Migraine & paediatric obesity: a plausible link?

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Received November 11, 2013

Obesity and migraine are both highly prevalent disorders in the general population, influenced by genetic and environmental risk factors. In recent studies, obesity was found to be a strong risk factor for transformed migraine and, among migraineurs, obesity was associated with frequent headaches and higher disability scores. Suggested mechanisms included: (i) obesity as a pro-inflammatory state may be associated with neurovascular inflammation in patients with migraine; (ii) elevated levels of plasma calcitonin gene-related peptide (CGRP) in obese individuals may play a role as an important post-synaptic mediator of trigeminovascular inflammation in migraine; (iii) dismodulation in the hypothalamic neuropeptide, orexin, in obese persons may be associated with increased susceptibility to neurogenic inflammation causing migraine attacks; and (iv) leptin and adiponectin can activate proinflammatory cytokine release that is involved in the pathogenesis of migraine. In addition, both conditions are associated with psychiatric co-morbidities, such as depression and anxiety, that can further increase headache frequency and disability. Therefore, the effect of obesity on migraine outcome is important. Weight and BMI should be measured and calculated in all children presenting with migraine, and weight control should be a part of the treatment.

Key words Body mass index - children - disability - headache - migraine - obesity - proinflammatory cytokine

Introduction

Obesity and migraine represent two major public health problems in adults as well as in children. Obesity is expressed by excessive accumulation of bodyweight. Since simple measuring of body fat in children is difficult, obesity is usually estimated using body mass index (BMI). BMI is calculated as weight in kilograms divided by height in meters squared, and country-specific charts have been developed. According to the US Centers for Disease Control and Prevention health data, among children 2-19 yr old, at risk for overweight is defined as BMI 85th to <95th percentile for age and gender, and overweight is defined as BMI ≥95th percentile for age and gender. Childhood obesity has become a serious public health problem and increase in obesity rates has been observed in children of all ages. Recent studies indicate that approximately 20 per cent of school-age children in European countries are overweight or obese and 5 per cent are obese. In North America, these figures are 30 and 15 per cent, respectively. Overweight and obese children are likely to maintain their status into adulthood and are
at a higher risk for developing chronic diseases such as hypertension, dyslipidemia, diabetes, heart disease and stroke. Obesity has also been associated with psychiatric co-morbidity, such as depression, eating disorders and especially loss of control over eating.

Headaches are also a common complaint in children and adolescents, with prevalence ranging from 40-75 per cent. Previous epidemiological studies suggest that more than 15 per cent of schoolchildren report headaches that occur once a week or more. A systemic review of population-based studies showed that the prevalence of migraine reaches almost 8 per cent when the International Headache Society (IHS) criteria are used for diagnosis; prevalence varies with age and sex. No single hypothesis can explain all the phenomena that occur with migraine. A primary event may occur in the brainstem in an area that is involved in the modulation of pain, sensory processing, and craniovascular afferents that control trigemino-meningeal nociceptive inputs. The stimulation of the trigeminal nerve results in the release of substance P, calcitonin gene-related peptide and other vasoactive polypeptides that cause pain and vasodilatation. An alternative theory proposes cortical spreading depression as a first neurologic event that causes migrainous aura and activates trigeminal nerve afferents. The activation of trigeminal afferents causes inflammatory changes in the pain-sensitive meninges that produces headache. Symptoms of migraine vary with age. Vomiting, pallor, irritability and behavioural disorders are common in young age; headaches tend to be generalized and shorter, lasting less than one hour in 8-25 per cent of patients. Migraine in children is associated with school impairment, behavioural problems and increased risk of affective and anxiety disorders.

**Obesity and migraine - clinical aspects**

The association between obesity and headache has been well-established in adults. High prevalence of chronic daily headaches (CDH) in obese adults was first described by Scher et al. In his population-based study, obese individuals with episodic headaches had 5-fold increased odds of developing CDH. These results were later confirmed by Bigal and Lipton, who showed that the association between obesity and headache was stronger in transformed migraine than in chronic tension type headache (CTTH). Other studies showed the association between obesity and migraine prevalence and frequency among reproductive age subjects. In a large population study of over 15,500 participants, the odds of migraine were increased by approximately 39 per cent in both younger men and woman with total body obesity (woman: OR 1.39; 95% CI: 1.24-1.56; men: OR 1.38; 95% CI: 1.20-1.59). These findings were not significant in older individuals (≥55 yr). A high prevalence of migraine was also found in obese adult patients undergoing corrective obesity surgery. In adults with migraine, a high BMI was associated with more frequent and severe migraine attacks.

Only a few studies have examined the association between obesity and migraine in children. In a multicenter study by Hershey et al on children with primary headaches, obesity was associated with headache frequency and disability, with significant improvement after weight loss. In a study by Pinhas-Hamiel et al., overweight adolescent females had an almost 4-fold excess risk of headache when compared with normal-weight girls. In both studies children with migraine were not specifically evaluated. In a cross-sectional study of over 5,500 adolescents from Norway, adolescents with recurrent headaches in general demonstrated a 40 per cent increased odds of being overweight or obese, while adolescents with migraine demonstrated a 60 per cent increased odds of being overweight or obese.

Ravid et al. investigated the influence of obesity on headache frequency, duration, and disability in 181 children with primary headache. In this study, obese children had a significantly higher rate of very frequent headaches (more than 15 attacks per month) as well as higher disability grades compared to normal-weight children. The association between BMI percentile and higher disability grades was similar for both migraine and tension-type headache. Additionally, they found a significantly higher rate of acute drug treatment in children with obesity compared to normal-weight children, that may also reflect the more frequent and disabling attacks among those children. In another study, migraine attacks frequency but not severity of attacks or migraine-associated symptoms was associated with obesity in children with migraine (Table I).

**Obesity and migraine - suggested pathogenesis**

The association between obesity and migraine is likely to be multifactorial, and to involve both central and peripheral pathophysiological processes as well as environmental factors. Central and peripheral pathways regulating feeding and adipose tissue function share extensive overlap with pathways implicated in migraine.
Similarly, specific proteins and peptides, such as serotonin and orexin, play a role in both feeding and migraine pathophysiology. Inflammatory mediators: Expansion of adipose tissue during weight gain leads to induction of several pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF α), interleukin (IL)-1 and IL-6, all of which can contribute to local and systemic inflammation. Likewise, increased levels of serum TNFα and IL-6 have been reported at the onset of migraine attack. BMI was significantly correlated with headache frequency (r=0.1, P=0.003) and disability (r=0.08, P=0.02). Reduction in BMI was significantly correlated with HA frequency (r=0.32, P=0.01).

Obese patients had significantly more frequent attacks (P=0.018). There was positive correlation between relative BMI and number of attacks (r=0.2, P=0.026).

Recurrent headaches were associated with overweight (OR=1.4, 95% CI 1.2-1.6). The association of frequent headaches was stronger for migraine (OR=2.2, 95% CI 1.5-3.3) than for TTH (OR=1.4, 95% CI 1.0-1.9).

Migraine was significantly associated with being at risk for overweight (OR=2.37, 95% CI 1.21-4.67, P=0.01) or overweight (OR=2.29, 95% CI 0.95-5.56, P=0.04). A significant independent risk for overweight was present in females with migraine (OR=4.93, 1.46-8.61, P=0.006). High BMI percentile was associated with increased headache frequency and disability.

### Table I. Headache and obesity in children and adolescents

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample size</th>
<th>Age (yr)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinhas-Hamiel et al; 2008</td>
<td>Total:273 HA: 39</td>
<td>9-17</td>
<td>Subjects with HA were heavier (P=0.03). Overweight females had almost four-fold excess risk of headaches (OR=3.9, 95% CI 1.28-12.1).</td>
</tr>
<tr>
<td>Hershey et al; 2009</td>
<td>HA: 913 M:831</td>
<td>3-18</td>
<td>BMI was significantly correlated with headache frequency (r=0.1, P=0.003) and disability (r=0.08, P=0.02). Reduction in BMI was significantly correlated with HA frequency (r=0.32, P=0.01).</td>
</tr>
<tr>
<td>Kinik et al; 2009</td>
<td>M: 124</td>
<td>4-17</td>
<td>Obese patients had significantly more frequent attacks (P=0.018). There was positive correlation between relative BMI and number of attacks (r=0.2, P=0.026).</td>
</tr>
<tr>
<td>Robberstad et al; 2010</td>
<td>Total:5847 HA: 1701 M: 392 TTH: 950</td>
<td>13-18</td>
<td>Recurrent headaches were associated with overweight (OR=1.4, 95% CI 1.2-1.6). The association of frequent headaches was stronger for migraine (OR=2.2, 95% CI 1.5-3.3) than for TTH (OR=1.4, 95% CI 1.0-1.9).</td>
</tr>
<tr>
<td>Ravid et al; 2013</td>
<td>HA: 181 M: 81 TTH: 87</td>
<td>4-18</td>
<td>Migraine was significantly associated with being at risk for overweight (OR=2.37, 95% CI 1.21-4.67, P=0.01) or overweight (OR=2.29, 95% CI 0.95-5.56, P=0.04). A significant independent risk for overweight was present in females with migraine (OR=4.93, 1.46-8.61, P=0.006). High BMI percentile was associated with increased headache frequency and disability.</td>
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BMI, body mass index; CI, confidence interval; HA, headache; M, migraine; OR, odds ratio; TTH, tension type headache.

### Pathophysiology

Inflammatory mediators: Expansion of adipose tissue during weight gain leads to induction of several pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF α), interleukin (IL)-1 and IL-6, all of which can contribute to local and systemic inflammation. Likewise, increased levels of serum TNFα and IL-6 have been reported at the onset of migraine attack. Increased cerebrospinal fluid TNFα levels have been demonstrated in individuals with chronic daily headaches.

Calcitonin gene-related peptide (CGRP): CGRP is a neuropeptide that is released into the cranial circulation after stimulation of the trigeminal ganglion during acute migraine attack. CGRP is a potent vasodilator of cerebral and dural vessels, and may mediate trigeminovascular pain transmission as well as neurogenic inflammation. CGRP levels are higher in obese individuals, and increase further after fat intake.

Serotonin: Serotonin, a neurotransmitter synthesized from tryptophan and hydroxylated to 5-hydroxytryptophan (5-HT), has been implicated as one of the components in the pathogenesis of migraine. Chronically low brain serotonin levels have been noted in migraine sufferers, with secondary supersensitivity of neuronal 5-HT1 receptors. During the acute migraine attack there is a 60 per cent increase in plasma 5-HT levels, which may trigger the pain-generating process.

Orexin: The orexins are hypothalamic peptides reported to be involved in a variety of functions, including feeding, sleep, and hormone secretion, and even in modulation of nociceptive processing. Orexin A was able to inhibit neurogenic dural vasodilatation, resulting in reduced release of CGRP from trigeminal neurons. Low levels of orexin in obese persons may be associated with increased susceptibility to neurogenic inflammation causing migraine attacks.

Adiponectin: Adiponectin (ADP) is a protein primarily secreted from adipocytes, can exist as one of several characteristic oligomers, and has receptors expressed in the brain, blood vessels, liver and muscle. ADP has...
been reported to have both pro- and anti-inflammatory effects, which may be explained by the differential effects of ADP oligomers. Limited data have previously suggested that the pro-inflammatory oligomers are elevated in women and in those with chronic migraine as compared with controls, and that changes in these oligomers are associated with migraine severity. Levels of the hormone are inversely correlated with BMI, and low levels have been associated with platelet aggregation.

**Leptin:** Leptin is an adipocyte-derived hormone that acts as a major regulator for food intake and energy homeostasis. Leptin deficiency or resistance can result in profound obesity. Leptin also has inflammatory properties and, it has been demonstrated that leptin also exerts vascular effects via leptin receptors widely distributed on endothelial cells. Lower leptin levels were found in episodic migraineurs; however, this difference did not persist after adjusting for fat mass.

Table II summarizes the possible substances that may play a role in the migraine and obesity relationship.

### **Other possible relationships between migraine and obesity**

Some caution is required in assessing the type of relationship between obesity and headache frequency and disability in children. Current data are not sufficient to establish a significant causal relation, and both physiological and environmental factors probably play a role. Obesity was found to be associated with increased prevalence and severity of other chronic pain disorders besides headache, such as musculoskeletal and abdominal pain. Furthermore, children and adolescents being seen in special pain clinics were more likely to be obese, and were more likely to report higher levels of pain intensity. Lifestyle may also have an impact on both weight and headache. In a population-based study physical inactivity was strongly associated with headache disorders independent of economic and psychosocial factors. Lack of physical activity has been demonstrated to be associated with a 21 per cent increased risk of migraine attacks in adults and a 50 per cent increased risk of migraine in adolescents. Reduced physical activity can also contribute to weight gain and increased body fat and obesity in children. On the other hand, recurrent headaches were found to be associated with low physical activity that can further contribute to overweight and further increase in headache frequency.

In addition, certain psychological factors can have a role in the migraine-obesity relationship. Both conditions are associated with psychiatric co-morbidities, such as depression and anxiety, that can further increase headache frequency and disability.

### **Table II. Substances that play a role in migraine and obesity pathophysiology**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Migraine</th>
<th>Obesity</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory mediators (TNF α, IL-1, IL-6)</td>
<td>Elevated ictaly</td>
<td>Expressed and modulated by adipocytes</td>
<td>Obesity is recognized as a pro-inflammatory state, which may be associated with neurovascular inflammation in patients with migraine.</td>
</tr>
<tr>
<td>CGRP</td>
<td>Vasodilator of cerebral and dural vessels, mediate trigeminovascular pain transmission and neurogenic inflammation</td>
<td>Elevated in obese individuals</td>
<td>High levels may trigger migraine attacks.</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Condition of relative deficiency</td>
<td>Feeding control</td>
<td>Low levels cause increased appetite.</td>
</tr>
<tr>
<td>Orexin A</td>
<td>Antinociceptive properties. Inhibits neurogenic vasodilatation.</td>
<td>Increases food intake. Reduced in obese individuals.</td>
<td>In obese persons may be associated with increased susceptibility to neurogenic inflammation causing migraine attacks.</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Pro-inflammatory oligomers are elevated in chronic migraine.</td>
<td>Levels are inversely correlated with BMI.</td>
<td>Low levels may trigger cytokine release and migraine attacks.</td>
</tr>
<tr>
<td>Leptin</td>
<td>Lower levels in episodic migraineurs. This difference did not persist after adjusting for fat mass</td>
<td>Levels increase with BMI.</td>
<td>Trigger cytokine release.</td>
</tr>
</tbody>
</table>

BMI, body mass index; CGRP, calcitonin gene-related peptide; IL, interleukin; TNF, tumour necrosis factor

*Source:* Ref. 29
and influence eating behaviour. Finally, medications prescribed to migraine patients for migraine prevention, such as valproic acid and amitriptyline, may be associated with substantial weight gain.53.

Weight loss and migraine

Only a few clinical studies have evaluated the association between weight loss and headache frequency. In a small prospective observational study by Bond et al54, migraine frequency, pain severity and disability were significantly reduced after large weight loss via bariatric surgery. Moreover, patients who had greater weight loss were more likely to experience a 50 per cent or greater reduction in headache frequency.54

Similar results were reported by Novack et al55 in 29 obese women with migraine following bariatric surgery. In children, Hershey et al53 examined the effect of weight loss on various headache parameters; greater decreases in BMI were associated with greater reduction in headache frequency but not in headache disability for children who were initially overweight or obese. Further large longitudinal studies are needed to establish the relationship between weight loss and migraine control.

Conclusions

Obesity and migraine are associated in both adults and children, and the association is likely to be multifactorial. No matter what the leading explanations for the correlation between obesity and migraine are, given the evidence, weight is a modifiable risk factor for migraine in children. Weight and BMI should be measured and calculated in all children presenting with migraine, and education regarding weight control should be a part of treatment. Further research is needed to evaluate the contribution of weight control to migraine treatment.

References


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