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Treating Alzheimer's Dementia With CT-Induced Low-Dose Ionizing Radiation: Problematic, Yet Potential for More Precise Inquiry

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Abstract

This commentary evaluates a recent single-case study by Cuttler et al that posits that a series of computerized tomographic (CT) scans ameliorated symptoms and signs of advanced Alzheimer's dementia in an elderly female patient. The report proposes that CT scanning delivered low-dose ionizing radiation (LDIR) that activated adaptive mechanisms in the brain to induce the effects observed and reported. However, the report evidenced methodologic problems that threaten the validity and value of its approach, stated results, and conclusions. We provide discussion of these issues, with view and intent toward developing more precise investigations of the potential mechanisms and utility of LDIR in treating Alzheimer's dementia and possibly other neurodegenerative disorders.

Keywords

low-dose ionizing radiation (LDIR), computerized tomography (CT), Alzheimer's dementia, methods, post hoc fallacy, hormesis

Introduction

A recent single-case report by Cuttler et al claimed that administration of low-dose ionizing radiation (LDIR) via computerized tomographic (CT) scanning of the brain afforded considerable amelioration of signs and symptoms of advanced Alzheimer's dementia in an 81-year-old female patient.[1] Employing what seems to be implicit ex juvantibus reasoning (note 1), the report asserts that the patient showed notable improvement in memory, speech, movement, and appetite, which are claimed to be due to LDIR induction of adaptive mechanisms. These claims might serve to instigate additional research to study LDIR to advance approaches that are relevant to applications in clinical neurology. But if such findings are to prompt and guide additional studies, then the report (and its methods) should be regarded—and stand—as valid and of value.

Thus, we believe that a key starting point is to examine the methods undertaken, in order to establish the veridicality of findings presented, so as to (1) ensure scientific rigor in investigation, documentation, and reporting, (2) justify additional investment of time, effort, and support for subsequent studies, and (3) ensure that the probity and benefit(s) of such research are sustained. To be sure, there has been, and continues to be controversy about the potential and putative mechanisms of therapeutic benefit incurred by LDIR[2]; a limited number of animal studies and historical reviews have suggested positive health benefits.[2-5] However, we argue that the report by Cuttler et al appears to have a number of methodologic problems that may impede its value to provide adequate evidence to substantiate a role for CT scan-based LDIR to induce empirically significant clinical improvement of signs and symptoms of Alzheimer's dementia. Overall, we believe that the report suffers from 2 fundamental flaws:

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1. Failure to Provide Logical Rationale for the Case Study

Granted, the impetus for repeating CT scanning was likely based upon some perceived improvement in the patient's condition. And the rationale may have been that such interventions might provide sustained—or even increased—improvement in some aspect(s) of the patient's condition (ie, perceived benefit) while incurring only slight, if any, risk of further decrementing her condition (ie, some calculus of benefit vs burden or risk). However, even given these considerations, in any attempt to assess benefit, burden, and harms, it would be important to qualify (if not quantify) perceived changes in condition so as to justify (1) ethically sound continuation of treatment and (2) continuing use of resources and services (that are not futile). Moreover, absent such substantiation, to then offer any such findings as basis for others to engage in similar use of these techniques is (methodologically and therefore ethically) additionally problematic.

In the main, it is not clear (from the report, as published) that the initial CT scan actually produced clinically relevant improvement in the patient's signs and symptoms. Although novel interventions (eg, off-label treatments, use of new techniques) have been and may be initiated from unanticipated and/or unusual outcomes and effects that are apparently observed, as has been the case with the use of LDIR for other applications,[3,4,6] clinical investigation is axiomatically purposed to address, examine, and parse whether purported outcomes/effects are artifactual, confounding, or (therapeutically) real. Moreover, while controls (eg, sham treatment) may not always be possible, some attempt at differentiating artifact/confound from real effect is essential, as is the need to engage in accurate assessment(s) of any effects that are anticipated or evoked (see below for further discussion of evaluative methods).

Although statistical evaluation is ideal, at very least any observed changes should be measured as a percentage of change from an established (preintervention) baseline. Absent this level of (minimal) methodologic rigor, reported outcomes tend to be suspect, if not unsound. In this latter regard, it is of particular concern that clinical safety, dose, and/or effect(s) of employing multiple, sequential CT scans for patients with Alzheimer disease have not been established. The report did not provide an evidence-based rationale for the dosage, duration, or some (description of the reasoning and method of) estimation of the relative benefit, risk, and/or harms of the interventions, and the references cited are not directly relevant to the clinical application of continuous low-dose CT scans in an Alzheimer patient model.[5,6]

2. Lack of Methodological Rigor: Failure to Acknowledge and/or Address Alternate Hypotheses, Confounding Variables, and Potential Biases

As a noncontrolled single-case report, it is important to at least account for, if not specifically address, those factors that could affect the conduct, outcomes, and conclusions rendered. The report fails to acknowledge alternate hypotheses and confounding variables (eg, possible effects of altering the patient's daily routine, enriching the patient's environment via contact with novel surroundings and people, incurring exercise, etc), all of which have been shown to affect cognitive function in persons with dementia.[7] Furthermore, the report's claims of "remarkable improvement"[1] is based solely upon what appears to be weak qualitative evidence as acquired and provided by individuals within—or closely connected to—the patient's family, incurring considerable potential for bias (which was neither addressed nor counterbalanced/controlled). Although the report states that cognitive assessments were conducted, specific information (ie, type of test[s], schedule of pre- vs post-CT scan testing, detailed presentation of testing method, and results) pertinent to and supportive of the rigor, validity, and value of such evaluations was not provided. As a result, the report as published provides little more than anecdote, and we argue it is not representative of a soundly *ex juvantibus* approach but rather is strongly suggestive of evidencing *post hoc ergo propter hoc* reasoning (ie, the post hoc fallacy [note 2]), and as such is controversial, at best, and may be suspected to be spurious, at worst.

Future Opportunities: Toward a Gap Identification, Analysis, and Compensatory Approach

Clearly, a more valid, viable, and therefore valuable (*n-of-one*) approach would have been to (1) note that an apparent change was observed in the patient's condition consequential to a CT scan; (2) justify the subsequent CT scans by attempting to quantify such changes—and any/all other effects—with as much methodologic rigor as possible, (3) account for extraneous and confounding factors, (4) report any quantitatively notable (ie, both positive and negative outcomes/effects) findings, (5) fully identify constraints and limitations, and (6) explicitly state that conclusions to be drawn from such results should remain purely speculative. This would provide a valid basis for consideration of further studies that would be aimed at delimiting impeding and/or potentially confounding factors and elucidating if and to what extent positive therapeutic effect(s) and benefit(s) are—and could be—incurred.

However, there is also question of whether a single-case report, irrespective of how rigorous methods are employed and how scrupulously presented, justifies (or should even prompt) the need for subsequent clinical investigations in the absence of preclinical evidence to provide rationale for possible effects and/or underlying mechanisms. It may be that additional studies in an animal model of Alzheimer's dementia (and perhaps other neurodegenerative disorders) are required to more precisely assess relative and relevant dosimetry of LDIR (that are identical or similar to doses provided

and incurred via CT scanning in humans), effects on cerebral pathology, physiology, cognition and behavior, short- and intermediate-term effects (incurred via various schedules of repetitive dosing), and time course and duration of any observed changes and outcomes.

Therefore, perhaps the best route forward would be to (1) continue animal studies and (2) engage a more well-conceived, methodologically rigorous investigator-initiated research study of CT-provided LDIR effects on symptoms and signs of Alzheimer's dementia and perhaps other neurodegenerative disorders (as based upon findings/outcomes of animal investigations), which include neurocognitive and behavioral as well as functional neuroimaging (eg, magnetic resonance and tractographic) evaluations. To be sure, multiple, low-cost tools are available with which to facilitate these types of studies, including the Alzheimer's Disease Assessment Scale, Mini-Mental Status Examination, Informant Questionnaire on Cognitive Decline in the Elderly, Barthel Index, Behavioral pathology in Alzheimer's disease (BEHAVE-AD) and Alzheimer's Disease–Related Quality of Life.[8]

Conclusion

We assert that the report provided by Cuttler et al is burdened by a number of methodologic issues, which strongly suggest *post hoc ergo propter hoc* reasoning, and thus fails to provide strongly valid evidence that LDIR via administration of repetitive CT scans significantly affects the symptoms and signs of advanced Alzheimer dementia. We appreciate—and acknowledge—that desperate situations sometimes, if not oftentimes, prompt extreme and perhaps untried measures, in hope of providing help. As well, we recognize that perceived burden and/or risk of harm may seem negligible, given the relatively poor and/or terminal condition of a patient. In this light, any benefit might be seen viable, if the intervention could not make the patient's condition any worse. One might be tempted to employ a version of the principle of double effect (PDE; note 3) to justify such action. But this too may be suspect, if not inapt, in that the real value of an intervention (beyond the proximate emotional reinforcement to caregivers of "trying everything") cannot be substantiated, and therefore used to sustain the PDE, absent valid evidence that supposedly beneficial outcomes are, in fact, real (ie, the "first and final criteria"; see a and c of note 3). Certainly, this report will foster additional discourse, as we believe it should. And we posit—and hope—that the identified limitations may serve as signposts and guideposts for correction if and when considering and developing more rigorous, precise methods of any future investigation(s) of potential therapeutic benefit of LDIR against neurodegenerative disorders.

Authors' Note

The views in this commentary are those of the authors and do not necessarily represent those advocated by the US Department of Health and Human Services Secretary's Advisory Committee for the Protection of Human Subjects (HHS-SACHRP), or EU Human Brain Project Ethics and Philosophy Sub-Program, for which J.G. serves as an appointed member.

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Notes

1. Literally "... from that which helps." The process of making an inference about the mechanisms of disorder or its amelioration from observed responses to a particular treatment. Such reasoning is not necessarily fallacious but instead can be used toward a process of differential diagnosis.
2. An error of logic in which the temporal sequence of events (A ... B) appears to suggest causality (ergo A "causes" B). The fallacy is inherent to the failure to logically account for other factors that could be/are potentially responsible for the result, thereby invalidating the causal connection.
3. An ethical argument for justifying a legitimate act (eg, relieving a terminally ill patient's suffering) that might also incur an effect that would usually be avoided (eg, causing harm, such as damaging tissues). The principle of double effect is maintained by adhering to 3 criteria:

    a. the nature of the act is inherently good, not harmful (and/or ethically neutral);
    b. the intent is to elicit the good effect and not the harmful effect, either as a means to incur the good or as an end in itself;
    c. the good effect can be demonstrated and irrefutably shown to outweigh any harmful effect, and there is demonstrable diligence and effort to identify and minimize harms incurred.

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