Confusional migraine is an adult as well as a childhood disease

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Confusional Migraine is an Adult as well as a Childhood Disease

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Abstract

**Background.** Acute confusional migraine (ACM) is considered a rare migraine variant primarily seen in children and adolescents.

**Methods & Results.** We present a series of eight adults and two adolescents suffering from migraine attacks associated with transient confusional states. Eight patients reported two or more such attacks. One of them reported mild head trauma in the past. One patient reported mild head trauma as a possible trigger. Further investigations were unremarkable in all patients and did not suggest underlying structural abnormalities, epilepsy or cerebrovascular disease. In none of these patients we found another cause to explain the observed phenomenon.

**Conclusion.** Based on this series of patients we suggest expanding the concept of confusional migraine from the pediatric population to adults. The temporal course of the confusion as well as the association with visual and other aura symptoms suggest cortical spreading depression as the underlying pathophysiology.
Introduction
In childhood migraine occasionally occurs as migraine variant, e.g. cyclic vomiting, abdominal migraine, vertigo, as well as migraine associated with confusional states. The term “acute confusional migraine” (ACM) was introduced by Gascon & Barlow in 1970 (1) who described this entity in 4 pediatric patients. However, Liveing had already described migraine with alterations of consciousness or confusion in 1873 (2). Several other cases and series have been published. In 2000 Neinstein and Milgrom (3) reviewed the literature summarizing a total of 61 cases of acute confusional migraine. Except for the series of Pietrini et al (4) where 4 adult patients were included, all patients were younger than 18 years (see table 1 for details of the published cases with confusional migraine). Only recently ACM was reported as a possible presenting feature of CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy) (5). In this series, 7 of 20 adult patients suffered from ACM usually before the occurrence of the first stroke. We present a case series of acute confusional states in association with migraine in eight adults and two adolescent patients. Also other migraine variants such as abdominal migraine (6) and cyclic vomiting (7) had been described in adulthood.

Cases
Case 1
A 16-year-old adolescent had a slight frontal head pain towards the end of a soccer game. On the way home he vomited repeatedly. At home he experienced left-sided numbness slowly spreading from the lips to the cheek. He was seen by his GP who diagnosed a migraine attack. When he became disorientated in time and place, he was sent to our emergency department. He had a history of episodic migraine since childhood occurring up to 4 times a year, with a similar confusional episode associated with a migraine attack one year ago. His mother also suffered from headaches. At the emergency department, the patient was not continuously orientated towards time and place, otherwise the neurological examination was normal. The numbness had completely resolved before admission. He fully regained orientation within 2 hours. He had normal blood tests and a normal CT scan. An MRI scan of the brain was normal.
Case 2
A 36-year-old lady presented to our outpatient headache clinic with a history of migraine with and without visual aura beginning at the age of 11. On average she had two attacks per month. In the last year she had experienced several episodes of transient disorientation with impairment of episodic memory and spatial orientation following her migraine attacks and lasting for several hours. For instance she did not remember whether her best friend was married or not, and after another attack she had difficulties in orientating in her familiar environment. She was treated with citalopram and clomipramine because of social phobia with panic attacks and depressive episodes. Otherwise she was healthy. The family history was negative for headaches. The neurological examination did not reveal any pathology except for amblyopy of the left eye since childhood. A neuropsychological examination showed discrete verbal and spatial short-term memory deficiency which was attributed to perinatal damage. An MRI scan of the brain was normal. She had previously been investigated for epilepsy, but all EEGs were normal.

Case 3
A 22-year-old lady presented to our outpatient headache clinic with a history of migraine with and without aura for 7 years. She had migraine attacks with preceding visual and/or sensory aura on 4 to 5 days per month. Occasionally she had isolated auras. About 6 months prior to referral she had a typical migraine with visual aura followed by a state of confusion lasting for 2 to 3 hours. She had problems in finding words. Trying to phone her mother she was unable to recall the pin code of her mobile phone. She mistook her alarm clock for the telephone receiver. The confusion resolved completely during sleep; the headache lasted for another 3 hours. Otherwise she was healthy. Her father suffered from migraine with and without aura. The neurological examination was normal, as well as a previous MRI of the brain. An interictal EEG three months after the confusional state showed no pathology. The patient refused neuropsychological testing and cancelled her follow up-visit, as she had only suffered from one isolated visual aura in the month after her first visit. No further confusional episode had occurred in that period, as the patient reported on the phone.
Case 4
A 16-year-old right-handed girl suddenly had difficulties reading during a French lesson at school due to a scotoma in her right visual field. Following the visual problems she was unable to write. While leaving the classroom she was afraid of her classmates, whom she did not recognize anymore. She even forgot her own name. Subsequently she developed a severe throbbing unilateral headache. She had a history of recurrent unilateral throbbing headaches for one year which were triggered by stressful events at school. Otherwise she was healthy and did not take any medication. Her mother suffered from migraine with visual aura. The neurological and a thorough neuropsychological examination were normal. An MRI scan of the brain, an ictal EEG and routine blood screening were also unremarkable.

Case 5
A 30-year-old man with a history of severe episodic unilateral headache with nausea, which occurred about once per week consulted his GP because of a common cold lasting longer than three weeks. During arterial blood taking from the finger tip he felt a slight dizziness. After 10-15 minutes he was seeing the GP for discussion of the blood test (CRP) that was normal. During the consultation the GP noticed slurred speech with some paraphasia. Then the patient appeared agitated and confused with signs of apraxia: He was helpless, unable to put on his coat when leaving. After 30 minutes he developed a severe throbbing pain on the right forehead, associated with nausea and vomiting. When admitted to our emergency department 2 hours later the pain had already improved and the mental status was normal. The neurological examination was unremarkable. As the patient was free of any complaints he refused further examinations such as an MRI scan of the brain and an EEG. He did not have similar episodes in the next 3 months.

Case 6
A 41-year-old man was admitted to the emergency ward because of an acute confusional state with temporal and spatial disorientation. He had been standing in his kitchen, fully disorientated, speaking incoherently and not recognizing his neighbors. A CT-scan of the brain was normal. He suffered from moderate frontal headache with nausea. The next day he had severe holocranial headache with associated with unilateral visual disturbances and nausea. He was fully orientated at
that time. He was followed up in our outpatient headache clinic seven months later. No further confusional episode had occurred in the mean time. The neurological examination was normal. An EEG did not reveal any abnormalities. The patient had complete amnesia for the confusional episode described above.

He had a history of migraine with visual and sensory aura since childhood. He had four to five headache days per month and treated attacks with naratriptan. Confusional episodes associated with migraine had occurred several times before. The patient always had complete amnesia for these episodes lasting several hours. He also had a history of major depression and anxiety disorder and was treated with venlafaxin 37.5 mg/d. The patient was scheduled for cranial MRI but was lost for follow up.

Case 7
For several years, this 41-year old man had moderate headaches preceded by visual aura in about 50% of the cases. The headaches changed approximately 6 weeks after he was attacked by a group of adolescents and suffered from a polytrauma with head trauma, luxation of the shoulder, rib fractures, and contusions of the cervical spine. Since then headaches following visual aura became more severe and were accompanied by nausea, sometimes emesis, photo- and phonophobia. During the headache phase he was in a state of confusion for about 60-90 minutes, e.g. he did not recognize his physiotherapist on the phone or he forgot about appointments. These attacks occurred up to three times per week over a period of 4 months. Thereafter he went back to the previous less severe migraines. He was otherwise healthy. An MRI scan of the brain was normal.

Case 8
A 62-year-old man had suffered from migraine since the age of 9 years, with mostly one to two attacks per month. He had severe unilateral or holocranial headaches, lasting for about 5 hours associated with photo-, phonophobia, and nausea. In the last 10 years he suffered from typical visual auras once or twice per year, occasionally followed by the headaches described above. Sometimes the patient suffered from numbness of the tongue during headache attacks. He also reported of three confusional episodes associated with migraine attacks. The first episode occurred several years ago while the patient was working in his office. He had
difficulty to realize what was going on. Thinking and speech were slowed with distorted words. And later he could not remember names of his colleagues. He suffered from another two similar episodes. All episodes were associated with migraines and fully reversible after about one hour. The patient’s father also suffered from migraine. The neurologic examination was normal. An MRI of the brain four years ago showed frontal microinfarcts. A recent EEG showed discrete intermittent right temporal slowing.

Case 9
A 19-year-old man suffered from severe migraine attacks with or without aura since the age of 6 years. As a child he had attacks only occasionally. For the last 2 years he had 2-4 attacks per month. The severe headache was unilateral, mostly frontoparietally located with a duration of up to 2 days without treatment. It was accompanied by photo-, phonophobia and nausea. In most attacks naratriptan relieved the headache after 2-4 hours. Aura symptoms were always associated with migraine headache and included most often visual symptoms followed by aphasia. At the age of 19 the patient was referred to our hospital since he developed unusual aura symptoms and headache after playing soccer. At the beginning he experienced a moderate right hemispheric headache which became severe after one hour. He developed left-sided central facial palsy which lasted for about half an hour. After that he was not responsive for few minutes and then presented with dysphasia with strong reduction in spontaneous speech, use of simple and short words, incomplete sentences and incorrect grammar. He understood simple sentences only. His actions appeared apractic. He was confused about the situation and could not recognize his parents as those. This episode lasted for about 6 hours and symptoms dissolved slowly. The migraine headache did improve with intravenous acetaminophen and after 12 hours the patient did not complain about headache anymore. An MRI of the brain 3 hours after symptom onset and an EEG 12 hours after attack onset were normal. The patient’s mother, who was also suffering from migraines, reported a similar attack including speech disturbances associated with disorientation.

A continuous follow up of this patient revealed rather mild migraine with aura with one headache-attack per month in the last two years. No other confusional episode occurred. Once he developed aura symptoms with dysphasia and hemiparesis lasting for 30 minutes before headache.
Case 10
A 22-year-old patient suffered from migraine with aura since childhood. She was admitted to the emergency department of a local hospital twice because of a confusional state with agitation and incoherent speech following the onset of typical migraine headaches. On admission, she showed disorientation in time and space and reduced spontaneous speech. Otherwise the neurological examination was normal. Because of increasing agitation sedation was necessary for cranial CT scan with contrast agent and a spinal tap. Results of these examinations were within normal limits. Within 24 hours, the headaches subsided and the patient recovered completely. An MRI of the brain and an EEG performed after the first episode were also normal.

Discussion
Acute confusional migraine is considered a rare migraine variant primarily seen in children and adolescents. In all of our patients, the syndrome is comparable with ACM that has been described for pediatric patients; in none of them an underlying disorder has been found.
In line with previous reports (4, 8-11) disorientation, memory problems, difficulty in recognizing familiar people, and speech disturbance were frequently observed in our patients. As in the literature the confusional state usually lasted for several hours (3, 12). Also in accordance with the literature (10, 12), recurring confusional episodes were observed in several of our patients (n=7). In contrast to some reports agitation (3) and amnesia (4, 11, 13) were not major symptoms in most of our patients. Also the frequent association with mild head trauma as a trigger (3) was less consistent in our series. (Patient No. 7 had suffered from a polytrauma, but head trauma was not considered as a direct trigger for the individual confusional episode. Two patients (cases 1 and 9) were playing soccer, but no head trauma was reported). Two of our patients appeared to have apraxia, which has not been reported in the context of ACM. However, recently apraxia was described as a complex aura symptom (14). As episodes were fully reversible after hours in our patients, neuropsychological testing could not be performed in the emergency setting. Interictal neuropsychological
testing was performed in patient No. 2. She showed discrete short-term memory deficiency probably attributable to perinatal damage.

Confusion subsequently developed after visual, sensory or dysphasic aura symptoms in most patients (table 2). Therefore it can be considered as a complex aura phenomenon per se or as the consequence of a multitude of aura-related cortical dysfunctions. The “confused” patient might have to cope with aphasia and complex neuropsychiological dysfunctions, such as apraxia or amnesia, all of which are likely to cause anxiety. Cortical spreading depression (CSD) (15) is thought to be the underlying pathophysiological mechanism for migraine aura including complex auras (14). CSD was proposed as the pathophysiological mechanism in ACM by Pietrini et al (4). ACM has been related to cortical dysfunction of the posterior dominant hemisphere (10, 11) or temporo-basal regions (4, 13) but evidence remains limited. Ictal investigations are scarce as the prevalence of ACM is probably as low as 0.4% in children (10). Most ictal abnormalities have been found in EEG-studies. Frontal and occipital slowing in the EEG can outlast clinical symptoms in ACM (4, 11). In our series only one EEG was recorded ictally (Case No 9), which was normal. In the literature ictal SPECT showed hypoperfusion in the left splenium of the corpus callosum (11) in one patient and ictal magnetic resonance angiography (MRA) demonstrated reversible narrowing of the left middle and posterior cerebral arteries in another patient (10). In our series only one patient (No. 9) had MR-angiography during the confusional episode, which was normal.

In the literature only a few cases of ACM in adults have been published but confusional states have been described in adult patients with CADASIL (5), “migrainous syndrome with CSF pleocytosis” (16, 17) and familial hemiplegic migraine (18). Clinical presentation and investigations (table 2) ruled out any of these conditions in our series. Conditions similar to ACM have been termed “benign post traumatic encephalopathy” in the literature (19). In the context of familial hemiplegic migraine the term “encephalopathy” was used for patients with severe alterations in consciousness, who subsequently developed aphasia or agitation (20). Those patients also showed MRI abnormalities such as cortical swelling. Therefore we suggest that ACM might be the most appropriate term for a transient benign disorder that is likely to be a complex aura phenomenon, whereas “migraine encephalopathy” might be preferred in the context of trauma or in association with alterations of consciousness and/or abnormalities in imaging or other investigations.
The main differential diagnoses of ACM are epileptic seizures, vascular disorders, encephalitis, and intoxication. However, the clinical course with remission within hours and its rather typical presentation with migraine headache make it easier to distinguish. Epilepsy is probably the most challenging differential diagnosis for an episodic disorder with focal neurological signs, headache and confusion. This topic has been reviewed elsewhere (21).

Based on this series of patients we suggest expanding the concept of confusional migraine from the pediatric population to adults. The temporal course of the confusion as well as the association with visual and other aura symptoms suggest cortical spreading depression as the underlying pathophysiology. Confusional migraine should be added to the International Classification of Headache Disorders (22) as a subtype of migraine with aura.
References

Table 1: Demographics and clinical features of the published cases of acute confusional migraine (adapted from Neinstein et al (3)).

Abbreviations: NR = not reported. *All patients had CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy)
<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Age</th>
<th>Age</th>
<th>M:F</th>
<th>Migraine history</th>
<th>Family history of headaches</th>
<th>Trauma</th>
<th>Duration of confusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gascon &amp; Barlow (1)</td>
<td>4</td>
<td>8–16</td>
<td>0</td>
<td>3:1</td>
<td>2/4</td>
<td>3/4</td>
<td>0/4</td>
<td>4 – 24</td>
</tr>
<tr>
<td>Haas &amp; Sovner (23)</td>
<td>6</td>
<td>1–12</td>
<td>0</td>
<td>3:3</td>
<td>2/6</td>
<td>6/6</td>
<td>6/6</td>
<td>1 – 24</td>
</tr>
<tr>
<td>Emergy (24)</td>
<td>4</td>
<td>5–14</td>
<td>0</td>
<td>2:2</td>
<td>4/4</td>
<td>4/4</td>
<td>2/4</td>
<td>1.5 – 9</td>
</tr>
<tr>
<td>Ehyai &amp; Fenichel (25)</td>
<td>5</td>
<td>9–14</td>
<td>0</td>
<td>3:2</td>
<td>0/5</td>
<td>4/5</td>
<td>1/5</td>
<td>0.5 – 24</td>
</tr>
<tr>
<td>Shaabat (12)</td>
<td>13</td>
<td>6–15</td>
<td>0</td>
<td>11:2</td>
<td>7/13</td>
<td>10/13</td>
<td>4/13</td>
<td>1.5 – 24</td>
</tr>
<tr>
<td>Ferrera (26)</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>0:1</td>
<td>0/1</td>
<td>1/1</td>
<td>0/1</td>
<td>0.5</td>
</tr>
<tr>
<td>Nezu et al. (11)</td>
<td>2</td>
<td>7–12</td>
<td>0</td>
<td>1:1</td>
<td>NR</td>
<td>2/2</td>
<td>0/2</td>
<td>6 – 12</td>
</tr>
<tr>
<td>Pietrini et al. (4)</td>
<td>12</td>
<td>8–60</td>
<td>4</td>
<td>6:6</td>
<td>10/12</td>
<td>8/12</td>
<td>4/12</td>
<td>1 – 12</td>
</tr>
<tr>
<td>Haan et al. (27)</td>
<td>1</td>
<td>13</td>
<td>0</td>
<td>0:1</td>
<td>0/1</td>
<td>1/1</td>
<td>1/1</td>
<td>12</td>
</tr>
<tr>
<td>D'Cruz &amp; Walsh (28)</td>
<td>3</td>
<td>11</td>
<td>0</td>
<td>0:3</td>
<td>1/3</td>
<td>3/3</td>
<td>1/3</td>
<td>6</td>
</tr>
<tr>
<td>Bechtel (8)</td>
<td>2</td>
<td>11–14</td>
<td>0</td>
<td>1:1</td>
<td>1/2</td>
<td>2/2</td>
<td>1/2</td>
<td>several hours</td>
</tr>
<tr>
<td>Khatri et al. (9)</td>
<td>2</td>
<td>11–16</td>
<td>0</td>
<td>1:1</td>
<td>1/2</td>
<td>1/2</td>
<td>0/2</td>
<td>0.5–72</td>
</tr>
<tr>
<td>Sathe et al. (5)*</td>
<td>7</td>
<td>42–58</td>
<td>7</td>
<td>5:2</td>
<td>6/7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>1–60</td>
<td>11</td>
<td>36:26</td>
<td>34/60</td>
<td>45/55</td>
<td>20/55</td>
<td>0.5–72</td>
</tr>
</tbody>
</table>
Table 2: Clinical features and investigations of patients with acute confusional migraine.

Abbreviations: MwoA = Migraine without aura, MwA = Migraine with aura, hi = history (occurred in earlier attacks, not associated with confusion), # these patients were playing soccer at symptom onset, but no head trauma was reported. Temporal relation of confusion and headache is indicated by a blue-green frame in the column “before, during, after headache”. Temporal occurrence of aura is indicated with an asterisk * (see text for further details).
<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>Migraine history</th>
<th>Sensory / Speech disturbance</th>
<th>Family history of headaches</th>
<th>Head trauma</th>
<th>Epis. Confusion</th>
<th>First (age)</th>
<th>Total</th>
<th>Confusion duration</th>
<th>before headache</th>
<th>during headache</th>
<th>after headache</th>
<th>Investigations</th>
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</thead>
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<tr>
<td>1</td>
<td>16</td>
<td>m</td>
<td>MwoA since childhood</td>
<td>Sensory</td>
<td>Headache (mother)</td>
<td>No#</td>
<td>15</td>
<td>2</td>
<td>4–6 h</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>f</td>
<td>Mw/woA since childhood</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>35</td>
<td>&gt;10</td>
<td>Several h</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>f</td>
<td>Mw/woA for 7 years</td>
<td>Sensory (hi), speech</td>
<td>MwA (father)</td>
<td>No</td>
<td>22</td>
<td>1</td>
<td>2–3 h</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>f</td>
<td>MwoA for 1 year</td>
<td>None</td>
<td>MwA (mother)</td>
<td>No</td>
<td>16</td>
<td>1</td>
<td>Several h</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>m</td>
<td>MwoA since childhood</td>
<td>Speech</td>
<td>None</td>
<td>No</td>
<td>30</td>
<td>1</td>
<td>1–2 h</td>
<td>*</td>
<td></td>
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<td></td>
<td>Refused</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>m</td>
<td>Mw/woA since childhood</td>
<td>Sensory (hi)</td>
<td>None</td>
<td>No</td>
<td>40</td>
<td>Several</td>
<td>Several h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None – CT normal</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>m</td>
<td>Mw/woA, for years</td>
<td>None</td>
<td>None</td>
<td>Yes</td>
<td>40</td>
<td>&gt;10</td>
<td>1–1.5 h</td>
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<td>Normal</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>m</td>
<td>Mw/woA since age 9</td>
<td>Sensory, speech</td>
<td>Father and cousin migraine</td>
<td>No</td>
<td>48</td>
<td>3</td>
<td>1 h</td>
<td>Not reported</td>
<td></td>
<td></td>
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<td>Frontal microinfarcts</td>
</tr>
<tr>
<td>9</td>
<td>19</td>
<td>m</td>
<td>Mw/woA since age 6</td>
<td>Speech</td>
<td>MwA (mother)</td>
<td>No#</td>
<td>19</td>
<td>2</td>
<td>6 h</td>
<td>*</td>
<td></td>
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<tr>
<td>10</td>
<td>22</td>
<td>f</td>
<td>MwA since childhood</td>
<td>?</td>
<td>No</td>
<td>22</td>
<td>2</td>
<td>Several h</td>
<td>*</td>
<td></td>
<td></td>
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