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Lithium and dementia: A preliminary study

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Abstract

Recent studies have shown that lithium may block the accumulation of amyloid-β (Aβ) peptides and to inhibit the hyperphosphorylation of tau via the inhibition of GSK-3α in the brain of mice. The purpose of the present study is to examine whether lithium could potentially be effective for the prevention of Alzheimer's disease. We investigated the clinical records of 1423 outpatients at a university psychiatric outpatient clinic and classified patients according to the following criteria: (a) absence of a diagnosis of dementia, (b) age 60 years or older, and (c) lithium had been prescribed and/or was currently prescribed. We compared these patients with randomly selected age and gender matched control group who had never been prescribed lithium. Despite no significant difference in MMSE scores between the lithium group, which consisted of patients receiving lithium treatment, and the control group, those who had previously received lithium and/or were currently prescribed lithium had significantly better MMSE scores than the control patients. The findings provide partial evidence to support the contention that lithium could offer hope as a preventive treatment for Alzheimer's disease. Further prospective studies with a large number of patients are warranted to investigate this potentially important effect.

Keywords: Dementia; Lithium; Prevention

1. Introduction

Recently, lithium has been reported to block the accumulation of amyloid-β (Aβ) peptides in the brain of mice that overproduce amyloid precursor protein (APP)(Phiel et al., 2003). The target of lithium in this respect is glycogen synthase kinase-3α (GSK-3α)(Phiel et al., 2003). In addition, lithium has been shown to inhibit the GSK-3β-mediated phosphorylation of tau (Phiel and Klein, 2001) which, in its hyperphosphorylated state, is the main component of neurofibrillary tangles. Therefore, if these findings could be extrapolated to the human brain, lithium could be considered for the prevention of Alzheimer's disease. Other findings such as lithium effects on the production of brain-derived neurotrophic factor (BDNF)(Hashimoto et al., 2002) and B cell lymphoma protein-2 (bcl-2)(Chen et al., 1999) and the enhancement of hippocampal neurogenesis(Chen et al., 1999, 2000; Kim et al., 2004) further support this possibility.

Very recently, Dunn et al. (2005) reported the results of a case-control study where they found no effects of lithium on dementia. In the present study, we report the results of historical cohort study regarding the cognitive functioning of psychiatric elderly outpatients with and without lithium exposure.

2. Methods

2.1. Subjects

We investigated the clinical records of 1423 outpatients at a university psychiatric outpatient clinic and identified individual patients according to the following criteria: (a) no initial diagnosis of dementia, (b) age 60 years or older, and (c) lithium had been previously prescribed and/or was currently prescribed. This is a historical cohort study.

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2.2. Patients currently receiving lithium v.s. controls

First, we hypothesized that patients currently receiving lithium therapy may have better memory and may be less likely to suffer from dementia. To investigate this hypothesis, we collected all the patients corresponding to the above (a), (b), and (c) criteria where lithium was currently prescribed. As a result, 30 patients (20 females and 10 males) were included as lithium group. The mean age of the group was 68.4±5.2 years and their initial ICD-10 psychiatric diagnoses included; one for F23 [acute and transient psychotic disorders], 16 for F31 [bipolar affective disorder], 1 for F32 [depressive episode], and 12 for F33 [recurrent depressive disorder]. The mean lithium dose of the group was 503±206 mg/day and the mean lithium level was 0.66±0.18 mmol/L. The mean duration of lithium treatment was 48.4±51.8 months. Medication included; antidepressants (N=13), antipsychotics (N=6), benzodiazepines (N=21) and other mood stabilizers (N=3).

A statistician (N.I.) randomly selected a group of gender and age (within 3 years of difference) matched control patients from the remaining 1393 patients with the condition who were not taking lithium and whose initial diagnoses were *not* of dementia. Consequently, the control group consisted of 27 patients (17 females and 20 males) with a mean age of 69.1 ±5.8. This group's initial psychiatric diagnoses included; 4 for F22 [persistent delusional disorders], 2 for F31, 10 for F 32, 8 for F33, and 1 for F41 [other anxiety disorders]. The patients received antidepressants (N=15), antipsychotics (N=5), benzodiazepines (N=20) and other mood stabilizers (N=3).

2.3. Patients with the history of lithium treatment v.s. controls

Secondly, we hypothesized that patients with the history of lithium treatment (at present or in the past) may have better memory and would be less likely suffer from dementia. To investigate this hypothesis, we collected all patients corresponding to the abovementioned criteria (a), (b) and (c) who were either currently on lithium or who had ever had lithium in the past. As a result, an additional 6 patients were added to the lithium group from the group not currently on lithium but on lithium in the past. Consequently, 36 patients (25 females and 11 males) were included as lithium history group. The extracted 6 patients had a history of relatively short lithium treatment (2 for 1 month, 1 for 2 months, 1 for 3 months, 1 for 6 months, 1 for 7 months) but the treatment had been close to this study. The mean age of the group was 68.5±5.5 years and psychiatric diagnoses included; one for F23 [acute and transient psychotic disorders], 16 for F31 [bipolar affective disorder], 3 for F32 [depressive episode], and 16 for F33 [recurrent depressive disorder] according to ICD-10. Medication included; antidepressants (N=10), antipsychotics (N=9), benzodiazepines (N=26) and other mood stabilizers (N=4). The remaining control group consisted of 21 patients (12 females and 9 males) with a mean age of 70.0±6.3. There was no significant difference in age between the groups. This group's psychiatric diagnoses included; 4 for F22 [persistent delusional disorders], 2 for F31, 9 for F 32, 5 for F33, and 1 for F41 [other anxiety disorders]. The patients had received antidepressants (N=18), antipsychotics (N=2), benzodiazepines (N=15) and other mood stabilizers (N=2).

Table 1
The comparison between currently receiving lithium group and control group

	Currently receiving lithium group	Control group	p
Number	30 (F, 67%)	25 (F, 64%)	N.S.
Age	68.4±5.2	69.1±5.8	N.S.
Bipolar disorders	16 (53%)	2 (8%)	p=0.0002
MMSE score	27.4±2.5	26.3±3.3	N.S.
HAM-D score	3.8±5.0	6.3±5.0	p=0.042

2.4. Procedures

On our request, psychiatrists who were blind to the purpose of the present study measured cognition and memory using the Mini-Mental State Examination (MMSE) as a routinely administered measure for both groups. Specifically, the occurrence of dementia was determined using ICD-10. In addition, depressive state was identified with the Hamilton Rating Scale for Depression (HAM-D) in order to exclude depressive pseudo-dementia. Since these tests were routinely performed in our hospital, informed consent was obtained from the patients as such, and both psychiatrists and patients who were blind to the specific purpose of the present study.

2.5. Statistical analysis

To investigate the two hypotheses, MMSE scores were compared between lithium group and the control group and between lithium history group and the control group by unpaired t-test. Additionally, age and HAM-D scores were compared by unpaired t-test. The distribution of psychiatric diagnoses and medication were compared between individual 2 groups by χ^2 test. If necessary, further analyses were performed by multiple regression analysis.

3. Results

3.1. Patients suffering from dementia

At the time of the present study, two patients were subsequently diagnosed with Alzheimer's disease (F00) during psychiatric treatment and were placed on maintenance 5 mg/day of donepezil. One was a 65-year-old female patient whose initial diagnosis was F32 [depressive episode] while another was a 72-year-old male patient whose initial diagnosis was F33 [recurrent depressive disorder]. Neither of these patients were receiving lithium at the time of this study but one had a history of lithium therapy. The data and analytic results excluding these two patients are presented as follows.

3.2. Patients currently receiving lithium v.s. controls

With regard to the comparison between lithium and control groups, there was no significant difference in MMSE scores or

Table 2
The comparison between lithium history group and the control group

	Lithium history group	Control group	p
Number	35 (F, 71%)	20 (F, 55%)	N.S.
Age	68.4±5.5	70.3±6.4	N.S.
Bipolar disorders	16 (46%)	2 (10%)	$p=0.0003$
MMSE score	27.6±2.4	25.8±3.3	$p=0.021$
HAM-D score	4.6±5.5	5.6±4.4	N.S.

in HAM-D score (Table 1). Therefore, the first hypothesis was not supported.

3.3. Patients with the history of lithium treatment v.s. controls

Secondly, regarding the comparison between lithium history group and the control group, the analyses found that mean MMSE score was significantly different between the lithium and control groups but there was no significant difference in mean HAM-D score (Table 2). Further analyses were performed due to significant differences in psychiatric diagnoses ($\chi^2=23.3$, $p=0.0003$) particularly the presence of bipolar disorder, although the type of medication other than lithium was not significantly different between lithium and control groups. We used multiple regression study investigate the influence of a bipolar diagnosis and exposure to lithium as independent variables, with MMSE scores as the dependent variable. The overall regression equation was significant ($F=3.31$, $p=0.045$) as was a history of lithium treatment ($t=-2.57$, $p=0.013$), but the presence of bipolar diagnosis did not predict significant variance in MMSE scores. Therefore, the second hypothesis was supported.

Even if the two patients suffering from dementia with donepezil treatment were included, MMSE scores were significantly better in lithium history group than in the control group and the lithium history significantly predicted MMSE scores by multiple regression analysis.

4. Discussion

Although there was no significant difference in MMSE scores between the 'currently receiving' lithium group and the control group, when combined with those who had a history of lithium exposure, the treated patients demonstrated significantly greater MMSE scores compared to the control patients. The difference between the lithium group and the lithium history group was the addition of 6 patients who had been treated but were not receiving lithium at the time of the study. Although this addition might have somewhat impaired the matching quality with the remaining control patients, with the exception of psychiatric diagnoses, their patient characteristics were not significantly different. Furthermore, as the patients had discontinued lithium treatment not long before the study, the lithium effects may have persisted to some extent. Actually, there was no significant correlation between duration of lithium treatment and MMSE scores in the lithium treated group. Another possibility is that the lack of difference between between the 'currently receiving' lithium group and the control group on MMSE scores could be a power issue. For the given effect size (means of 27.4 and 26.3), SD (2.5, 3.3), sample size (30 and 25), and alpha (0.050, two-tailed), the study will have 0.281 (28.1%) to yield a statistically significant result. This means that 28.1% of studies would be expected to yield a significant effect, rejecting the null hypothesis that the two group means are equal. To obtain the power of 80%, the sample size (if equal number for both groups) should be 113. On the other hand, regarding the comparison of patients with the history of lithium treatment v.s. controls, for the given effect size (means of 27.6 and 25.8), SD (2.4, 3.3), sample size (35 and 20), and alpha (0.050, two-tailed), the study will have power of 62.8% to yield a statistically significant result. We could not, however, recruit more controls in our data settings because of the lack of appropriate controls whose initial diagnoses were *not* of dementia. This is the limitation of the present study and the results should be considered as a preliminary one.

Pachet and Wisniewski (2003) reviewed the recent literature relating to lithium exposure and cognition and suggested that lithium may be associated with mild impairment in psychomotor speed and verbal memory. As the authors pointed out, however, there were numerous methodological flaws in this area of research. The impairments, if any, might have been due to bipolar disorder itself. To investigate this possibility, drug-free euthymic patients would be ideal, but actually scarce (Martinez-Arán et al., 2004). In any case, bipolar disorder is increasingly recognized as an illness that may progress to impairment in neurocognitive functioning and cell loss in cortical and limbic brain regions whereas lithium has been shown to exert neuroprotective effects in vitro and to stimulate neurogenesis in the hippocampus (Bauer et al., 2003). Although Dunn et al. (2005) performed a case-control study, they unexpectedly found that patients who received lithium had a higher risk of a diagnosis of dementia compared with those who did not.

Although this study is preliminary and the effect seems to be modest, its strength lies in the fact that both patients and rating psychiatrists were blind to the purpose of the study. With this in mind, the finding that lithium treatment history rather than having bipolar disorder resulted in significantly better MMSE scores provides at least partial support for the notion that lithium could offer hope as a preventative treatment for dementia. Further prospective studies with a large number of patients are warranted to investigate this important effect.

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