

Adult attention deficit hyperactivity disorder is associated with migraine headaches

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Abstract Attention deficit hyperactivity disorder (ADHD) is now recognized as a common disorder both in child and adult psychiatry. Adult patients with a diagnosis of ADHD ($n = 572$) and community controls ($n = 675$) responded to auto-questionnaires rating past and present symptoms of ADHD, co-morbid conditions, including migraine, treatment history and work status. The prevalence of migraine was significantly higher in the patient group compared to the controls (28.3% vs. 19.2%, $P < 0.001$, OR = 1.67, CI 1.28–2.17). The difference from controls was particularly marked for men (22.5% vs. 10.7%, $P < 0.001$, OR = 2.43, CI 1.51–3.90) but was also significant for women (34.4% vs. 24.9%, $P = 0.008$, OR = 1.58, CI 1.13–2.21). In both patients and controls, migraine was associated with symptoms of mood and anxiety disorders. These findings point to a co-morbidity of migraine with ADHD, and it is possible that these patients represent a clinical and biological subgroup of adult patients with ADHD.

Keywords Migraine · ADHD · Adults · Co-morbidity

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Introduction

During recent years, attention deficit hyperactivity disorder (ADHD) has received increasing interest in adult psychiatry [1–5]. It has become evident that many children with ADHD still have impairing symptoms as adults which cause them to suffer both socially and at work [6, 7]. ADHD prevalence estimates are in the range of 2–12% in children [8–10] and 1–4% in adults [4, 11, 12]. In addition, ADHD is associated with many other psychiatric disorders, in particular anxiety and mood disorders [7, 12], but apart from asthma [13] and obesity [14], there has been little interest in the possible co-morbidity with somatic disorders.

Compared to ADHD, migraine has a very different profile with regard to prevalence, gender distribution and age of onset [15]. However, both migraine [16, 17] and ADHD [18] have a strong genetic basis. Furthermore, it is interesting to observe that migraine has also a well-established co-morbid connection with mood and anxiety disorders. This has been shown both in clinical [19–21], epidemiological [22, 23] and genetic studies [24, 25].

The aims of the present study were to (1) investigate the prevalence of migraine among clinically diagnosed adults with ADHD, compared to controls from a normal population and (2) investigate whether the presence of migraine is associated with differences in symptom patterns and demographic variables in patients and controls.

Methods

Subjects

This is a cross-sectional study of 572 Norwegian patients diagnosed with adult ADHD and a comparison group of

675 persons from the general population. The patients were recruited as part of a genetic study using a national registry of adults diagnosed with ADHD in Norway during 1997–2005 [7, 26, 27]. The diagnostic assessment of the patients in the registry was made by one of three national expert committees for ADHD and was based on detailed clinical information (including information from informants) provided by the referring clinicians, mainly psychiatrists. The diagnosis of ADHD was made according to the ICD-10 research criteria, with two modifications; allowing the inattentive subtype, as in DSM-IV, as sufficient for the diagnosis, and allowing for the presence of co-morbid psychiatric disorders, as long as the criteria for ADHD were present before the appearance of the co-morbid disorder. In addition, to enhance recruitment and to include patients diagnosed also later than May 2005, psychiatrists and psychologists nationwide were invited to recruit formally diagnosed adult patients with ADHD. The inclusion criteria were a diagnosis of ADHD according to the criteria described above and age above 18 years. There were no formal exclusion criteria. The intention behind this strategy was to recruit a clinically representative sample of adult ADHD patients from all over the country.

A control group was recruited using the database of the Medical Birth Registry of Norway (MBRN). The MBRN includes all people born in Norway after 1 January 1967. Invitation letters were sent out to a randomly selected sample of persons between 18 and 40 years from all over Norway. Data from the first 675 persons recruited are presented in the present report. For further details about the recruitment strategy and the patient sample, see Johansson et al. 2008 [27], Halleland et al. 2009 [28], Halmøy et al. 2009 [7], 2010 [26].

Informed consent based on detailed written information about the project was obtained from all patients and controls. The study was approved by the Regional Research Ethical Committee of Western Norway.

Questionnaires

The following self-report questionnaires were used in this study: The Wender Utah Rating Scale (WURS), measuring the presence and frequency of childhood ADHD symptoms [29], the Adult ADHD Self-Report Scale (ASRS) that measures the presence and frequency of current symptoms of ADHD [30, 31], and the Mood Disorder Questionnaire (MDQ), a screening questionnaire for bipolar spectrum disorders (BSD) [32].

The WURS is designed to retrospectively record symptoms and signs of ADHD in childhood. The version of the scale used in this study contains 25 questions, each rated on a 5-point severity scale. The WURS-25 has been

validated by several investigators in different countries and populations [33, 34].

The ASRS is the World Health Organization's (WHO) rating scale for adult ADHD designed to measure current ADHD symptoms. It consists of 18 items based on DSM-IV symptoms/criteria for ADHD which are measured on a 5-point scale (0 Never/seldom and 4 Very often), yielding a possible score range from 0 to 72. The items 1–9 cover the symptoms of inattention; items 10–18 the symptoms of hyperactivity and impulsivity. In this study, we used a continuous scoring method [31].

The MDQ is a screening instrument for BSD that has been validated for use in the general population and in psychiatric patient populations [32, 35]. The MDQ consists of 15 items. The first 13 questions concern periods of lifetime symptoms of mania and hypomania, and the last two ask about co-occurrence of symptoms and ranking of functional impairment caused by the symptoms. A standard MDQ positive score is defined as 7 or more 'yes' on the first 13 items, 'yes' on question 14 (co-occurrence of symptoms) and level '3 or more' on question 15 (moderate to severe impairment).

In addition, the patients answered questions concerning socio-demographic and clinical factors including educational and occupational levels and co-morbid symptoms and problems. The questions related to co-morbidity were scored as 'yes' or 'no'. 'Have you ever experienced significant anxiety and/or depression? Have you ever had problems with alcohol? Have you ever had migraine? Do you have bipolar or manic-depressive disorder?'

Statistical analyses

The data were analysed using chi-square tests, *t* tests for independent samples and logistic regression analyses. All analyses were performed using the Statistical Package for Social Sciences (SPSS) version 15.0.1.

Results

Clinical and socio-demographic characteristics of patients and controls are shown in Table 1. In the control group, there were a higher proportion of women than in the patient group (59.7% vs. 48.4%). The frequency of self-reported migraine was higher for women both in the control group (24.9% vs. 10.7%) and among the patients (34.4% vs. 22.5%). Considering these clear gender differences, we analysed data for men and women separately. For both genders, the mean age was lower in the control group compared to the patients. The level of education was lower among the patients and the relative number holding an ordinary job far lower. The proportions of patients

Table 1 Clinical and socio-demographic characteristics of patients and controls

	Males			Females		
	Patients <i>N</i> = 290	Controls <i>N</i> = 271	<i>P</i>	Patients <i>N</i> = 274	Controls <i>N</i> = 402	<i>P</i>
Age (mean ± SD)	33.9	30.3	<0.001	34.4	29.0	<0.001
Educational level (%)						
Junior high school	30.6	4.2		23.5	4.7	
Senior high school	46.9	39.4		51.4	35.7	
College/university	22.4	56.4	<0.001	25.1	59.7	<0.001
Occupational level (%)						
Working	30.7	83.0	<0.001	27.4	79.9	<0.001
Self-reported co-morbidity (%)						
Depression/anxiety	66.2	14.9	<0.001	71.8	16.5	<0.001
Bipolar disorder	10.7	1.5	<0.001	12.3	1.2	<0.001
Alcohol problems	32.6	2.9	<0.001	15.1	1.7	<0.001
WURS (score, range 0–100)	58.2	19.1	<0.001	59.6	16.3	<0.001
ASRS (score 0–72)	44.2	23.5	<0.001	47.7	22.2	<0.001
MDQ+ (%)	54.7	9.0	<0.001	42.2	4.9	<0.001
Migraine (%)	22.5	10.7	<0.001	34.4	24.9	0.008

reporting a life-time history of depression and/or anxiety, bipolar disorder and alcohol problems were significantly increased compared to the controls, and scores on all the self-report scales were far higher in the patient group than in the control group. All these differences were similar for men and women.

In the patient group, 28.3% reported having migraine, compared to 19.2% among controls ($P < 0.001$, chi-square, OR = 1.67, 1.28–2.17). When controlling for gender and age in a logistic regression, the OR was only slightly altered (OR = 1.65, 1.24–2.20). The difference in migraine prevalence between patients and controls was somewhat higher for men (OR = 2.43, 1.51–3.90, $P < 0.001$, chi-square) than for women (OR = 1.58, 1.13–2.21, $P = 0.008$, chi-square).

Table 2 shows the same clinical and socio-demographic characteristics as in Table 1, but this time contrasting ADHD patients with and without self-reported migraine. For both genders, the educational and occupational levels were very similar for patients with and without migraine. Self-reported problems with alcohol did not differ, but more patients with migraine reported a life-time history of depression and/or anxiety, and the findings were very similar for men and women. However, bipolar disorder was reported significantly more often by men with migraine (21.3%, compared to controls 7.5%), but not by women (12.5% vs. 12.4%). The reported levels of ADHD symptoms in childhood (WURS), current ADHD symptoms (ASRS score) and life-time symptoms of bipolar disorder (MDQ) did not differ between the two groups.

In Table 3 are shown the characteristics of controls with and without migraine. The proportion of women was higher in the group with migraine (77.5% vs. 55.5%). Women with migraine had a slightly lower level of education than women without migraine, and the number holding a job was lower for men with migraine compared to men without migraine. For both genders, the proportions of self-reported depression and/or anxiety were markedly higher in the migraine groups. However, only men with migraine reported a higher frequency of bipolar disorder (10.3% vs. 0.4%) and problems with alcohol (10.3% vs. 1.7%) compared to men without migraine, with no differences among women. On a symptom level, persons with migraine, both men and women, reported more ADHD symptoms in childhood (WURS), and women had also significantly higher scores on current ADHD symptoms (ASRS). The proportion screening positive for bipolar disorder (MDQ) was also higher in the migraine groups, for both genders.

Discussion

The main finding of the present study is a higher prevalence of migraine in a clinical sample of adult patients with persistent ADHD, compared to a control group from the general population. Among the controls, the presence of migraine was associated with higher scores on two self-report forms providing information on ADHD symptoms (WURS, both genders, and ASRS, women only), giving

Table 2 Clinical and socio-demographic characteristics of patients with and without migraine

	Males			Females		
	Migraine <i>N</i> = 64	Not migraine <i>N</i> = 221	<i>P</i>	Migraine <i>N</i> = 93	Not migraine <i>N</i> = 177	<i>P</i>
Age (mean ± SD)	34.7	33.8	NS	35.6	34.0	NS
Educational level (%)						
Junior high school	32.1	30.9		24.1	23.4	
Senior high school	41.5	48.2		50.6	51.3	
College/university	26.4	20.9	NS	25.3	25.3	NS
Occupational level (%)						
Working	36.1	29.3	NS	21.6	30.1	NS
Self-reported co-morbidity (%)						
Depression/anxiety	78.1	63.0	0.024	79.8	67.2	0.029
Bipolar disorder	21.3	7.5	0.002	12.5	12.4	NS
Alcohol problems	35.9	31.8	NS	19.6	13.0	NS
WURS (score, range 0–100)	58.9	58.1	NS	62.2	58.2	NS
ASRS (score 0–72)	46.9	43.5	NS	48.8	47.0	NS
MDQ+ (%)	49.2	56.6	NS	40.7	42.9	NS

NS Not significant

Table 3 Clinical and socio-demographic characteristics of controls with and without migraine

	Males			Females		
	Migraine <i>N</i> = 29	Not migraine <i>N</i> = 241	<i>P</i>	Migraine <i>N</i> = 100	Not migraine <i>N</i> = 302	<i>P</i>
Age (mean ± SD)	30.8	30.3	NS	30.7	28.5	0.004
Educational level (%)						
Junior high school	3.4	3.9		8.3	3.4	
Senior high school	34.5	40.2		41.7	33.9	
College/university	62.1	55.9	NS	50.0	62.7	0.031
Occupational level (%)						
Working	72.0	84.7	0.002	81.5	79.3	NS
Self-reported co-morbidity (%)						
Depression/anxiety	31.0	12.1	0.006	25.0	14.0	0.01
Bipolar disorder	10.3	0.4	0.002	2.0	1.0	NS
Alcohol problems	10.3	1.7	0.005	3.0	1.3	NS
WURS (score, range 0–100)	25.5	18.1	0.009	19.2	15.3	0.014
ASRS (score 0–72)	24.7	23.2	NS	24.3	21.7	0.025
MDQ+ (%)	18.5	7.1	0.041	9.3	3.8	0.035

NS Not significant

additional support for the contention that migraine is related to ADHD.

The ADHD patients in the present study are very impaired as a group, with a low level of education compared to controls, and less than one-third being employed [7]. This is in line with previous studies showing a low level of occupational functioning in adult patients with persistent ADHD [6]. Clinical and socio-demographic

characteristics of these patients have been described in previous publications [7, 27, 28], including the relationship between ADHD and bipolar spectrum disorders [26].

It has been suggested that bipolar disorder associated with migraine might represent a more severe variant of bipolar disorder, based on an earlier onset of the bipolar disorder and greater social impairment [36, 37]. However, other studies do not support such a contention [38]. We

found no indication that ADHD patients with migraine represent a more impaired subgroup of ADHD patients. The level of education, employment status and scores on the ASRS and WURS scales were not significantly different from patients without migraine. However, among the controls, the presence of migraine in women was associated with a lower level of education, and in men with a lower likelihood of being employed.

In epidemiological studies, migraine is clearly more prevalent in women than in men [15, 39–41]. This was also found for the controls in the present study, 25% of the women reported migraine, compared to 11% of the men. These prevalence figures are somewhat higher compared to a previous epidemiological study from Norway, reporting a prevalence of 16% in women and 8% in men [42]. In several clinical investigations of patients with mood disorders and migraine co-morbidity, gender differences are far less marked. In a study from Bergen, we found that 42% of men compared to 55% of women with mood disorders had migraine [38]. Low and co-workers [21] described comparable findings in bipolar patients; 31% of men and 44% of women met the criteria for migraine. Similarly, Mahmood, Romans and Silverstone [36] found, in a sample of bipolar patients, an almost equal prevalence of migraine in men (25%) and women (27%). Kececi et al. [43] reported, in a population study from Turkey, that major depression was strongly associated with migraine, and although the prevalence of major depression was higher in women (22% vs. 9%), in persons with migraine this gender difference in prevalence was no longer present (33% prevalence of major depression in women vs. 32% in men). In the present study, the prevalence of migraine in female ADHD patients (34%) was higher than in men (23%), but the difference was smaller than one would expect from a random population sample. Therefore, it seems that the relationship between migraine, ADHD, and gender in our patient sample resembles findings from patients with mood disorders.

The present results imply a co-morbidity between ADHD and migraine. This may appear counterintuitive. Migraine and ADHD are very different disorders. Migraine is an episodic disorder, with attacks of pain and time-limited neurological dysfunction [15]. Several genetic variants have been identified to cause migraine in subsets of patients, providing a valid model for disturbances causing hyperexcitability of neurons and migraine symptoms [44]. In contrast, ADHD is a chronic disorder comprising problems with attention and concentration, combined with behavioural symptoms such as hyperactivity/restlessness and impulsivity [2]. Deficits of executive function are probably of central importance [2, 5]. However, our contention is that this apparently paradoxical relationship between migraine and ADHD may be related

to their shared co-morbidities and possibly related pathogenetic mechanisms. Co-morbid psychiatric disorders were highly prevalent in our sample of ADHD patients. We found a higher frequency of depression and/or anxiety in ADHD patients with migraine compared to ADHD patients without migraine, both in men and in women. Self-reported bipolar disorder was higher in male ADHD patients with migraine, but not in women. However, migraine was not associated with a higher number of patients having positive scores on the MDQ scale.

There is a well-documented co-morbidity between migraine and psychiatric disorders, in particular mood and anxiety disorders [38, 45, 46]. This was also seen in the controls from the present study, those having migraine reported more depression and/or anxiety, and men also reported more bipolar disorder. Furthermore, a larger number had positive scores on the MDQ scale, both men and women. The same pattern of co-morbidity with mood and anxiety disorders is seen for ADHD [12]. Concerning bipolar disorders, both migraine [19] and ADHD [47] may be linked to bipolar II disorder. Increased motor activity and impulsivity are central symptoms of both ADHD [2] and bipolar disorders [48]. Impulsivity is not regarded as a part of the ordinary symptom pattern of migraine, but the connection of migraine with bipolar disorders, and the finding of a high frequency of migraine (44%) among patients (predominantly men) with intermittent explosive disorder [49], suggest that impulsivity and/or mood dysregulation may be a common link between migraine and ADHD.

Cognitive dysfunction is not thought to be associated with migraine, apart from changes occurring during acute attacks [15, 50]. However, there is increasing evidence that there are cognitive impairments in migraine patients in periods between attacks [51, 52], including slower response times during cognitive set-shifting and deficits in memory. All these findings point to a possible link of migraine with ADHD.

While it is not possible on the basis of such a cross-sectional study to answer the question of why such a connection between migraine and ADHD exists, it is tempting to speculate that this is related to common underlying pathophysiological mechanisms. Much of the current thinking on the pathophysiology and genetics of ADHD has focused on alterations in dopaminergic systems [27], and there is also substantial evidence that dopaminergic mechanisms are involved both in migraine [23, 53] and in mood disorders [54, 55]. It is therefore possible that changes in dopaminergic systems or other signalling mechanisms represent common etiological factors for these disorders and that there could be a subgroup of patients sharing underlying pathophysiological disturbances causing hyperexcitability of neurons and symptoms of

combined neuropsychiatric disorders like migraine, ADHD and mood disorders.

Recent genome-wide association studies have revealed unique susceptibility genes for co-morbid migraine and bipolar disorder. Interestingly, one of these genes was also associated with co-morbid ADHD and migraine, supporting the hypothesis that migraine has shared pathogenetic mechanisms with ADHD and mood disorders [56].

Concerning limitations, it is evident that we are not studying the whole range of ADHD patients. Not all patients with such problems consult a doctor, and those who are recruited to the present study probably represent a more severely affected group [7]. It is therefore uncertain if the present results are applicable to ADHD patients in general. The ASRS, the WURS and the MDQ are well-known and widely used auto-questionnaires, and even though they have not been subject to official validations in Norway, validation studies performed in various other populations have found them suitable for use [7, 26]. The diagnosis of migraine was made on the basis of self-reports, and this is obviously a departure from the ideal. It is a limitation of the present study that diagnoses were not obtained by a doctor skilled in the diagnosis of migraine. However, a diagnosis of migraine on the basis of questionnaires is inherently difficult [57], and it is not certain that a more detailed questionnaire would have given more valid results [58, 59]. Furthermore, asking for the persons' own opinion concerning migraine will give prevalence figures that include persons who have migraine without ever consulting a doctor because of such a complaint [60, 61]. We have no reason to suppose that the patient and control groups are different in this regard. We therefore consider that the present findings on migraine prevalence are valid, allowing for a comparison of ADHD patients and controls. With regard to the other questions on co-morbidity, we have, in a separate paper, shown that for ADHD patients there is a moderate to strong correlation between self-reported problems and formal diagnoses obtained during a clinical interview, for depression/anxiety and alcohol problems, and a moderate to weak correlation between self-reported and interview-diagnosed bipolar disorder [26].

In conclusion, we have shown that adults with persistent ADHD have an increased prevalence of migraine compared to controls from the general population. This points to a co-morbidity between these two disorders of the brain, possibly related to their shared underlying pathophysiological and co-morbidities with other neuropsychiatric disorders, like mood and anxiety disorders. We suggest that future studies should explore underlying pathophysiological mechanisms that may explain the co-occurrence of ADHD and migraine.

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Conflict of interest None.

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