Case Report

Subcortical signal alteration of corticospinal tracts. A radiologic manifestation of ARIA: A case report

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\textbf{A B S T R A C T}

Patients with Alzheimer’s disease who have been given monoclonal antibodies targeting amyloid-\(\beta\) (A\(\beta\)) (eg, gantenerumab, donanemab, lecanemab, and aducanumab) for scientific purposes may have a spectrum of imaging findings known as amyloid-related imaging abnormalities (ARIA), shown on brain magnetic resonance imaging (MRI) scans. These neuroimaging abnormalities are caused by antibody-mediated destruction of accumulated A\(\beta\) aggregates in cerebral blood vessels and brain parenchyma. ARIA may demonstrate as brain edema or sulcal effusion (ARIA-E) or as hemosiderin deposits caused by brain parenchymal or pial hemorrhage (ARIA-H). The current study explores 2 cases with interval development of FLAIR hyper signal intensity along the bilateral corticospinal tracts in the motor cortex/precentral gyri after treatment by aducanumab. We believe this manifestation is a subtype of ARIA-A that has not been explored earlier. Our first case was a 72-year-old woman with a history of HTN and kidney transplant (polycystic kidney) who presented with mild cognitive impairment with clinical findings consistent with early Alzheimer’s disease. After receiving 3 doses of aducanumab and experiencing cognition improvement, she underwent a brain MRI because of dizziness and vertigo. The brain MRI demonstrated new FLAIR hyper signal intensity in subcortical regions of precentral gyri (motor cortex) symmetrically as well as trace subarachnoid hemorrhage at the vertex compatible with ARIA-E and ARIA-H. Our second case was an 85-year-old woman with a history of small lymphocytic leukemia which was treated 20 years earlier. After orthopedic surgery 2 years ago, she developed dementia.

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Abbreviations: AD, Alzheimer’s disease; ARIA, amyloid-related imaging abnormalities; A\(\beta\), amyloid-beta peptide; MRI, magnetic resonance imaging.
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 Introduction

Alzheimer’s disease (AD) is the most prevalent type of dementia, affecting nearly 50 million people worldwide [1] and responsible for 60%-80% of demented people. The clinical presentation of AD, marked by memory loss and cognitive decline, is preceded by neuropathological alterations that result in the gradual deterioration of function and brain structure [2]. The burden of AD impacts people, their families, and the economy, with yearly worldwide expenses estimated at $1 trillion USD. In 2021, more than 11 million family members and unpaid caregivers gave a projected 16 billion hours of care to Alzheimer’s and other dementia patients [1]. To date, there is currently no cure for AD; however, there are treatments that may alleviate its symptoms [3].

The accumulation of misfolded proteins, synaptic dysfunction, and neuronal death are regarded as the most prominent characteristics of neurodegenerative disorders, including AD. AD is mainly characterized by amyloid-beta peptide (Aβ) deposition in the medial temporal lobe and neocortical regions, resulting in neuritic plaques and neurofibrillary tangles [4]. Before cognitive impairment is recognized, the gradual course of the disease is driven by alterations in neurons, microglia, and astroglia [5]. Neuroinflammation [6], vascular alterations [7,8], aging [9], and lymphatic dysfunction [10] work upstream or in parallel to amyloid accumulation in this cellular pathological environment. Amyloid β causes the propagation of tau pathology [11], which is related to the emergence of neurotoxic markers in neurons exhibiting granulovacuolar degeneration [12].

Aducanumab (ADUHELMTM) was recently authorized to treat AD in the United States. This anti-amyloid monoclonal antibody impacts the cerebral amyloid plaque load and demonstrated initial proof of efficacy in individuals who received significant dosages [13]. Moreover, numerous further phase III trials using anti-amyloid antibodies are now ongoing and may expand the repertory of anti-amyloid treatments for AD, including gantenerumab, donanemab, and lecanemab. These treatments might significantly alter the AD treatment landscape.

Patients with AD who have been given monoclonal antibodies targeting amyloid-β (Aβ) (eg, gantenerumab, donanemab, lecanemab, and aducanumab) may have a spectrum of imaging findings known as amyloid-related imaging abnormalities (ARIA), shown on brain magnetic resonance imaging (MRI) scans [14-18]. ARIA may demonstrate as brain edema or sulcal effusion (ARIA-E) or as hemorrhoids deposited caused by brain parenchymal or pial hemorrhage (ARIA-H) [19]. In previous clinical trials, ARIA-E disappeared radiographically within weeks or months, yet ARIA-H might persist on subsequent images [20,19,21]. ARIA is considered to be caused by antibody-mediated destruction of accumulated Aβ aggregates in cerebral blood vessels and brain parenchyma; however, the underlying processes have not been completely explained in previous clinical studies [22]. This breakdown of cerebrovascular Aβ may compromise the structural integrity of the vessel wall, causing increased permeability and proteinaceous fluid leaks into neighboring tissues [22,23]. Moreover, mobilization of parenchymal plaques may impede perivascular clearance and/or induce an immunological response that contributes to perivascular inflammation [22,23]. Although ARIA-E has been observed mostly during clinical trials of Aβ-lowering therapeutics [13,17,24-29], it may also develop spontaneously in AD patients, likely indicating the inflammatory phase of cerebral amyloid angiopathy [30]. Similarly, microhemorrhages and superficial siderosis spontaneously develop in cerebral amyloid angiopathy patients, regardless of anti-Aβ therapy [31,32].

In this article, we report 2 cases with interval development of FLAIR hyper signal intensity along the bilateral corticospinal tracts in the motor cortex/precentral gyri after treatment by aducanumab. We believe this manifestation is a subtype of ARIA-E which happen exclusively in bilateral subcortical corticospinal tracts. None of these patients had clinical findings compatible with amyotrophic lateral sclerosis (ALS).

Case 1

Our first case was a 72-year-old woman with a history of HTN and kidney transplant (polycystic kidney) who presented with mild cognitive impairment with clinical findings consistent with early AD. Baseline MRI demonstrated microvascular angiopathy without acute findings. Subsequently, she underwent 3 doses of therapy by aducanumab without significant adverse effects. She experienced an improvement in cognition at the end of the therapy sessions (per her husband’s reports). Because of dizziness and vertigo, she underwent Brain MRI on day 84 after the first dose, demonstrating new FLAIR hyper sig-
nal intensity in subcortical regions of precentral gyri (motor cortex) symmetrically as well as trace subarachnoid hemorrhage at the vertex compatible with ARIA-E and ARIA-H. The subsequent MRI on day 116 demonstrated stable ARIA-H with interval resolution of the abnormal signal intensities in the subcortical motor cortex. Lastly, the following brain CT and MRI did not demonstrate any acute findings with stable ARIA-H and no recurrent ARIA-E (Fig. 1).

Case 2

An 85-year-old woman with a history of small lymphocytic leukemia was treated 20 years earlier. After orthopedic surgery 2 years ago, she developed dementia with anterograde amnesia. Since then, Aricept and Namenda have been started, but there have been no improvements in her subjective condition. Although the patient was on anticoagulation therapy and not a candidate for LP, the amyloid PET/MR imaging showed diffuse cerebral amyloid deposition. She tolerated the 6 doses of treatment with aducanumab. On day 154, a safety MRI revealed new bilateral symmetric FLAIR hyper signal intensity in the subcortical motor cortex. The follow-up MRI on day 203 showed interval resolution of abnormal signal intensity (Fig. 2).

Discussion

Conventional AD therapeutics target cholinergic and glutamatergic neurotransmissions, which solely ameliorate the symptoms [33]. Thereby, investigating leading-edge therapeutics targeting the main pathologic pillars of the disease is in high demand. Accumulation of amyloid-β (Aβ) peptides has been considered one of the primary critical pathologies of AD. Moreover, its dyshomeostasis has been demonstrated to be a crucial component of AD onset. As a result, it has been considered an excellent curative target to investigate [34].

Aducanumab is an amyloid-targeting monoclonal antibody that has been approved by the US Food and Drug Administration for the treatment of AD. It is titrated to a dose of 10 mg/kg and is delivered monthly intravenously over a 6 months treatment window. ARIA (ARIA-E and ARIA-H) has been reported as the main side effect of aducanumab, occurring approximately in 35% of patients on high doses of this drug. Also, Patients with APOE ε4 genotype are more susceptible to ARIA-E episodes, with 42% experiencing ARIA-E rather than non-carriers who experience 20% [35].

Amyloid-related imaging abnormalities (ARIA) encompass a spectrum of imaging findings detected on brain MRI following the use of amyloid-β (Aβ)-targeting monoclonal antibodies [26] ARIA-E includes FLAIR signal abnormalities representing parenchymal vasogenic edema and sulcal effusions. ARIA-H is specified by hemosiderin deposits due to hemorrhage in the brain parenchyma or on the pial surface [19,20]. Most of these abnormalities occur during the titration phase in the first 8 months of treatment. It has been reported that ARIA episodes can be successfully managed and typically will be resolved in 4-16 weeks [36].

We have reported 2 cases of novel ARIA manifestations in the current study. Our patients presented mild adverse symptoms accompanied by dizziness, confusion, and headache, similar to most ARIA cases [37,38]. However, we observed ARIA-E compatible abnormalities in subcortical regions of corticospinal tracts symmetrically that has not been reported in the past. ARIA-E usually appears as a patchy area and not in a bilateral symmetric distribution. It has been shown that the corticospinal tracts in the spinal cord are among the less common regions that could be impacted by amyloid plaques leading to AD [39–41]. However, to the best of our knowledge, the subcortical corticospinal tracts have not been reported to be dominantly involved in amyloid deposition. Results of our study might suggest that the subcortical corticospinal tract is another hotspot for ARIA findings. Hence, these regions might be an unknown site of action and adverse effects of aducanumab on amyloid plaques with secondary inflammation.
In addition, radiologists must know this phenomenon, and the FLAIR hyper signal intensities should not be misinterpreted as motor neuron disease (eg, ALS).

Conclusion

We presented 2 cases of AD receiving aducanumab and experiencing episodes of ARIA with unusual MR findings of symmetrical FLAIR hyper signal intensities in the subcortical corticospinal tracts (the location that traditionally does not consider having a high burden of amyloid deposition). The imaging presentation is indistinguishable from motor neuron disease/ALS; however, knowing the history of treatment by monoclonal antibody against amyloid can differentiate these 2 conditions. Further studies are needed to determine the possible role of amyloid deposition in the corticospinal tract of the motor cortex in the pathophysiology of Alzheimer’s dementia.

Patient consent

Informed consent was obtained from each patient upon admission regarding the scientific publication of the patient’s data.

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