Previous adult attention-deficit and hyperactivity disorder symptoms and risk of dementia with Lewy bodies: a case–control study

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Introduction: Previous reports have shown that in Dementia with Lewy body (DLB) and attention-deficit and hyperactivity disorder (ADHD) a hypodopaminergic and noradrenergic substrate seems to play a central role in developing the diseases. We investigated the hypothesis that attention deficit may precede DLB expressed as adult ADHD symptoms long before the clinical onset of dementia.

Methods: Patients with DLB, Alzheimer disease type (ADT) and controls were recruited from the membership of the Italian Hospital Medical Care Program in Argentina from 2000 to 2005. The DSM-IV criteria adapted for the identification of adult patients with ADHD and validated to Spanish Wender Utah Rating Scale were used to identify individuals with preceding ADHD symptoms during their adult life. Analysis of categorical variables was carried out using chi-square. Mann–Whitney test was used for continuous variables. Statistical significance was $P < 0.05$.

Results: A total of 109 patients with DLB and 251 patients with ADT were matched by age, sex and year of education with 149 controls. The frequency of preceding ADHD symptoms in DLB cases was 47.8% in ADT 15.2% and 15.1% in the control group. The prevalence of ADHD symptoms in DLB cases was significantly higher compared with the control group ($P \le 0.001$, OR 5.1 95%CI 2.7–9.6) and also higher when compared with ADT ($P \le 0.001$, OR 4.9, 95%CI 2.8–8.4).

Conclusion: We found a higher risk of DLB in patients with preceding adult ADHD symptoms. To date, there is no clear explanation for the association found; however, further investigation will widen our understanding about both disorders.

Introduction

Dementia with Lewy bodies (DLB) is a neurodegenerative condition characterized by progressive, disabling cognitive impairment and one or more additional core clinical features [1]. These include recurrent, well-formed visual hallucinations, fluctuations in cognition and spontaneous motor features of parkinsonism [1].

Dementia with Lewy body is the second most common cause of degenerative dementia in the elderly [1].

Histologically, numerous Lewy bodies in the brain stem (substantia nigra and locus coeruleus) and in subcortical (nucleus basalis of Meynert) and cortical regions have been noted in DLB [2]. Correspondingly, there are neuronal losses and gliosis in the substantia nigra, locus coeruleus and nucleus basalis of Meynert, with associated loss of dopamine (DA) in the basal ganglia [2].

Attention-deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders in child and adolescent psychiatry. This disorder affects 8–12% of children worldwide and is characterized by impaired attentional functions, hyperactivity and increased impulsivity [3]. In previous reports of the behavioral and biological bases of ADHD, a hypodopaminergic function in three striato-cortical loops has been suggested as responsible for core deficits in this disorder [4–7]. This was supported by observations that both children and adults with ADHD have abnormally high densities of dopamine transporters which remove an excess of DA from the synapse [8,9]. This hypothesis is also supported by genetic studies that showed an association between ADHD and genes involved in dopaminergic neurotransmission (dopamine receptor

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genes DRD4 and DRD5, and the DAT gene DAT1) [3,10]. In addition to DA depletion, noradrenalin (NA) regulation is also disturbed in ADHD [11]. The NA hypothesis is particularly well supported by the beneficial effects of specific NA transporter blockers [12]. As previously mentioned, NA-releasing neurons in the locus coeruleus are one of the main sites histologically affected in DLB.

Considering these investigations, in both disorders (DLB and ADHD) a hypodopaminergic and noradrenergic substrate seems to play a central role in developing the diseases. However, to date there is not a single study in which an association between clinical ADHD and DLB has been established. For this reason, we investigated the hypothesis that attention deficit may precede DLB expressed as adult ADHD symptoms long before the clinical onset of dementia. To further examine this association between ADHD symptoms and DLB, we conducted a case–control study in a large representative sample including patients with DLB, Alzheimer disease type (ADT) and normal controls.

Methods

Participants

This study was conducted at the Italian Hospital Medical Care Program (IHMCP) in Buenos Aires, Argentina with approval from the institutional Review Board of the IHMCP research committee.

Patients and controls were analyzed after informed consent was signed. In demented patients, researchers ensured that patients fully understand and appreciate the consequences of their participation throughout the course of the study. When a demented patient was not able to make informed decisions, the researchers ensured that the substitute decision maker (a direct family member) made the choice regarding that patient's wishes.

Patients with dementia and controls were recruited from the membership of the IHMCP, a large prepaid health maintenance organization model. IHMCP provides comprehensive medical and health services through two medical center hospitals and 24 medical office buildings to over 140 000 members primarily located in the urban areas around the Autonomous City of Buenos Aires, Argentina. Approximately 5–7% of the population in this geographic area is affiliated to the IHMCP. The IHMCP population characteristics are closely representative of the metropolitan population of the Autonomous City of Buenos Aires, as demonstrated by 2001 census data in a series of socioeconomic categories (Table 1).

The period of the study was conducted from 2000 through 2005. The sample included three groups of

Table 1 Socioeconomic level and ethnic origin of the Autonomous City of Buenos Aires inhabitants and IHMCP affiliates, based on 2001 Argentinean census

	City of Buenos Aires (%)	IHMCP (%)
Upper class	10	5
Upper middle class	16	19.4
Middle class	30	37.5
Lower middle class	21	25.6
Lower class	17	12.5
Poor	13	0
Total	100	100
Ethnic origin		
Caucasian	92	95.5
Asian	4	2
African American	1	0.5
Mestizos[a]	3	2

IHMCP, Italian Hospital Medical Care Program.
[a]Mestizos (Spanish term used to designate people of mixed European and Amerindian ancestry living in the region of Latin America).

subjects: a group of patients with clinical features of early mild to moderate probable DLB; a group with early probable Alzheimer disease; and a group of healthy controls.

Patients

Patients with dementia (DLB and ADT) were matched as groups on a range of demographic and dementia severity variables to ensure comparability. Severity of illness was determined by the clinical Dementia Rating Scale (CDR) and the mini mental status examination (MMSE). Clinical diagnosis for probable ADT was made according to the NINCDS-ADRDA criteria [13], and consensus criteria were used for the diagnosis of DLB [1]. All patients were evaluated and diagnosed by a trained neurologist. Patient selection was restricted to subjects in a mild to moderate stage of illness (MMSE 14–26 or CDR 1–2). Routine clinical investigations were conducted to exclude reversible causes of dementia. Patients were excluded if formal examination showed evidence of any other brain disorder or physical and or mental illness sufficient to contribute considerably to the clinical picture. Patient selection was strictly consecutive and included all the prevalent cases in the center who met previous criteria.

Controls

We matched controls to patients with dementia by sex, age, geographic area of residence and years of education. For each patient, we identified two people from the same general practice list of the same sex and closest in age to the index patient. We sent study information

to all potential controls and, from those replying, the researcher searched out the closest in age to check eligibility and obtain consent. If a potential control was ineligible or refused consent, we approached the next closest in age. Controls were never duplicated. Records of potential controls were reviewed by a neurologist to exclude those controls in which the presence of dementia of any type or any other neurological disease was suspected before or during the index year (year of diagnosis of dementia in the matched case). The list of the entire population from which potential controls were randomly drawn was provided by the record database system of the epidemiological center of the IHMCP, and control subjects were selected for cases using a statistical program.

Ascertainment of attention-deficit and hyperactivity disorder

The DSM-IV criteria adapted for the identification of adult patients with ADHD and the validated to Spanish Wender Utah Rating Scale were used as an instrument for retrospective diagnosis of childhood ADHD [14–17] to identify patients and controls with preceding ADHD during their adult life.

DSM-IV criteria and the Wender Utah Rating Scale have been successfully adapted for the identification of adult patients with ADHD and have been used in numerous studies in the past [16,18]. To obtain a full diagnosis of adult ADHD, subjects were required to have the following criteria: (i) fully met the DSM-IV criteria for diagnosis of ADHD within the past years; (ii) described a chronic course of ADHD symptoms from adolescence to adulthood; and (iii) endorsed a mild to severe level of impairment attributed to those symptoms (in demented patients obtained by a direct informant). Participants were also provided with the validated to Spanish Wender Utah Rating Scale for retrospective diagnosis of ADHD in childhood [17]. The validated to Spanish version scale comprises 25 items which are rated on a 5-point scale (0–4) [17]. The total score ranges from 0 to 100. Factor analysis of the scale yielded the following components: attention deficit/hyperactivity, impulsivity, anxious and depressive symptoms, oppositional behavior and deficit in social adaptation. The factorial analysis of these components divide the validated to Spanish scale into four factors. These are as follows: Factor I: emotional factor; Factor II: impulsivity and oppositional behavior abnormalities; Factor III: impulsivity and hyperactivity; Factor IV: attention-deficit disorder [17]. For the retrospective diagnosis of ADHD in childhood, the authors recommended a cutoff score of 32 or higher to obtain a sensibility of 91.5% and specificity of 90.8%,

with a positive and negative predictive value of 81% and 96%, respectively, and a Cronbach's coefficient of 0.94. This cutoff score was used because it demonstrated the best behavior (ROC curve) of the validated scale [17]. In patients with cognitive impairment, diagnosis was obtained by a direct informant who had known the patient for at least 10 years and had information obtained from a close relative who knew the patient in childhood. As this method has not been validated, we considered cases as ADHD symptoms and not as ADHD.

To avoid premorbid symptoms of DLB, we considered as adult ADHD symptoms only those patients who presented symptoms that fully met the DSM-IV criteria for diagnosis of ADHD and who fulfilled the cutoff score of the Spanish Wender Utah Rating Scale of 32 points or higher during their infancy. For example, if a patient had ADHD symptoms in adult life but the caregiver did not remember or did not know if those symptoms were present during childhood, the patient was not considered as a positive case of ADHD symptoms.

Procedure and data analysis

The evaluation of cases and controls regarding the identification of preceding ADHD using the DSM-IV criteria and the Wender Utah Rating Scale was performed by two trained neurologists unaware of the objective of the study. Only cases and controls fulfilling ADHD criteria by both evaluators were considered as positive exposure. In cases of discordant evaluations between blinded neurologists regarding previous ADHD symptoms, a third blinded neurologist assessed the patient for previous ADHD symptoms. If the patient had two positive evaluations for ADHD symptoms, the patient was considered positive for previous exposure to ADHD symptoms. Raters who collected the information about ADHD symptom status were blind to the dementia subtype and control status. When the evaluation was completed, data were analyzed by an unblinded neurologist aware of the objective of the study.

Analysis was performed using Stata 8.0 version. Analysis of differences in the frequency of categorical variables was carried out using the chi-square test. The Mann–Whitney test for independent samples was used for continuous variables.

Statistical significance was set up at $P < 0.05$. As in the original validated to Spanish Wender-Utah Rating Scale version [17], we analyzed the components of the scale (divided it into the four factors previously mentioned), using VARIMAX rotation in a principal component analysis. This rotation allowed us to maximize the sum of the variances of the squared loadings,

so all the coefficients were either large or near zero, with few intermediate values. Consequently, each variable was associated with one only factor. The factor analysis was derived from the entire sample. Comparisons in continuous variables amongst groups were carried out by means of ANOVA test with Bonferroni adjustment.

Results

We identified 241 patients with DLB and 473 with ADT from 2000 to 2005, of whom 109 and 251, respectively, fulfilled inclusion criteria. Patients were matched by age, sex and year of education with 149 control subjects. All patients authorized the use of their medical records for research. In all demented patients, the information regarding previous ADHD symptoms used was obtained from a direct informant. There were 2% of discordant evaluations regarding previous exposure to ADHD symptoms in DLB, 4% in ADT and 2.5% in controls that were solved as previously mentioned in the methods section. Amongst DLB cases, 32.6% were men, the median age was 75.1 years (range 51–89 years) and the mean years of education was 8.2 (range 1–18). There were no significant differences in these variables evaluated between the three groups, including MMSE and CDR (Table 2). No patients were exposed to psychostimulant medication.

The frequency of preceding ADHD symptoms was 47.8% in DLB cases, 15.2% in ADT and 15.1% in the control group (Table 3). The prevalence of ADHD symptoms in DLB cases was significantly higher when compared with the control group ($P \leq 0.001$, OR 5.1 95%CI 2.7–9.6) and also when compared with ADT ($P \leq 0.001$, OR 4.9, 95%CI 2.8–8.4). There were no differences in the frequency of preceding ADHD symptoms in the control group when compared with the ADT group ($P = 0.12$). When factors of the scale were analyzed in each group of patients, Factor III (impulsivity and hyperactivity) was significantly higher in

patients with DLB when compared with ADT and the control group, P value < 0.001 (Table 4). Factor I (emotional) was also higher in patients with DLB when compared with the other groups analyzed; however, there was no significant difference between groups, P value 0.05 (Table 4).

Discussion

In this case–control study, we identified a significantly higher risk of DLB amongst patients with past ADHD symptoms. Our study is the first of its kind to examine the clinical association between ADHD symptoms and DLB.

Considering that in DLB and ADHD there is a hypodopaminergic substrate, a possible explanation for our findings could be that both disorders may be closely related pathophysiologically. In ADHD there are low levels of tonic DA, and the abnormalities in NA regulation may affect the maturation of central dopaminergic systems. This may be a risk factor for the development of DLB as well as Parkinson's disease [19]. A recently published study evaluated the association between childhood symptoms of ADHD and the development of Parkinson's disease following the hypodopaminergic substrate observed in both pathologies. In that study, investigators used the Wender Utah Rating Scale to find symptoms of ADHD in childhood;

Table 2 Main characteristics of the groups compared

	DLB	ADT	Controls	P
N	109	251	149	
Mean age, years (SD)	75.1 (7.4)	74.2 (7.1)	74.1 (8)	NS
Years of education (SD)	8.2 (6.1)	8.3 (5.3)	8.2 (6.9)	NS
Male percentage	32.6	31.9	33.3	NS
Relation men/women	1.42/1	1.37/1	1.28/1	NS
Mean MMSE (SD)	21.7(4.6)	21(3.4)	29(0.6)	NS*
Mean CDR (SD)	1.11(0.5)	1.09 (0.5)	0	NS*

DLB, dementia with Lewy bodies; ADT, Alzheimer dementia type; SD, Standard deviation; MMSE, Mini mental status examination; CDR, Clinical Dementia Rating Scale.
*Comparisons includes DLB vs. ADT

Table 3 ADHD prevalence and comparisons between groups

Group compared	Percentage of ADHD	P	OR	95%CI
DLB vs. control	47.8 vs. 15.1	< 0.001	5.1	2.7–9.6
DLB vs. ADT	47.8 vs. 15.2	< 0.001	4.9	2.8–8.4
ADT vs. control	15.2 vs. 15.1	0.12	1.1	0.7–1.5

DLB, dementia with Lewy bodies; ADT, Alzheimer dementia type; ADHD, attention deficit and hyperactivity disorder.

Table 4 Factorial analysis of the validated Wender Utah Rating Scale among participants

Factor	DLB N = 109	ADT N = 251	Controls N = 149	P
I (mean ± SD)	13.1 ± 6.4	8.8 ± 5.6	7.6 ± 6.8	0.05
II (mean ± SD)	9.8 ± 5.2	7.5 ± 4.3	6.9 ± 6.2	0.28
III (mean ± SD)	14.7 ± 2.9	5.9 ± 3.5	6.4 ± 5.5	**< 0.001**
IV (mean ± SD)	7.3 ± 2.5	7 ± 4.6	5 ± 3.4	0.11
Total (mean ± SD)	51.9 ± 18	30.8 ± 14.8	25.2 ± 15.8	**< 0.001**

Factor I: emotional factor; Factor II: impulsivity and oppositional behavior abnormalities; Factor III: impulsivity and hyperactivity; Factor IV: attention-deficit disorder.
DLB, dementia with Lewy bodies; ADT, Alzheimer dementia type; SD, Standard deviation. Bold values denote significant differences ($P < 0.001$) .

although they showed increased scores of ADHD symptoms, they could not conclude that the patients with PD enrolled had suffered ADHD from childhood. Further investigation is currently testing that hypothesis [19]. A possible explanation for the differences found between the results observed in our study and those performed in patients with PD could be that we investigated demented patients and that, as frequently occurs with demented patients, an indirect method was used (an informant who knew the patient for at least 10 years) to evaluate preceding symptoms of ADHD in trying to avoid report bias.

In light of these observations, when we evaluate the factorial analysis displayed in Table 4 (which shows that only the impulsivity and hyperactivity factor was significantly higher in patients with DLB), three main observations may be considered: (i) The results appear to support our catecholamine hypothesis. Evidence to reinforce this observation may be drawn from a recently published animal study in which the blockage of the NA alpha(2A)-receptors with yohimbine in the prefrontal cortex developed impulsivity, hyperactivity and poor working memory symptoms, whilst the increase in the alpha(2)-receptors agonists with guanfacine, methylphenidate and atomoxetine improved in the prefrontal cortex NA and DA activity with clinical reduction in impulsivity and hyperactivity. This observation provides a molecular physiopathology that allows us to explain our clinical observations in human beings [20]. (ii) The second observation drawn is the absence of differences in the other factors analyzed amongst the groups, particularly in Factor IV (attention-deficit disorder) (Table 4). This decreases the possibility of a biased association of ADHD and DLB secondary to recall bias from patient informants. (iii) The third observation concerns the differences observed in Factor I (emotional), which is higher in patients with DLB when compared with the other groups analyzed. Despite that the differences were not significant (P value 0.05), this clinical tendency may also be related to the impairment of NA and DA activity, as previously demonstrated [21], thereby contributing to our initial catecholamine hypothesis. However, this third issue would require further investigation.

Another observation that may pathophysiologically associate both diseases is the cholinergic denervation demonstrated in DLB as well as in ADHD, which involves the neuronal nicotinic acetylcholine receptors (nAChRs) that play a main role in the pathophysiology of ADHD as well as in DLB [22].

ACh has an important role in modulating attention [22,23]. Indeed, the attentional processes depend on the integrity of cholinergic system in the prefrontal cortex–nucleus basal Meynert pathway and intracortical connections to posterior parietal cortex and occipital lobe [22].

Dementia with Lewy body is characterized by a frontosubcortical pattern of cognitive impairment with deficit in executive function, attention and verbal fluency and is probably related to a prominent frontal cholinergic deficit that includes a reduction in nicotinic receptors [24]. The higher psychotic symptoms (visual hallucinations and delusions) and severe visuospatial dysfunction reported in the disease may also be related to greater reductions in cholinergic activity in temporal and parietal lobes [25].

In ADHD, cholinergic activity in CNS and particularly nicotinic receptors seems to have an important role in pathophysiology. This is further demonstrated by the strong association that has been found between ADHD and cigarette smoking, where acute nicotine improves behavioral inhibition in adolescents with ADHD [26].

It should be noted that neurotransmitters other than NA, DA and Ach, which have yet to be investigated, may play a role in the development of the abnormalities observed.

Finally, another explanation for our findings could be that both diseases may be a single illness that progresses as a continuum from ADHD manifested in childhood and goes on to appear in adulthood as DLB when neuronal loss and gliosis in the substantia nigra, locus coeruleus and nucleus basalis of Meynert occur [19]. A problem with this hypothesis is that it remains unclear as to why low DA levels in ADHD are not initially associated with Parkinson-like or DLB symptoms. Robbins and Everit [27] suggested that DA levels are not low enough to develop PD or DLB symptoms until DA is depleted by approximately 75–80%, whilst in patients with PD or DLB, who do not have DA, DA synthesis and availability is intact in ADHD. As the disorder progresses, a depletion in DA neurons develops PD or DLB diseases.

We consider that the major strengths of this study are the sample size of participants included in the analysis and that the study was based on a series of prevalent DLB cases and well-defined population controls, thereby avoiding referral bias. Nevertheless, our study may contain other types of bias or confounding factors. For example, ADHD may be more common in individuals with a certain personality type that may be linked to DLB. Additionally, ADHD exposure could be a reflection of DLB not yet recognized (preclinical DLB). This is why we strictly consider as adult ADHD symptoms only those patients who presented symptoms that fulfilled the DSM-IV criteria adapted for the identification of adult patients with ADHD and also

when patients obtained a cutoff score of the Spanish Wender Utah Rating Scale of 32 points or higher during their infancy, to avoid premorbid symptoms of DLB.

Recall bias inherent to case–control studies and the manner in which exposure was determined may be one of the most relevant factors to consider. We tried to overcome this limitation by using validated tests to look for adult ADHD symptoms and by blinding the objective of the study to the two neurologists responsible for obtaining the exposure in all three groups of participants. Finally, a limitation of these results may be that they come from an HMO and a selection bias could exist; however, comparison of this HMO population with the Autonomous City of Buenos Aires census data demonstrates that it is representative of the general population in demographic, ethnic and socioeconomic characteristics. It is also worth mentioning that the HMO covers a wide area from the Autonomous City of Buenos Aires; for this reason, results obtained may be cautiously extrapolated to the Autonomous City of Buenos Aires.

In conclusion, the association between ADHD symptoms and DLB that we observed may be explained by a common neurotransmitter pathway dysfunction in both entities. We hypothesized that a common process is involved in both illnesses: ADHD in the initial state of that dysfunction that progresses to DLB in senescence. Whilst there is still no clear explanation for this association, further investigation will contribute to increase our knowledge about both diseases.

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