life but may also predispose children to experience recurrent pain-related illnesses in adulthood. Most studies evaluating recurrent or chronic pain conditions in children have been limited to descriptions of pain intensity and duration. The effects of pain states and their impact on daily living have rarely been studied. The objective of one study, conducted in an elementary school and in two secondary schools in Germany by Roth-Isigkeit (129), was to investigate the impact of perceived pain on the daily lives and activities of children and adolescents. More than two thirds of the respondents reported restrictions in daily living activities attributable to pain. However, 30 to 40% of children and adolescents with pain reported moderate effects of their pain on school attendance, participation in hobbies, maintenance of social contacts, appetite, and sleep, as well as increased utilisation of health services because of their pain. Restrictions in daily activities in general and health care utilisation because of pain both increased with age. Girls ≥ 10 years of age reported more restrictions in daily living and used more medications for their pain than did boys of the same age. The authors found gender-specific differences in self-perceived triggers of pain. Boys more often than girls stated that their pain was triggered by physical exertion. Girls more often than boys stated that their pain was triggered by weather conditions, common colds, or internal factors such as anger, disputes, family conditions, or sadness. Previous studies confirmed the roles of school or everyday stress, examinations, and the overall school experience in the prevalence of paediatric headache. Psychosocial aspects (e.g. positive friendships and supportive relationships with parents or other adults) were indicated to influence the prevalence and severity of back pain among adolescents. Pain intensity was the most robust variable for predicting functional impairment in ≥ 1 areas of daily life. Increasing age of the child and increasing intensity and duration of pain had effects in predicting health care utilisation (visiting a doctor and/or taking medication), whereas restrictions in daily activities were predicted only by the intensity of pain. These results underscore the importance of paediatric pain for public health policy making. Additional studies are necessary and may enhance our knowledge about paediatric pain. This, in turn, might enable parents, teachers, and health care professionals to assist young people with pain management, allowing them to intervene positively in their conditions before they become recurrent or persistent (129).

Concluding remarks

Migraine and affective disorders can be present in the same subject. This seems to be particularly true of girls and women. The aim of this paper was to analyse the

different factors (medical vs psychological) that can, partially, explain this association.

Many questions remain unanswered.

Future epidemiological studies should be done to analyse migraine in postmenopausal women. Researchers should develop methods of tracking individuals from childhood through adulthood to assess the prevalence and natural history of this disorder. The influence of genetics, family environment, social learning, behaviour, and psychological comorbidities needs to be established. Furthermore, there is a need to develop and evaluate educational and counselling programmes targeting both children with migraine and their families.

A better understanding of the evolution and comorbidities of migraine in children may lead to improved clinical outcomes as they become adults.

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