High prevalence of incidental brain findings in primary dysmenorrhoea

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Abstract

Background: Primary dysmenorrhoea (PDM) is inexorably common. PDM women suffer from cramping pain in the lower abdomen that starts with menstruation and lasts for 24–72 h. Up to 90% of adolescent girls and more than 50% of menstruating women worldwide report suffering from it. Ten to 20% of PDM women describe their suffering as severe and distressing. However, nothing is known regarding the association of PDM with possible brain anomalies or abnormalities.

Methods: High-resolution T1-weighted anatomical brain magnetic resonance images (MRI) were acquired for each subject and inspected for incidental findings (normal variants and abnormalities) as a routine procedure in our PDM-related multimodal neuroimaging studies. Altogether, 330 right-handed young women [otherwise healthy PDMs = 163; non-PDM healthy controls (HCs) = 167] were enrolled during the period of 2006–2014. Binomial proportion test was performed for between-group comparisons.

Results: PDMs demonstrated significantly higher prevalence of overall incidental brain MRI findings (PDMs: n = 18, 11.0%; HCs: n = 6, 3.6%; p = 0.005) that should be ascribed to a preponderance of normal variants (PDMs: n = 16, 9.8%; HCs: n = 3, 1.8%; p = 0.001), especially cavum septum pellucidum. No significant between-group difference of abnormal findings was found (PDMs: n = 2, 1.2%; HCs: n = 3, 1.8%; p = 0.336).

Conclusions: We report here that otherwise healthy PDMs are associated with high prevalence of normal variants but not brain abnormalities. Our observations invite further epidemiological and neuroscientific studies.

1. Introduction

Primary dysmenorrhoea (PDM) is inexorably common. Women with PDM suffer from cramping pain in the lower abdomen that starts with menstruation and lasts for 24–72 h. Up to 90% of adolescent girls and more than 50% of menstruating women worldwide report suffering from it. Ten to 20% of PDM women describe their suffering as severe and distressing (Berkley, 2013). PDM preponderantly co-occurs with many chronic pain syndromes. Due to its both acute/cyclic nature of pain duration and chronic feature in the context of suffering for long period of lifetime, PDM has been considered a genuine chronic pain condition (Berkley, 2013).

We have previously unraveled differences in brain glucose metabolism and rapid morphological alterations between dysmenorrheic pain and pain-free state...
(state changes) (Tu et al., 2009, 2013). Notably, trait changes of brain structures occur throughout the cycle, that is, chronically, even when PDM women are not experiencing menstrual pain (Tu et al., 2010). Collectively, the observations indicate that the adolescent female brain is vulnerable to menstrual pain (Tu et al., 2013). However, nothing is known regarding the association of PDM with possible brain anomalies or abnormalities.

In this structural brain magnetic resonance imaging (MRI) study, we report for the first time in the literature a preponderantly higher prevalence of incidental findings (particularly normal variants) in young otherwise healthy PDM subjects as compared with that of age-matched non-PDM healthy controls (HCs). Our observation calls for a neuroscientific revisit of PDM.

2. Methods

2.1 Subjects

Altogether, 330 right-handed young women (otherwise healthy PDMs = 163, 23.6 ± 2.7 years old; criteria-matched non-PDM HCs = 167, 24.0 ± 2.4 years old) enrolled via Internet advertisement participated in our multimodal neuroimaging projects for PDM during the period of 2006–2014 (for inclusion/exclusion criteria and experimental procedures, see Tu et al., 2010, 2013). In brief, the inclusion criteria for the PDMs were a regular menstrual cycle around 27–32 days, the first occurrence of menstrual pain within the first 2 years of menarche, and average cramping pain level in the last 6 months rated higher than 4 on a verbal numeric scale (0 = not at all, 10 = the worst imaginable pain). For HCs, the inclusion criteria were similar to the dysmenorrhoea subjects but without menstrual pain. Exclusion criteria for all subjects were chronic pain disorders, pathological pituitary gland disease, organic pelvic disease, psychiatric disorder, neurological disease, childbirth, positive pregnancy test, immediate planning for pregnancy and having metal/pacemaker implant. All subjects were university students, university graduates or students of graduate school. All the PDM participants of 3T-MRI series and some suspected cases of 1.5T-PDMs were a regular menstrual cycle around 27–32 days, the first occurrence of menstrual pain within the first 2 years of menarche, and average cramping pain level in the last 6 months rated higher than 4 on a verbal numeric scale (0 = not at all, 10 = the worst imaginable pain). For HCs, the inclusion criteria were similar to the dysmenorrhoea subjects but without menstrual pain. Exclusion criteria for all subjects were chronic pain disorders, pathological pituitary gland disease, organic pelvic disease, psychiatric disorder, neurological disease, childbirth, positive pregnancy test, immediate planning for pregnancy and having metal/pacemaker implant. All subjects were university students, university graduates or students of graduate school. All the PDM participants of 3T-MRI series and some suspected cases of 1.5T-MRI series received pelvic ultrasonography to rule out organic cause for secondary dysmenorrhoea. Subjects were excluded from further neuroimaging study when any pelvic abnormality was found. PDM was finally affirmed and diagnosed by a gynaecologist (H.T. Chao). All the PDM-multimodal neuroimaging studies were approved by the Institutional Review Board of Taipei Veterans General Hospital and all subjects gave written informed consents.

2.2 MRI scanning

High-resolution T1-weighted anatomical brain MRI was acquired routinely for each subject in all the PDM-multimodal neuroimaging studies. One hundred seven subjects (year 2006–2011) were scanned with a 1.5T scanner (Excite; GE Medical Systems, Milwaukee, WI, USA) using a standard 3D-FSPGR sequence (TR = 8.548 ms, TE = 3.6 ms, TI = 400 ms, flip angle = 15°, matrix size = 256 × 256, field of view = 260 × 260 mm, 1.5 mm thickness). Two hundred twenty-three subjects (year 2011–2014) were scanned with a 3T scanner (MAGNETOM Trio, A Tim System; Siemens Medical Solution, Erlangen, Germany) using a standard 3D-MPRAGE sequence (TR = 2530 ms, TE = 3.03 ms, TI = 1100 ms, flip angle = 7°, matrix size = 224 × 256, field of view = 224 × 256 mm, 1 mm thickness). Additional MRI examinations were obtained when necessary for diagnostic purpose.

2.3 Assessment of incidental findings

The anatomical brain MRI images were routinely inspected for incidental findings (normal variants and abnormalities) by the same licensed MRI operator (W.C. Li) and confirmed by the neuroradiologist (T.C. Yeh, blinded to the clinical status of the participants). Images were classified into three categories: (1) normal; (2) normal variant; and (3) abnormal. We reported each and every incidental finding to our study subjects and referred them to the Departments of Neurology and Radiology for further examinations.

2.4 Statistical analyses

Chi-square test was first conducted for the comparison of categorical distribution of incidental findings between PDMs and HCs. Binomial comparison of proportions was then performed for the frequency difference of each category between PDMs and HCs. The significance level was set at \( p < 0.01 \). Confidence intervals (CIs) were calculated using Matlab (version 2014a; Mathworks Inc., Natick, MA, USA).

3. Results

Twenty-four subjects altogether in our series were found to have incidental findings in their brain MRIs (PDMs: \( n = 18, 11.0% \), 95% CI 6.2–15.9%; HCs: \( n = 6, 3.6%, 95% \) CI 0.8–6.4%). Chi-square test affirmed the distribution difference of incidental findings between the two groups (\( \chi^2 = 9.88, \ p = 0.007 \)). The subsequent proportional test revealed a significantly higher prevalence of normal variants (cavum septum pellucidum, mega cisterna magna, and inferior sagittal sinus dilatation found only) notably occurred in the PDM group as compared with that of the HC group (PDMs: \( n = 16, 9.8%, 95\% \) CI 5.2–14.4%; HCs: \( n = 3, 1.8%, 95\% \) CI 0–3.8%; \( p = 0.001 \)), especially cavum septum pellucidum (PDMs: \( n = 10, 6.1\%; \) HCs: \( n = 1, 0.6\%; \) \( p = 0.003 \)). No significant between-group difference of abnormal findings (arachnoid cyst, cerebellar tumour,
and hemangioma found only) was noted (PDMs: \( n = 2 \), 1.2%; HCs: \( n = 3 \), 1.8%; \( p = 0.336 \)) (see Table 1 and Fig. 1).

4. Discussion

The preponderantly higher prevalence of incidental brain findings in PDM (substantially attributed to higher incidence of normal variants, especially cavum septum pellucidum) as demonstrated in the current report is notable since PDM often co-occurs with many chronic pain conditions including fibromyalgia, temporomandibular joint disease, irritable bowel syndrome, chronic fatigue syndrome, chronic headache, low back pain, and many others (Berkley, 2013). The aforementioned conditions (many of them are deemed functional disorders) are evidenced to be associated with diffuse and sustained changes in the brain regarding the anatomy, resting state, pain matrix activity, neural connectivity and chemistry (Berkley, 2013). It should be noted that no significant difference was observed for the abnormal findings between PDM and HC groups, implicating that PDMs are not associated with higher prevalence of brain abnormalities.

A possible and good explanation for the overwhelmingly higher prevalence of cavum septum pellucidum in the PDM group (6.1%; absence of brain trauma history) as compared with that of the HC group (0.6%) is currently not available. In adults, prevalence of cavum septum pellucidum varies from 2.0% to 15% (or even greater) in normal individuals, but notably many times higher in neuropsychiatric patients (Weissleder, 2011; Rios et al., 2012). Enlarged cavum septum pellucidum has been particularly suggested to be indicative of a disrupted neurodevelopment associated with several neurodevelopmental and neuropsychiatric disorders (Kim et al., 2007; Trzesniak

<table>
<thead>
<tr>
<th>Radiological category</th>
<th>PDM (%)</th>
<th>95% CI</th>
<th>HC (%)</th>
<th>95% CI</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>145 (89.0)</td>
<td>84.1–93.8</td>
<td>161 (96.4)</td>
<td>93.6–99.2</td>
<td>0.005*</td>
</tr>
<tr>
<td>Normal variant</td>
<td>16 (9.8)</td>
<td>5.2–14.4</td>
<td>3 (1.8)</td>
<td>0–3.8</td>
<td>0.001*</td>
</tr>
<tr>
<td>Cavum septum pellucidum</td>
<td>10 (6.1)</td>
<td>2.5–9.8</td>
<td>1 (0.6)</td>
<td>0–1.8</td>
<td>0.003*</td>
</tr>
<tr>
<td>Mega cisterna magna</td>
<td>5 (3.1)</td>
<td>0.4–5.7</td>
<td>2 (1.2)</td>
<td>0–2.8</td>
<td>0.119</td>
</tr>
<tr>
<td>Inferior sagittal sinus dilation</td>
<td>1 (0.6)</td>
<td>0–1.8</td>
<td>0</td>
<td>–</td>
<td>0.845</td>
</tr>
<tr>
<td>Abnormal</td>
<td>2 (1.2)</td>
<td>0–2.9</td>
<td>3 (1.8)</td>
<td>0–3.8</td>
<td>0.336</td>
</tr>
<tr>
<td>Arachnoid cyst</td>
<td>1 (0.6)</td>
<td>0–1.8</td>
<td>2 (1.2)</td>
<td>0–2.8</td>
<td>0.288</td>
</tr>
<tr>
<td>Cerebellar tumour</td>
<td>1 (0.6)</td>
<td>0–1.8</td>
<td>0</td>
<td>–</td>
<td>0.845</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>0</td>
<td>–</td>
<td>1 (0.6)</td>
<td>0–1.8</td>
<td>0.845</td>
</tr>
<tr>
<td>Total incidental findings</td>
<td>18 (11.0)</td>
<td>6.2–15.9</td>
<td>6 (3.6)</td>
<td>0.8–6.4</td>
<td>0.005*</td>
</tr>
</tbody>
</table>

\( p < 0.01 \).

Figure 1 Categorical distribution of incidental findings of brain MRIs in primary dysmenorrhoea and healthy control.
et al., 2011; Rios et al., 2012). It is tempting to conceive that cavum septum pellucidum might also be linked with spontaneous clinical pain.

We do not consider that the recruitment procedure would have had biased the finding presentation. In our studies, subject recruitment had been done in unbiased, randomized and rigorous manner. Furthermore, it is implausible to relate the findings to developmental consociation since, organogenesis wise, uterus derives from mesoderm while brain from ectoderm; the two organs emanate from different embryological origins (Sadler, 2011). The clinical significance and explanations of why the otherwise healthy PDM subjects have many times more occurrence of normal variants than the female controls are currently unknown. However, it can be important to bear in mind the current findings into consideration in the future neuroimaging studies of PDM.

Enthusiasm for the knowledge available from functional and structural brain imaging studies regarding human neurocognitive and affective functions as well as brain resilience in the face of pain and stress is often paralleled by unexpected but ample evidence of incidental findings on brain MRI with potential implications for both research participants and researchers (Illes et al., 2004). Although the majority of the cases do not need urgent referral for clinical intervention, our observations do echo the recent mandate for a thorough revisit of PDM (Berkley and McAllister, 2011; Berkley, 2013), and invite further epidemiological and neuroscientific research of PDM.

Author contributions

W.C.L. is responsible for image data acquisition, image inspection and diagnosis, statistical analysis and manuscript drafting. C.H.T. is responsible for study conception and design and image data acquisition. H.T.C. is responsible for gynaecological examination and diagnosis. T.C.Y. is responsible for image inspection and diagnosis. L.F.C. is responsible for study conception and design, statistical analysis, manuscript drafting. J.C.H. is responsible for study conception and design, image inspection and diagnosis, manuscript drafting, critical revision and final approval. All authors discussed the results and commented on the manuscript.

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