

# Severe agitation in severe early-onset Alzheimer's disease resolves with ECT

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**Abstract:** Dementia-related behavioral disturbances are mostly treated with antipsychotics; however, the observed beneficial effects are modest and the risk of serious adverse effects high. We report the case of a 57-year-old woman with severe early-onset Alzheimer's disease and severe agitation, whom we treated with electroconvulsive therapy (ECT). A significant clinical improvement was achieved over eight ECT sessions, which were tolerated well without cognitive worsening, and lasted approximately 3 months. Our case demonstrates the safe and effective use of ECT in pharmacotherapy-resistant severe agitation in Alzheimer's disease. The risk–benefit profile of ECT for dementia-related agitation should be further investigated in clinical trials.

**Keywords:** dementia, electroconvulsive therapy, cognition, emotional distress, disinhibition.

## Introduction

Agitation, referring to a syndrome involving emotional distress, excessive psychomotor activity, aggression, irritability, disinhibition, and/or vocal disruptive behaviors unexplained by apparent needs, or confusion,<sup>1,2</sup> is a very common phenomenon in the course of dementia.<sup>3–5</sup> It can afflict patients at any level of dementia severity, but it occurs particularly in middle to later stages.<sup>3,6</sup> Agitation and resulting behavioral disturbances are closely associated with impairment in quality of life and more rapid cognitive decline on the part of the patient, caregiver distress, an increased likelihood of institutionalization, and increased health care costs.<sup>7</sup>

Trials of clinical management often combine nonpharmacological behavioral interventions and pharmacotherapy. Nonpharmacological strategies, especially multisensory stimulation therapy, seem to be promising,<sup>8</sup> yet evidence in support of their efficacy is still limited,<sup>9</sup> and there is insufficient research for severely impaired patients. Pharmacotherapy usually involves psychotropic medication – mostly antipsychotics; however these show only modest benefits compared with placebo.<sup>10,11</sup> Moreover, adverse effects of antipsychotics, such as extrapyramidal symptoms and excessive sedation, can be particularly dangerous in demented patients and can outweigh the moderate improvement of agitation symptoms,<sup>8</sup> emphasizing the need for other treatment options for dementia-related behavioral disturbances. It is also noteworthy that there is a definite need for medications with regulatory approval for the indication of management of agitation in patients with dementia, in most countries.

Electroconvulsive therapy (ECT) is regarded as a highly efficient and safe treatment option in severe psychiatric disorders, with only few adverse effects. Despite very rare serious adverse events, cognitive adverse effects in the elderly, including retrograde and anterograde amnesia, are common. Especially in patients with preexisting cognitive impairments, an acute cognitive deterioration occurs more often, but these impairments are reversible within weeks.<sup>12</sup> In numerous studies, the effectiveness and

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safety of ECT was confirmed for demented patients who also suffered from depression.<sup>12–18</sup> The evidence supporting the use of ECT for the treatment of agitation and aggression in dementia is limited to several case reports,<sup>19–22</sup> two case series,<sup>23,24</sup> and one recent study<sup>25</sup> but is clearly suggestive of benefit for this indication.<sup>26</sup>

## Case

Here, we report a case of successful use of ECT in a patient with severe early-onset Alzheimer's disease and severe agitation, after other nonpharmacological and pharmacological interventions were exhausted.

The patient was a 57-year-old, right-handed woman with a 4-year history of rapid progressive dementia of Alzheimer type, which was previously diagnosed outwards by neuropsychological examination. The diagnosis was confirmed by magnetic resonance imaging, fluorodeoxyglucose positron emission tomography, and examination of cerebrospinal liquid with measurement of dementia parameters. Her psychiatric history included two depressive episodes 26 and 18 years previous, following critical life events, which remitted in the course of months without specific therapy. She was admitted to our clinic for evaluation and treatment of severe behavior disturbances, including severe restlessness, yelling, crying, refusal to eat and drink, physical aggression, and resisting care, which made further caretaking of the patient at home by family members impossible. On hospital admission, she exhibited highly agitated behavior with anxiety, near-continuous pacing, crying, and repetitive local outbursts, and could not be redirected. She attempted hitting unit staff during washing and feeding. Whether psychotic symptoms were partly responsible for the observed behavioral disturbances remained unclear. On the Pittsburgh Agitation Scale (PAS), which rates the severity of four behavior groups (aberrant vocalizations, motor agitation, aggressiveness, and resisting care) on a scale of 0–4<sup>27</sup> with higher scores indicating more severe agitation, she scored 11 (out of 16) points.

Verbal communication with the patient and neurocognitive evaluation was substantially hindered by impairment of language comprehension. The patient was not able to perform specific neuropsychometrics, like the Mini-Mental State examination. She had difficulties falling and staying asleep and failed to assist in performing activities of daily living.

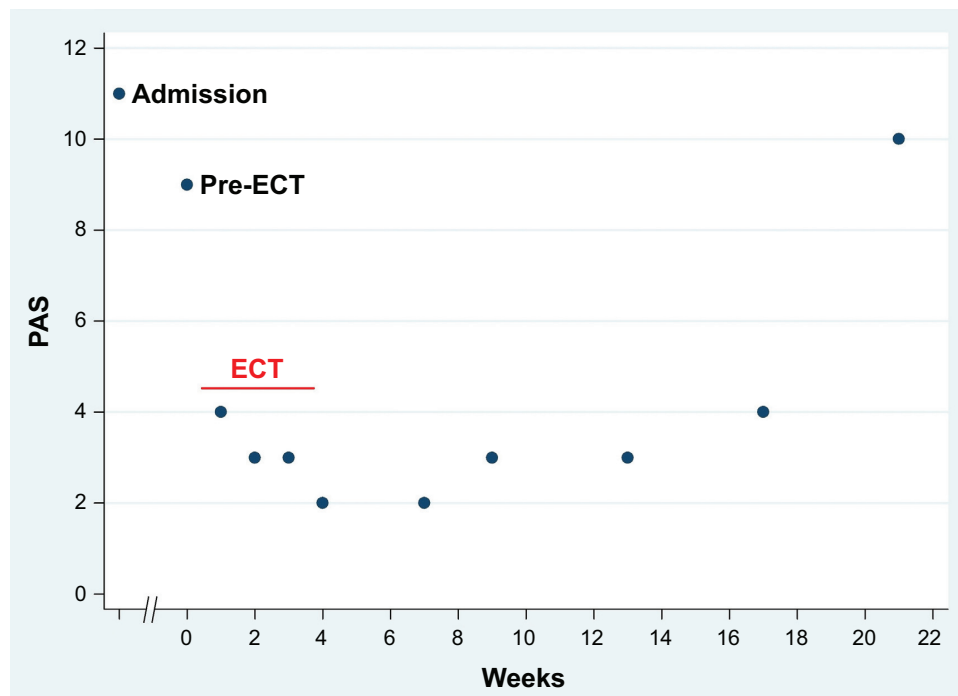
Her medication on admission included the acetylcholinesterase inhibitor rivastigmine patch (9.5 mg/d) and antipsychotic agent quetiapine (50 mg/d). Complete blood count, electrolytes, thyroid, liver, and kidney function tests, urinalysis, electrocardiogram, and physical exam were all normal.

Her agitation symptoms proved unresponsive to combined behavioral therapy. Multiple trials of various psychopharmacologic agents were also ineffective: no improvement could be observed with quetiapine at increased doses (up to 175 mg/d), risperidone (up to 2.5 mg/d), melperone (up to 100 mg/d), and pipamperone (up to 80 mg/d). In due consideration of depressive episodes in her medical history, we started an antidepressive combination therapy with sertraline (200 mg/d) and mirtazapine (30 mg/d), which induced an improvement of sleep but no decrease in agitated behavior. Treatment with lorazepam (up to 4 mg/d) brought about a temporary affective loosening, which lasted only 4 days.

After 9 weeks in our hospital, ECT was initiated. At this time, the patient was receiving rivastigmine (9.5 mg/d), sertraline (200 mg/d), and mirtazapine (30 mg/d). Due to her inability to give informed consent, her daughters – who were also her legal guardians – agreed to the treatment, after detailed information and discussion.

To potentially minimize reversible cognitive adverse effects of ECT we decided to use right unilateral electrode placement, dose titration (ie, evaluation of the patient's individual seizure threshold), a treatment frequency of two sessions per week, a pulse width of 0.25 ms, and S-ketamine for anesthesia.<sup>28,29</sup> ECT was administered with a Thymatron® IV device (Somatics, LLC, Lake Bluff, IL, USA). Weight-adjusted S-ketamine (~1.2 mg/kg) was used for anesthesia induction, followed by succinylcholine for muscle relaxation. The seizure threshold was determined at the first treatment (<50 mC). Following sessions were conducted at 150 mC (second – fifth session) and 200 mC (sixth – eighth session). Sufficient seizures, with respect to quantified ictal parameters, were achieved.<sup>30</sup> PAS scores were determined weekly to assess the clinical severity of agitation symptoms.

A marked difference in the clinical presentation of the patient was noted after just two ECT treatments: the patient was noticeably less agitated, and crying occurred only for short episodes. Her improvement continued throughout the entire course of eight treatments given over 26 days. She stopped yelling and crying, showed no aggression, smiled spontaneously, and was more redirectable. The patient continued to pace, but she was able to sit and lay down for longer periods. She showed significant reduction in her total PAS score from baseline (11 points) during and after ECT (2 points) (Figure 1). A worsening of cognitive functions under ECT was not observed. On the contrary, the patient started to eat and drink by herself and was more cooperative in other daily care activities, like washing and dressing. Family members claimed to be able to verbally and nonverbally



**Figure 1** PAS scores before and during ECT course and in the follow-up period.

**Note:** Maximum PAS score is 16.

**Abbreviations:** ECT, electroconvulsive therapy; PAS, Pittsburgh Agitation Scale.

communicate better with the patient (eg, she followed lowest level instructions).

The ECT treatment was tolerated well, with signs of headache after the first three sessions. In the third week of treatment, a single self-limiting, spontaneous generalized seizure was observed.

The patient was discharged 5 days after the last ECT treatment. The improvement in agitation symptoms was present on hospital discharge. The guardians refused maintenance ECT since the patient moved away from our clinic to be taken care of by other family members. Katamnestic data on clinical presentation and behavioral symptoms of the patient were collected, by caregiver interviews, every 2 weeks over a period of 4 months after hospital discharge. Based on this information, PAS scores were determined. The improvement of agitation symptoms initiated by ECT lasted for approximately 12 weeks without any additional therapy other than rivastigmine, sertraline, and mirtazapine (Figure 1). In the follow-up period, two further self-limiting, spontaneous generalized seizures were reported.

## Discussion

The etiology of behavioral disturbances in dementia is poorly understood. Abnormalities of neurotransmission

(eg, gamma aminobutyric acid [GABA]ergic and dopaminergic dysfunction, cholinergic and serotonergic deficiency, and noradrenergic hyperactivity) have been implicated to play a role in behavior modulation, promoting agitation and aggression.<sup>31</sup> It has been previously postulated that ECT may mediate its beneficial effects through its known enhancement of GABAergic transmission and inhibition.<sup>24</sup> It is also presumable that the efficacy of ECT relies upon its antidepressant and antipsychotic features since agitation and aggression are frequently associated with psychotic symptoms, and the underlying cause of behavioral disturbances in demented patients might be an agitated mood disorder. Clinically, it is very challenging to establish the presence or absence of a mood disorder in a highly agitated patient with severe Alzheimer's disease who cannot be interviewed due to impairment of language comprehension. In our case, the patient had a history of two depressive episodes in her past, and the clinical improvement initiated by ECT now persisted for approximately 3 months. The overall time course of the treatment effect was thus comparable with ECT applied in major depression.<sup>32</sup> In previous case reports on ECT use for dementia-related agitation in patients without a history of affective disorders, the time to relapse varied over a wide range, from 2 weeks<sup>21</sup> to 1 year.<sup>20</sup> Successful application of maintenance ECT as

well as successful reapplication of ECT in relapsed patients has been reported repeatedly.<sup>19–23</sup>

The patient described here tolerated the ECT treatment well without any adverse effects going beyond headache. The occurrence of spontaneous seizures was considered to be a result of extensive neurodegeneration in the course of Alzheimer's disease and not an adverse effect of the treatment since ECT is known to have considerable anticonvulsant effects<sup>33–36</sup> and not to cause epilepsy.<sup>37</sup> Our observation of rapid effectiveness and good overall tolerance of the procedure corroborates previous reports. The concern of greater long-term cognitive adverse effects of ECT in patients with severe dementia<sup>17</sup> is not supported by any evidence so far, considering that in most of the reported cases, patients suffering from behavioral disturbances were in the last stage of dementia. Furthermore, at least some evidence exists that in mild Alzheimer's disease, most patients do not suffer from long-term cognitive adverse effects and some even improve, which has been attributed to an amelioration of pseudodementia.<sup>12</sup>

Our case demonstrates that ECT can be safely and effectively used in treating pharmacotherapy-resistant severe agitation in early-onset Alzheimer's disease in its last stage, without any recognizable worsening of cognitive functions. Implementation of randomized and controlled trials with ECT seems justified, to outline potential beneficial effects of this treatment compared with other clinical management strategies of dementia-associated agitation and aggression.

## Disclosure

The authors report no conflicts of interest in this work.

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