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ORIGINAL PAPER

Restless legs syndrome as a possible predictor for psychiatric disorders in parents of children with ADHD

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Abstract Attention-deficit hyperactivity disorder (ADHD) is a common disorder with estimated prevalence of 5% in children and 3.4% in adults. Psychiatric disorders are a frequent concomitant feature. Restless legs syndrome (RLS) may mimic the symptoms of ADHD. The aim of the study is to evaluate whether the presence of RLS predicts occurrence of psychiatric disorders in parents of children with ADHD. Thirty-seven parents of 26 children with ADHD were examined for RLS and for lifetime prevalence rates of psychiatric disorders and personality disorders based on the Structured Clinical Interview for DSM-IV Diagnoses (SCID). Prevalence rates in parents were 29.7% for RLS, 67.6% for Axis I and 40.5% for Axis II disorders. Mothers revealed higher rates for depression, anxiety disorders and ADHD than fathers, whereas personality disorders occurred at higher rates in fathers. The presence of RLS predicted a diagnosis of ADHD (odds ratio (OR) 21.9), agoraphobia (OR = 20.4) and any anxiety disorder (OR = 8.5). Although limited by the small sample size, we found evidence for increased rates of cluster B personality disorders (OR = 59.3) in parents with RLS. All parents of the latter group (100%) reported a positive family history of psychiatric disorders which was not the case in parents without RLS (69.2%) excluding the index children with ADHD. RLS seems to indicate increased vulnerability for psychiatric disorders, i.e., ADHD and anxiety disorders, in a subgroup of parents from ADHD children. Synaptic dysfunction affecting dopaminergic transmission among other transmitter systems may be a common final pathway related to the phenotypic spectrum of ADHD.

Keywords Restless legs syndrome · ADHD · Psychiatric disorders · Personality disorders · Family history · Phenotypic spectrum

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is present in about 5% of children [1] and 3.4% of adults [2]. It is characterized by a consistent pattern of impaired attention, impulsive and disorganized behaviour, and hyperactivity which may present as an inner restlessness and inability to relax [3, 4]. Several family studies in ADHD confirmed its strong familial association [5, 6] with a two- to eightfold increased risk for ADHD in parents and siblings of children with ADHD

[7]. Recent genetic studies suggest a synaptic dysfunction affecting the dopaminergic pathway among other transmitter systems in the pathophysiology of ADHD [6, 8–10].

There is evidence for high comorbidity of ADHD with other clinical psychiatric diagnoses such as oppositional defiant disorder and conduct disorder during childhood (24–35%) [11, 12]. Prevalence rates for major depression (16–31%) [11, 12], anxiety disorders (approx. 25%) [13], borderline (63.6% in female offenders) [14], and antisocial personality disorder (12–36%) [15] have also been shown to be increased compared to both healthy controls and patients with psychiatric disorders who are not affected by ADHD. Rates of these psychiatric disorders were increased not only in adults with ADHD but also in parents and siblings of children with ADHD [5–7, 16, 17]. Furthermore, antisocial personality disorder is often accompanied by substance dependence or abuse of alcohol (21–53%) [18], cannabis or other drugs (14–27%) [19] in patients with ADHD.

Although information is still limited, clinical studies suggest an association of ADHD symptoms and restless legs syndrome (RLS) [20, 21]. RLS is a common neurological disorder with a prevalence rate of 2 [22] to 15% [23]. It is clinically characterized by paresthesias of the lower and, in a proportion of cases of also the upper extremities, as well as an intense urge to move the legs, which may mimic hyperactivity [23]. The RLS disease mechanisms are not completely understood but may be related to insufficiency of dopamine transmission and altered iron status in the brain, i.e. the neuromelanin cells of the substantia nigra [24]. Idiopathic RLS is characterized by high familial aggregation [25] with a heritability of approximately 50% [26]. Some studies addressed psychiatric comorbidity in patients with RLS [e.g. 27–29] suggesting that RLS is associated with symptoms of depression [27] and anxiety [28].

The aim of this clinical study was to further elucidate the possible relationship between ADHD and RLS by evaluating parents of children with ADHD for RLS and psychiatric disorders including personality disorders. Assuming that there is an overlap of RLS and ADHD, we expected to detect higher rates of ADHD, affective disorders, anxiety disorders and cluster B personality disorders in parents diagnosed with RLS compared to those without RLS.

Methods

Participants

Thirty-seven biological parents of 26 index children with a confirmed diagnosis of ADHD were recruited via the Department of Pediatrics at the university hospital in Luebeck, Germany. Each participant gave written informed consent after having carefully been informed about the study, parents gave written informed consent for their underaged children. The study was approved by the University of Luebeck Ethics Committee in accordance with the Declaration of Helsinki.

To assess lifetime prevalence rates for clinical psychiatric (Axis I) and personality (Axis II) disorders, a psychiatrist in training (V.S.) administered the German version of the Structured Clinical Interview for DSM-IV [30]. Diagnoses were independently evaluated by two additional experienced psychiatrists (S.S., R.L.) who were blinded to the diagnosis of RLS. Final diagnoses were established at a consensus conference, where all available clinical information was considered. According to DSM-IV, the diagnosis of antisocial personality disorder was not merely based on the item "being truant" in childhood and early adulthood, but rather being cruel to animals or to pick a fight on purpose. For ADHD, the parents were assessed on a German short form of the Wender-Utah Rating Scale [31] and on the self-rating behaviour questionnaire SB-ADHS [32].

Both the index children and their parents underwent a neurological examination by a movement disorder specialist (N.B.) and were evaluated for RLS according to the International RLS study group [33] by two independent specialists (N.B., and B.B., G.S. or A.B. respectively). Additionally, selected participants underwent electromyographic and neurographic testing to exclude polyneuropathy mimicking RLS symptoms. Iron deficiency, renal and thyroid dysfunction were also excluded as causes for secondary RLS.

A questionnaire based on the FH-RDC [34] was used to collect information about family members with respect to psychiatric disorders. We further included questions on possible neurological symptoms in family members.

Statistical analysis

Demographic data and prevalence rates were compared between individual groups using unpaired *t*-tests and Chi Square tests provided by the software package SPSS 17.0 (Chicago, IL). Stepwise logistic regression analyses including RLS, sex and age as independent variables and each of the psychiatric disorders as dependent variables were used to determine odds ratios with 95% confidence intervals and to evaluate the impact of RLS as a possible predictor for the occurrence of psychiatric disorders.

Results

Clinical characterization

Our sample of 37 parents included more mothers than fathers who neither differed with respect to age (mothers 43.4 years, SD 5.09; fathers 46.67 years, SD 5.2) nor

years of education (mothers 13.84 years, SD 2.67; fathers 14.25 years, SD 2.9). Evidence for RLS was found in 11 (30%) of these parents. None of these had been diagnosed with RLS previously or had received appropriate treatment with dopamine agonists. Neither occurrence of RLS [8/25 (32%) mothers, 3/12 (25%) fathers] nor age of onset of RLS symptoms [mothers 22 years, SD 13.02; fathers 17 years, SD 3.61] differed between mothers and fathers. Nine mothers and fathers (24.3%) had an index child, in whom the neurological examination showed evidence for RLS, as well. Taken together, 9 of 26 (35%) ADHD children were diagnosed with RLS.

Prevalence of psychiatric disorders in the whole parent sample

Twenty-nine parents [19/25 (76.0%) mothers, 10/12 (83.3%) fathers] were diagnosed with one or more psychiatric disorder including ADHD. Generally, clinical Axis I diagnoses were found at equal rates in mothers and fathers [mothers: 17/25 (68.0%), fathers: 8/12 (66.7%)], whereas personality disorders were significantly more frequent among fathers compared to mothers [mothers: 8/25 (32.0%), fathers: 8/12 (66.7%); $\chi^2_{(1)} = 3.97, P < 0.05$]. There were 12 parents with a comorbidity of both Axis I and Axis II disorders [6/25 (24.0%) mothers, 6/12 (50.0%) fathers].

A more detailed analysis of Axis I disorders disclosed that most parents ($N = 16$) reported a lifetime depressive disorder including 13 parents with major depression [10/25 (40.0%) mothers, 3/12 (25.0%) fathers; $\chi^2_{(1)} = 12.0$, $P < 0.001$] and nine with a dysthymic disorder [8/25 (32.0%) mothers, 1/12 (8.3%) fathers; $\chi^2_{(1)} = 73.8$, $P < 0.001$]. Thus, there were six parents with a double depression. Second most common were anxiety disorders [9/25 (36%) mothers, 3/12 (25%) fathers; $\chi^2_{(1)} = 6.45, P < 0.05$]. ADHD was diagnosed in five mothers (20%) and one father (8.3%).

Cluster C personality disorders [7/25 (28.0%) mothers, 6/12 (50.0%) fathers] were the most frequent Axis II disorders followed by those of cluster B [2/25 (8.0%) mothers, 3/12 (25.0%) fathers]. Among personality disorders, the highest prevalence was found for obsessive–compulsive personality disorder [4/25 (16.0%) mothers, 5/12 (41.7%) fathers]. Antisocial personality disorder was found in two fathers (16.7%) and one mother (4.0%).

Predicting psychiatric diagnosis by RLS

Prevalence rates of both Axis I and Axis II disorders were higher in parents with evidence for RLS ($N = 11$) than in those without RLS ($N = 26$) (for details, see Tables 1 and 2). The presence of RLS significantly increased the odds for ADHD and anxiety disorders, especially for agoraphobia. Thus, the presence of RLS predicted lifetime diagnosis of ADHD ($\text{Wald}_{(1)} = 6.56$, $P < 0.05$), agoraphobia ($\text{Wald}_{(1)} = 4.94$, $P < 0.05$), and any anxiety disorder ($\text{Wald}_{(1)} = 6.21$, $P < 0.05$) in parents of children with ADHD. All mothers with ADHD suffered from RLS, whereas the only father with ADHD did not have RLS (Table 1). With respect to personality disorders, the presence of RLS increased the risk for a cluster B personality disorder to 59.3; however, the confidence interval was large due to the small sample size. In regression analysis, RLS was considered a significant predictor for cluster B personality disorders ($\text{Wald}_{(1)} = 4.94$, $P < 0.05$). In contrast, the variables "age" and "gender" did not predict any Axis I or Axis II disorder.

Family history

Altogether, information on family history was available for 487 relatives of the 37 parents including the 26 ADHD index children. Major depression and alcohol-related disorders were reported most commonly in parents and siblings of ADHD parents. Notably, several relatives had committed suicide (Table 3). Within the children's group, which included information about 35 siblings of the index children, ADHD was nonetheless the most common diagnosis (Table 3). Regarding RLS, two parents with RLS and three other parents without RLS reported a positive family history for RLS (13.5%).

There was evidence for a clustering of ADHD, psychiatric diagnoses and RLS in certain families:

Nine of the 11 parents, who had been diagnosed with RLS, included a child diagnosed with RLS, too. Parents with RLS had significantly more often family members who were affected by psychiatric disorders than parents without RLS [11/11 (100%) vs. 18/26 (69.2%); $\chi^2_{(1)} = 4.32$, $P < 0.05$) excluding the index children with ADHD. The number of relatives with alcohol-related disorders was higher in families with RLS compared to those without ($t_{(35)} = 2.49$; $P < 0.05$).

Discussion

To our knowledge, this is the first study addressing RLS as a possible predictor for psychiatric disorders in relatives of children with ADHD. While the prevalence of RLS within the general population has been estimated as 2–15% [22, 23], one-third of the parents in our study were diagnosed with RLS, a finding that supports the notion of an association between ADHD and RLS [20, 21].

Our findings go beyond earlier reports about increased rates of psychiatric disorders such as ADHD, depression and anxiety disorders in parents and siblings of children with ADHD [5–7, 16, 17]. They imply that the presence of

Table 1 Prevalence rates of Axis I disorders in parents of children with ADHD

	N	%	Parents with RLS ($N = 11$)	%	Parents without RLS ($N = 26$)	%	Comparison of parents with and without RLS *P*-value	χ^2 ($df = 1$)	OR	CI
Psychiatric diagnosis	29	78.4	11	100.0	18	69.2	0.038	4.32		
Axis I	25	67.6	11	100.0	14	53.8	0.006	7.51		
Axis II	15	40.5	5	45.5	10	38.5	NS	0.16	1.6	0.4–6.9
ADHD	6	16.2	5	45.5	1	3.8	0.002	9.85	21.9	1.99–241.4
Anxiety	12	32.4	7	63.6	5	19.2	0.008	6.96	8.5	1.6–45.5
Social phobia	3	8.1	2	18.2	1	3.8	NS	2.13	6.7	0.4–103.5
Specific phobia	9	24.3	5	45.5	4	15.4	NS	3.79	4.8	0.9–25.2
Agoraphobic disorder	5	13.5	4	36.4	1	3.8	0.008	6.99	20.4	1.3–324.2
Panic disorder	2	5.4	2	18.2	0	0.0	0.025	5.00		
Mood disorder	16	43.2	6	54.5	10	38.5	NS	0.82	1.9	0.4–8.6
Major depression	13	35.1	5	45.5	8	30.8	NS	0.73	1.9	0.4–8.6
Dysthymic disorder	9	24.3	4	36.4	5	19.2	NS	1.23	2.5	0.5–12.7
Adjustment disorder	2	5.4	1	9.1	1	3.8	NS	0.42	0.4	0.0–7.9
Alcohol abuse	1	2.7	1	9.1	0	0.0	NS	2.43		
Drug abuse	1	2.7	1	9.1	0	0.0	NS	2.43		
Anorexia nervosa	1	2.7	0	0.0	1	3.8	NS	0.44		
Bulimia nervosa	2	5.4	2	18.2	0	0.0	0.025	5.00		
Somatization disorder	1	2.7	0	0.0	1	3.8	NS	0.44		
Suicidal attempts	1	2.7	1	9.1	1	3.8	NS	0.42		

In this sample, there was no parent found with any of the following Axis I diagnoses: Manic, Hypomanic, Bipolar I and II disorder, Generalized anxiety disorder, Obsessive–compulsive disorder, Alcohol and drug dependence and posttraumatic stress disorder

Table 2 Prevalence rates of personality disorders in parents of children with ADHD

Personality disorder	Total ($N = 37$)	Parents with RLS ($N = 11$)	Parents without RLS ($N = 26$)	χ^2 ($df = 1$)	Comparison of parents with and without RLS *P*-value	OR	CI
All	40.5% ($N = 15$)	45.5% ($N = 5$)	38.5% ($N = 10$)	0.16	NS	1.6	0.4–6.9
Cluster A	8.1% ($N = 3$)	9.1% ($N = 1$)	7.7% ($N = 2$)	0.20	NS	0.9	0.1–12.7
Paranoid	2.7% ($N = 1$)	0.0	3.8% ($N = 1$)	0.44	NS		
Schizoid	5.4% ($N = 2$)	9.1% ($N = 1$)	3.8% ($N = 1$)	0.42	NS	3	0.1–80.7
Cluster B	13.5% ($N = 5$)	36.4% ($N = 4$)	3.8% ($N = 1$)	6.99	0.008	59.3	1.2–2719.4
Antisocial	8.1% ($N = 3$)	27.3% ($N = 3$)	0.0	7.72	0.005		
Borderline	2.7% ($N = 1$)	9.1% ($N = 1$)	0.0	2.43	NS		
Histrionic	2.7% ($N = 1$)	0.0	3.8% ($N = 1$)	0.44	NS		
Cluster C	32.4% ($N = 12$)	36.4% ($N = 4$)	34.6% ($N = 9$)	0.01	NS	1.3	0.3–6.1
Obsessive–compulsive	24.3% ($N = 9$)	27.3% ($N = 3$)	23.1% ($N = 6$)	0.07	NS	1.5	0.3–8.20.3
Avoidant	10.8% ($N = 4$)	9.1% ($N = 1$)	11.5% ($N = 3$)	0.05	NS	0.9	0.1–11.4

Neither schizotypal, narcissistic or dependent personality disorder were found in this sample

RLS in parents of children with ADHD predicts lifetime occurrence of ADHD and anxiety disorders, especially agoraphobia. Although limited by a small sample size, we also found some evidence for increased rates of cluster B personality disorders in parents with RLS including antisocial, histrionic and borderline personality disorders. Notably, rates for depression and anxiety were higher in mothers than fathers, whereas personality disorders were more frequently present in fathers than mothers.

Various hypotheses have been proposed to explain the association of ADHD and RLS such as sleep disruption due to RLS leading to inattention, leg movements mimicking hyperactivity or impulsiveness, or just comorbid occurrence of RLS and idiopathic ADHD. It has also been

Table 3 Family history of psychiatric disorders in parents of children with ADHD as revealed by FH-RDC [34]

	Parents of ADHD parents ($N = 74$)	Siblings of ADHD parents ($N = 58$)	All children of ADHD parents ($N = 61$)	Children without index children ($N = 35$)	Further relatives ($N = 294$)
Depression	13.5% ($N = 10$)	8.6% ($N = 5$)	0	0	3.1% ($N = 9$)
Suicide committed	1.35% ($N = 1$)	3.4% ($N = 2$)	0	0	1.4% ($N = 4$)
Suicidal ideation	1.35% ($N = 1$)	0	0	0	0
Bipolar disorder	1.35% ($N = 1$)	0	0	0	0
Schizophrenia	2.7% ($N = 2$)	0	0	0	0
Alcoholism	10.8% ($N = 8$)	3.4% ($N = 2$)	0	0	4.4% ($N = 13$)
ADHD	0	1.7% ($N = 1$)	59.0% ($N = 36$)	28.6% ($N = 10$)	1.0% ($N = 3$)
Total	31.1% ($N = 23$)	17.2% ($N = 10$)	59.0% ($N = 36$)	28.6% ($N = 10$)	9.7% ($N = 29$)

suggested that mood and anxiety disorders may result from maladaptive coping with RLS symptoms [28], as seen in patients with sleep disorders [35], since RLS symptoms may be present prior to psychiatric symptoms. In our study, most of the parents were aware of their psychiatric symptoms, and some of them had received treatment, but none of them had realized RLS symptoms prior to the study examination. Therefore, it seems unlikely that the depressive symptoms we observed in the parents were resulting from maladaptive coping with RLS symptoms.

In accordance with previous reports, our exploratory data on family history suggests further evidence for a genetically conveyed vulnerability for psychiatric disorders and RLS in families with ADHD [5–7]. Our findings extend the phenotypic spectrum by showing frequent evidence of depression, ideated or committed suicide and alcoholism among parents, siblings of parents (i.e., aunts and uncles of the index children) and more distant relatives. Several studies demonstrated an association of polymorphisms in the dopamine receptor gene and alcoholism as well as suicidal attempts [36]. In line with this, our findings support the idea of shared alterations in synaptic, e.g. dopaminergic, transmission not only in ADHD, RLS and antisocial behaviour but also in alcohol-related disorders and suicidal behaviour.

Common disease mechanisms in ADHD, psychiatric disorders and RLS

Besides a synaptic dysfunction affecting a range of different neurotransmitter systems [37], disturbances in dopaminergic transmission have been suggested as a contributing factor to the pathogenesis in both RLS and ADHD [38]. Consistent with these findings, both conditions respond well to dopaminergic agents. Dopamine precursors (levodopa) and dopamine receptor agonists reduce RLS symptoms [39]. While long-acting preparations of methylphenidate represent an efficient treatment of ADHD in children and adults [40] that act as an indirect presynaptic dopamine transporter inhibitor [41]. Some case series point towards a small short-time effect of levodopa and selegiline on ADHD symptoms in adults and children (without RLS symptoms) [42, 43]. However, effects of levodopa lasted only 1 week with prominent side effects like nausea and fatigue. Until now, there are no randomized placebo-controlled trials showing significant reductions in ADHD symptoms by selegiline [44]. Walters and colleagues reported marked improvement of ADHD, RLS/periodic limb movements during sleep and sleep in seven children after they had been treated with dopaminergic agents [45]. They postulated that the improvement on ADHD symptoms was the result of either the exclusive improvement of RLS/PLMS or an improvement of the underlying common dopaminergic deficit of ADHD and RLS/PLMS, respectively. Nevertheless, it remained unclear whether RLS occurred comorbid with ADHD or whether RLS was mimicking ADHD symptoms. Notably, they also observed an improvement in oppositional defiant disorder behaviour [45]. Taking into account that children with oppositional defiant disorder are at greater risk of developing conduct disorder and antisocial personality disorder during adulthood [46] and that aggression might be related to a high dopamine turnover [47], this observation highlights the association of ADHD and RLS with antisocial behaviour as observed in our sample.

When discussing shared dopaminergic transmission pathology in ADHD and RLS, it has to be considered that recent alternative drugs for the treatment of ADHD act rather via noradrenergic and serotonergic transmitter systems, e.g. bupropion, clonidine, guanfacine, and theophylline [48–50]. Therefore, a more general synaptic dysfunction may underlie ADHD and RLS symptoms affecting further transmitter systems besides dopaminergic transmission.

We are aware of the fact that our clinical study with a rather small sample size is far away from meeting the criteria for an epidemiological investigation. Also, we may have missed parents with more severely affected ADHD

children or who had a major psychiatric disorder themselves who were not able to keep the multiple appointments that were required for this study.

Despite these limitations, our findings suggest RLS as an indicator for an increased vulnerability to psychiatric disorders in a subgroup of parents from ADHD children and imply RLS a possible feature of the ADHD spectrum. Future research including genetic and imaging studies is needed to unravel the complexity of the underlying mechanisms of both conditions. From a clinical perspective, patients with ADHD and their relatives can benefit from the evaluation of RLS symptoms which may help to optimize treatment by considering interactions between ADHD, comorbid psychiatric disorders and RLS.

Conflict of interest The authors declare that they have no conflict of interest.

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