

## Short Communication

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# Mining Clinical Case Reports to Identify New Lines of Investigation in Alzheimer's Disease: The Curious Case of DNase I

Neil R. Smalheiser\*

*Department of Psychiatry, University of Illinois College of Medicine, Chicago, IL, USA*

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**Abstract.** Mining the case report literature identified an intriguing, yet neglected finding: Deoxyribonuclease I (DNase I) as a possible treatment for Alzheimer's disease. This finding is speculative, both because it is based on one patient, and because the underlying mechanism(s) of action remain obscure. However, further literature review revealed that there are several plausible mechanisms by which DNase I might affect the course of Alzheimer's disease. Given that DNase I is an FDA-approved drug, with extensive studies in both animals and man in the context of other diseases, I suggest that investigation of DNase I in Alzheimer's disease is worthwhile.

**Keywords:** Case reports, Deoxyribonuclease I, incidental findings, literature-based discovery, lucidity, lucid dreaming, drug repurposing

## INTRODUCTION

The Alzheimer's disease (AD) field comprises more than 100,000 articles indexed in PubMed. Sometimes it seems that every possible hypothesis has already been published! Yet, since there still exist no effective treatments for AD patients, no generally accepted prevention protocols, and no clear etiology, searching for new lines of investigation may be warranted.

The present paper is the first of a series that will employ a variety of different literature-based discovery techniques. Here, I examine clinical case reports concerning AD, looking for unexpected, surprising, or serendipitous observations which 1) in my judgment, are scientifically intriguing, 2) have apparently not been followed up, 3) that suggest new potential

treatments, causes, or risk factors of AD, and 4) that are ripe for further investigation.

## METHODS

A PubMed query (Alzheimer AND case reports [publication type]), carried out in October 2018 retrieved 2,788 articles. To focus attention on articles that are particularly likely to report unexpected, surprising, or serendipitous observations, a series of more restricted queries were carried out (Table 1). Retrieved articles of potential interest were classified as belonging to one of the following categories:

- Treatments that produced improvement in AD patients
- Multi-modal, lifestyle, or behavioral interventions
- Incidental improvement of an AD patient when treated for some other condition
- Areas of preserved function in AD patients

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\*Correspondence to: Dr. Neil R. Smalheiser, Department of Psychiatry MC912, University of Illinois at Chicago, 1601 W. Taylor Street, Chicago, IL 60612, USA. Tel.: +1 312 413 4581; E-mail: neils@uic.edu.

- Conditions that masquerade as, or can be misdiagnosed as, AD
- Risk factors for development of AD
- Reports of adverse effects of drugs given to AD patients

## RESULTS AND DISCUSSION

Each of the categories of case reports yielded relevant articles which were analyzed further to learn what follow-up (if any) has appeared in the AD literature, and what scientific rationale (if any) might support them. Among hundreds of articles examined, a short-list of particularly intriguing reports were identified and examined further. Only the two most provocative examples will be discussed here.

1. A series of reports by Normann et al. indicated that AD patients commonly demonstrate temporary periods of lucidity during routine interactions with their family and caregivers [1–4]. Moreover, they suggest that lucid periods can be fostered, if not directly elicited, by controlling the nature of the conversations with the patient, e.g., by providing positive support while avoiding making demands on the patient [1–4]. This is in contrast to the general description of lucidity in the medical literature as a weird phenomenon that occurs in seriously impaired individuals just prior to death [5–7]. The reports by Normann et al. raise the possibility that behavioral or pharmacological interventions may predictably increase the occurrence of lucid intervals in AD patients. It is intriguing that the anticholinesterase inhibitors galantamine and donepezil, which are among the few approved drugs for AD, enhance lucid dreaming in healthy individuals in a dose related fashion [8–10].

As with awake lucidity in AD patients, lucid dreaming can, at least in part, be fostered using behavioral induction techniques [10]. In turn, these parallels raise two questions: a) Is there a connection between lucidity and self-awareness in awake AD patients, and the phenomenon of lucid dreaming in normal individuals—whereby people are aware of the fact that they are dreaming? b) Might the effects of galantamine and related anticholinesterase drugs on AD patients occur, at least in part, by increasing the incidence or duration of periods of awake lucidity? The study of lucid dreaming is amenable to objective measurement and even to randomized controlled trials [9], so it may be interesting to explore further whether lucid dreaming can provide an insightful model for lucid intervals in awake AD patients.

2. Another set of intriguing case reports involves FDA-approved drugs that were being repurposed as possible treatments for AD. Twenty-three articles were found describing treatments that produced improvement in AD patients, including bexarotene, amantadine, nicotine, and ketogenic diet and related ketone supplements. However, most of these FDA-approved agents have not been neglected by the field (e.g., [11]).

The single exception appears to be a most surprising report which used orally administered deoxyribonuclease I as adjunctive therapy: A patient with severe AD with deterioration of functioning was given 40 mg of human recombinant DNase I (1500 KU/mg) three times a day in conjunction with continued memantine therapy (10 mg daily), and apparently produced rapid and lasting improvement of cognition [12].

Table 1  
PubMed queries examined in this study

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Alzheimer AND case reports[pt] AND (surprise OR surprising OR surprisingly), 15 reports
Alzheimer AND case reports[pt] AND (unexpected OR unexpectedly OR counter-intuitive OR counter-intuitively OR nevertheless OR nonetheless), 34 reports
Alzheimer AND case reports[pt] AND (amazing OR amazingly OR dramatic OR dramatically OR fantastic OR fantastically OR breakthrough OR miracle OR miraculous OR miraculously), 38 reports
Alzheimer AND case reports[pt] AND (reversal OR reversible OR improved OR improvement), 203 reports
Alzheimer AND case reports[pt] AND (fortuitous OR fortuitously OR “by accident” OR accidental OR accidentally OR serendipitous OR serendipitously OR “by mistake” OR mistaken OR mistakenly), 53 reports
Alzheimer AND case reports[pt] AND (unusual OR unusually OR anomalously OR anomalously), 79 reports
Alzheimer AND case reports[pt] AND potential treatment, 62 reports
Alzheimer AND case reports[pt] AND (recover OR recovery), 26 reports
Alzheimer AND case reports[pt] AND (paradox OR paradoxical OR paradoxically), 7 reports
Alzheimer AND case reports[pt] AND (folk OR unconventional OR unorthodox OR new-age OR holistic OR counter-culture OR counter-cultural), 1 report
Alzheimer AND case reports[pt] AND preserved, 81 reports
Alzheimer AND case reports[pt] Publication Date 1950-1990 inclusive.

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Queries were entered into pubmed.gov during October and November 2018.

The rationale for trying this enzyme is not specified in the paper—its FDA-approved use is to reduce viscosity of secretions in cystic fibrosis patients! The authors mention that extracellular DNA may be involved in metastasis of cancer cells, but they made no explicit hypothesis regarding the role(s) if any of extracellular DNA in AD. The authors, Victor and George Tetz, are affiliated with TGV-Laboratories, a firm developing new treatments for several medical diseases including cystic fibrosis. They had previously published studies of DNase I on microbial biofilms, which probably explains their familiarity with deoxyribonuclease I, and had published a short abstract stating that DNase I given to mice partially protected them from graft-vs-host disease [13]. They also head the non-profit Human Microbiology Institute, which studies the role of the human microbiota in human health and lifespan. The authors were awarded U.S. patent 9,845,461 to employ DNase I as an anti-cancer agent. However, to my knowledge, they do not appear to have a commercial or proprietary interest in DNase I in AD.

To provide further context, I looked for registered clinical trials of DNase I listed in clinicaltrials.gov. Several trials evaluate topical DNase I in ocular diseases, and several evaluate inhaled or intranasal DNase I in cystic fibrosis and other pulmonary diseases. A variety of trials employ DNase I together with tissue-type plasminogen activator for treating pleural infections. Other conditions such as myocardial ischemia were also studied. No trials involved oral administration.

Of studies of DNase I carried out in experimental rodent models *in vivo*, endogenous DNases participate in the destruction of extracellular DNA released by cell damage, apoptosis, necrosis or neutrophil release into the blood and other tissues [14], and exogenous DNase I can reduce elevated levels of extracellular DNA found in pathological conditions. Systemic administration of DNase I can reduce cancer metastases [15–18]. DNase I does not appear to inhibit growth of cancer cells *in vivo* when given alone, but one report found that it was effective when given with proteases [19]. Systemic DNase I can protect intestinal injury and survival during sepsis [20–22], tissue damage following renal ischemia [23], and myocardial damage following myocardial ischemia [24–26]. Thus, evidence supports the use of DNase I in both animals and humans, at least for conditions in which extracellular DNA present in bodily fluids may be involved.

The Tetz and Tetz case report has not been cited (except quite incidentally in a paper on biophysics of amyloidogenesis [27]) or apparently followed-up by anyone as yet. This apparent neglect may reflect: a) the unknown mechanism(s) of action, b) uncertainty whether orally administered DNase I is bioactive and safe, c) the origin of the report coming from a non-academic research group, and d) the fact that only a single patient is described.

#### *Possible mechanisms of action*

As far as possible mechanisms of action are concerned, a further examination of the literature reveals several places where extracellular DNA may have an influence on the course of AD:

First, circulating extracellular DNA levels are associated with inflammatory markers [28, 29] and in very old individuals, its levels are predictive of all-cause mortality [29]. Thus, assuming that DNase I given orally remains bioactive and enters the circulation, it may play a role by acting upon extracellular DNA within peripheral tissues.

Second, neutrophil extracellular traps containing DNA have been described within the brain, in both humans dying of AD as well as animal models of AD, where they may play a role in disease progression [30, 31]. Thus, DNase I could potentially act in the brain to “dissolve” neutrophil extracellular traps.

Third, extracellular DNA has been shown to associate with amyloidogenic proteins in a variety of situations. Bacterial DNA fosters formation of amyloid and is a structural component within biofilms [32–36]. Extracellular DNA also binds to proteins such as serum amyloid P [37], alpha-synuclein [38], prion protein [39], and superoxide dismutase [40], and stimulates aggregation or fibril formation. It is well documented that DNA binds to amyloid- $\beta$  peptides, especially those capable of aggregating [41–43], and in turn, amyloid can alter the conformation of DNA itself [44–47]. Jiménez has hypothesized that protein-DNA interactions not only occur but are key to the origin of neurodegenerative diseases [48].

But what is the evidence that extracellular DNA is a constituent of amyloid soluble aggregates or insoluble plaques in the brain? One study by Miklossy reported that bacterial amyloid and DNA are constituents of senile plaques, and in fact that senile plaques have features of bacterial biofilms [49]. The evidence was based upon DAPI staining of plaques and sensitivity to DNase I treatment, as well as *in situ* hybridization studies. Wozniak et al. reported

that herpes simplex type 1 virus DNA is located within amyloid plaques [50]. Their evidence was based upon *in situ* PCR specific for herpes DNA. And, *E. coli* lipopolysaccharide and K99 pili protein were enriched in AD brains; LPS was associated with amyloid plaques, and K99 with neurons; in contrast, *E. coli* DNA detected by sequencing was found equally both in AD and control brains (its localization was not determined) [51]. These studies remain controversial due to the concern that the presence of infectious agents could reflect contamination of postmortem tissues.

Neurons, glial cells, and microglia all secrete exosomes and other extracellular vesicles that contain proteins and RNAs, and at least in other tissues, exosomes have been shown to contain DNA as well (reviewed in [52, 53]). DNA within intact exosomes is resistant to digestion by DNase I, but insofar as exosomes contain A $\beta$ PP as well as beta- and gamma-secretases, and may be involved in the processing, spread, and clearance of amyloid- $\beta$  peptides (reviewed in [54]), any events which accompany rupture or fusion of exosomes might potentially provide another source of extracellular DNA in brain.

To my knowledge, no studies have examined to what extent extracellular DNA released endogenously from neurons or other cell types, whether damaged or healthy, might become associated with soluble amyloid aggregates or insoluble amyloid plaques. This is, in itself, an important research question that deserves investigation, since DNA might be one of the driving factors in the amyloid- $\beta$  cascade, and since DNase I might have inhibitory effects on that target.

Finally, orally administered DNase I might potentially exert its effects within the gut. For example, bacteria within the gut employ extracellular DNA in their physiology [55] and so DNase I would be expected to alter the gut microbiome. This is speculative, of course, but there is increasing appreciation that the gut may play roles in the initiation or pathogenesis of neurodegenerative diseases [56].

### Conclusions

I have discussed two possible new lines of investigation that were mined from the AD case report literature: 1) the idea that the mechanisms underlying lucid dreaming may provide a model for fostering lucid intervals in awake AD patients, and 2) the possibility that DNase I may be an effective new treatment

in AD. Of the two, the latter appears to be more surprising, more testable, more actionable clinically, and thus more promising.

Repurposing of FDA-approved drugs for new indications is especially appealing in AD where no existing drugs have shown great promise. A systematic search for “intriguing yet neglected” case reports identified a case of dramatic improvement in an AD patient given deoxyribonuclease I [12], and further examination confirms that there are potentially several plausible mechanisms of action that might mediate such an effect. In fact, this review of the literature highlights the issue of extracellular DNA affecting progression of AD pathogenesis, whether the DNA arises from circulating DNA, neutrophil extracellular traps, DNA released from neurons and other cell types within the brain, or DNA of infectious agents including bacteria and viruses. To my knowledge, no one has tested in animal models whether DNA is associated with soluble amyloid aggregates or insoluble amyloid plaques, nor if DNase I administered systemically, or by direct administration to the brain, can affect the amyloid cascade and other pathological and cognitive hallmarks of AD pathogenesis. In humans, DNase I was reportedly safe when given orally in the single patient so treated [12]. I suggest that this finding deserves follow up (does oral DNase I even remain bioactive? Does it achieve effective levels in the circulation?), and further testing of oral and/or systemic DNase I in AD patients appears to be justified.

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### CONFLICT OF INTEREST

The author has no conflict of interest to report.

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