The neuro-inflammasome in Alzheimer’s disease and cerebral Stroke

JONG HOON LEE (✉ science@research.re.kr)
Seoul National University  https://orcid.org/0000-0003-1775-5656

Chul Joong Lee
Zein Pain Clinic Seongbuk  https://orcid.org/0000-0001-5388-8945

Jungwuk Park
Chungdam Hospital

So Jeong Lee
Rice University  https://orcid.org/0000-0003-4665-415X

Su-hee Choi
Seoul National University Hospital

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Abstract

Aim/Background: This Review investigated a patient with Alzheimer's disease (AD) treated with 4,4'-diaminodiphenyl sulfone (DDS) as a neuro-inflammasome competitor.

Methods: We monitored AD's progression through Numeric Clinical staging (NCS) with a new biomarker. NCS was determined by the AD symptoms and neuropsychiatric (NP) symptoms caused by anti-AD drugs (AAD) as a biomarker (D). We also monitored the function of DDS for Stroke in a no-intake emergency state.

Results: By introducing (D), AD's progression was monitored through NCS staging; AAD side effects and neuropsychiatric symptoms were distinguished. DDS was stopped in the Stroke with NCS 6 by AAD, and it rapidly proceeds to cerebral infarct.

Conclusions: AADs can occasionally exacerbate AD and Stroke. DDS can alleviate mild cognitive impairment (MCI), early AD and Stroke. We clinically confirmed the role of DDS as a neuro-inflammasome competitor after Stroke. DDS keep neuronal survivals within 24 - 55 hours in the Seoul cohort.

1. Introduction

In an attempt to prevent progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD), a prospective cohort was created in 2010 based on the prevention and treatment of dementia by 4,4'-diaminodiphenylsulfone (DDS) [1], its didextrose sulfonate derivatives, and other closely related sulfones (sulfone and thiazolsulfone) [2, 3]. A prospective cohort study reported patients who had MCI from February 2008 to January 2019 [1]. The patient took DDS 100 mg once a day from 2010 to 2015 for the treatment of MCI (Supplement_7.pdf (page 1-4) (online suppl. 7 [4])). In 2016, the production of DDS ceased in Korea [5]. In June 2018, the patient was then diagnosed with AD (Supplement_6.pdf (pages 1-2) (Online Suppl. 6 [4])). This study introduces the application of a new biomarker that can be used to treat and manage AD by applying step-by-step numeric clinical staging (NCS) according to the treatment of neuroinflammases.

DDS, initially approved for leprosy, has potent antimicrobial effects, even at a small dose [6]. The present study shows that DDS is also a neuroinflammasome competitor. To demonstrate this, the study introduces the application of a new biomarker that can be used to treat and manage AD by applying step-by-step numeric clinical staging (NCS) according to the treatment of neuroinflammation.

2. Materials And Methods

The Seoul study was a prospective cohort study of patients diagnosed with MCI from February 2008 to June 2020. The Science and Research Center at Seoul National University of College of Medicine
approved the clinical study of patients ethically based on FDA guidelines in accordance with the World Medical Association Declaration of Helsinki. All methods were carried out in accordance with relevant guidelines and regulations.

2.1. AAD use, or (D), as a new biomarker of NCS

The raw data for AD were prepared according to the 'symptom-based categorical cognitive impairment stage', divided into three stages: cognitively unimpaired, mild cognitive impairment (MCI) and dementia. This three-category division serves as the basis for cognitive categorization in many extensive ongoing studies [7]. NCS was recorded according to the 2018 'NIA-AA Research Framework' [7]. NCS was recorded as 05-02-2008 Stage 3, 27-06-2018 Stage 4, 06-11-2018 Stage 5, and 14-01-2019 Stage 3 recorded based on Korean neuropsychiatric medical records and magnetic resonance imaging (MRI) reading reports. When recording NCS stage 2à3à4à5à3, we used the following biomarkers: β-amyloid deposition (A), pathologic tau (T), and neurodegeneration (N).

In this study, AAD use, or (D), was used as a new biomarker of NCS [8]. In the periods 27-06-2018 to 01-10-2018 and 06-11-2018 to 21-11-2018, AAD use caused side effects. We also examined other patients who had the same symptoms [9-12]. After AAD use was stopped from 01-10-2018 to 22-11-2018, the NCS changed from stage 6 to 5. After neuroinammasome treatment, it was changed from stage 5 to 3.

We recorded the following NCS values: 05-02-2008 Stage 3, 27-06-2018 Stage 4, 27-06-2018 ~ 01-10-2018 Stage 6, 01-10-2018 ~ Stage 5, 06-11-2018 Stage 5, 06-11-2018 ~ 16-11-2018, 21-11-2018 Stage 6, 22-11-2018 ~ Stage 5, and 14-01-2019 Stage 3.

2.2. Case report of cerebral infarction & a neuroinammasome competitor

This study is based on the results of the Seoul cohort. The patient's medical records were issued in accordance with Korean medical law. All medical records in this Supplement are copies of the patient's medical charts.

DDS blocks the bacterial synthesis of dihydrofolic acid via competition with p-aminobenzoic acid for dihydropteroate synthetase's active site [13]. In addition to its antimicrobial effects, DDS is a potent anti-inflammatory agent with high effectiveness in dermatitis herpetiformis and a wide variety of other inflammatory dermatological conditions [6]. DDSs that inhibit inflammation without compromising the adaptive immune response could be the most effective therapeutic strategy. DDS, as an inflammasome competitor [14], should be effective against neuroinflammasomes.

Therefore, we analyzed the Seoul study cohort of elderly patients with MCI who underwent precise MRI examinations for stroke in May 2020. DH Hospital conducted medical examinations (Supplement 1, Supplement 1-1 [11-05-2020-diffusion MRI- Rx image], Supplement 1-2 [12-05-2020-diffusion MRI- Rx image], Supplement 1-3 [12-05-2020-perfusion MRI- Rx image]), CT (Supplement 1 [page 15, 18, 19], Supplement 1-4 [11-05-2020-CT- Rx image], Supplement 1-5 [13-05-2020-CT- Rx image]), chest AP
We hypothesized that the deterioration of ischaemic stroke to cerebral infarct should be prevented by NLRP3 inflammasome inhibitors [15], such as DDS. DDS tablets were produced by the local pharmaceutical company, which stopped the production of DDS. Since then, the Korea Food and Drug Administration has designated DDS as an anti-retraction drug and produced it only for HD. The Korea Orphan & Essential Drug Center imported it from Germany. After administering the two types of DDSs to patients, we found a large difference in clinical effectiveness. DDS from the local pharmaceutical company had one-third the effective dose (ED$_{50}$) of Germany’s drugs.

On 10 May 2020, the patient was dosed twice daily with 200 mg (2T po bid) and closely monitored, revealing the following: rash/exanthema/erythema/erythroderma/mucosal involvement leukocytosis/eosinophilia [16], the appearance of a mononucleosis infection/acute renal failure/hepatitis/liver toxicity [17], haemolytic anaemia/methaemoglobinæmia [18], cholangitis/colitis/thyroiditis/myocarditis/dapsone-induced hypersensitivity syndrome-associated complete atrioventricular block/pneumonitis [19], pancreatitis/pleural effusion [20] and myocardial injury/pneumonia/multiple organ failure [21].

### 2.3. Corroboration of the findings of the Seoul study regarding the neuroinflammasome

In Korea, during the SARS-CoV-2 epidemic, children were prohibited from visiting their parents in nursing hospitals [22]. It has become difficult for carers to interact with older adults at close range. In nursing hospitals, chemical restraint increased substantially to reduce hospital labour costs during the same period [23].

Medical staff found the patient to suffer from endocarditis and pulmonary effusion symptoms (Supplement 2, 2-1). The patient took DDS at lunch (12:00) on 12 September 2020, was transferred to Inje University Seoul Paik Hospital, and stopped taking DDS until 7 pm on 15 September 2020. Only after the patient's guardian submitted a memorandum of responsibility (Supplement 2 [page 6], 2-2 [page 25]) was the patient able to retake DDS with the permission of Professor Jong-Chun Nah, a cardiology specialist at Seoul Paik Hospital. The patient’s cognitive state over the course of 55 hours was observed through medical records (Supplement 2, 2-2).

### 3. Results

#### 3.1. AAD as a new biomarker of NCS (D)

Observational studies of AD after treatment of neuroinflammation are as follows.

i. Observational study: Syndromal staging of the cognitive continuum (SSC)
December 2007 'Cognitively unimpaired', → 05-01-2008 'mild cognitive impairment (MCI)', 27-06-2018 'Dementia'. → 11-06-2018 'Dementia', → 14-01-2019 'MCI'.

ii. Observational study: NCS 2007 stage 2 → 05-02-2008 stage 3 → 27-06-2018 stage 4 → 06-11-2018 stage 5 → 14-01-2019 stage 3.

iii. Observational Study: NIA-AA (A) (T) (N)) + new biomarker (D)

NCS 2007 stage 2 → 05-02-2008 Stage 3 → 27-06-2018 Stage 4 → 27-06-2018 ~ 01-10-2018 Stage 6 → 01-10-2018 Stage 5 → 06-05-2018 Stage 5 → 06-11-2018 – 16-11-2018 Stage 6 → 22-11-2018 Stage 5 → 06-05-2018 Stage 5 → 06-11-2018 – 16-11-2018 Stage 6 → 22-11-2018 Stage 5 → 14-01-2019 Stage 3.

The comparison table of study results 1, 2 and 3 is as follows. (Table 1)

AD Cases 1-5 of the Seoul study followed a similar path. There were two-stage 6 cases concealed by the appearance of stage 4 or 5, which could not be monitored. (Figure 1)

3.2. Cerebral infarction and DDS as a neuroinflammasome competitor in the Seoul study

The attending physician stopped taking the brain cell protective drug (DDS) that the patient had been taking in a stable state after stroke onset on 10 May. He prescribed aspirin for antithrombotic treatment and acetylcholine precursor. The patient's NCS was Stage 6 after 5 hours of administration according to the increase in acetylcholine (Supplement 1 [page 8, 22:44, 01:00]).

The patient did not take DDS between 11 and 12 May 2020. After antithrombotic treatment, the patient's muscle power was changed from grade 1(+) to (4+) at 8:00 am. However, it suddenly changed from (4+) to (1+) at 11:30 am on 12 May 2020. In the MRI scan, the patient's left cerebral infarct was further enlarged (Supplement 1 [page 16, 17], 1-2, 1-3). After 72 hours, the patient underwent DDS again (Supplement 1 [page 12, 08:50]). The patient's condition did not worsen due to pneumonia, cardiomegaly or suspicious pulmonary hypertension (Supplement 1 [page 19]).

Although traditional cardiovascular risk factors account for the majority of strokes, infectious pathogens may add additional risk and, in some cases, have a direct causal role. Systemic infections have been associated with an increased risk of strokes, and inflammation stimulation has been thought to be the predominant mechanism by certain pathogens [24]. Cerebral stroke, in this case, was caused by pneumonia. (Supplement 1 [page 19, 20], Supplement 1-5 [13-05-2020- CT- Rx image], 2-6 [11-05-2020, 20-05-2020-Chest- Rx image]) S. pneumonia & H. influenza were found in the culture test (Supplement 1 [page 21]).

3.3. Neuro-inflammasome exacerbates and DDS weakens it again.

After the patient was discharged on 20-05-2020, medical staff stopped the acetylcholine precursor in the rehabilitation hospital and recovered to NCS Stage 3.
Medical staff found the patient to suffer from endocarditis and pulmonary effusion symptoms again (Supplement 2, 2-1). From lunch (12:00) on 12 September 2020 to 7 pm on 15 September 2020, the patient's progress during and after 55 hours of DDS discontinuation was as follows: DDS was loaded at 7 pm on 15 September 2020. Below are the data from the patient's medical record from 09/12/2020 to 09/28/2020 (Supplement 2 [page 1, 2]).

After administering DDS at 7 pm on 15 September 2020 and at 18:53 on 16 September 2020, the patient became drowsy from stupor. The patient's cognitive condition is recorded in Table 2.

Except for taking DDS, the patient's treatment did not change, but there was a clear change in consciousness, and infective endocarditis improved to stable states.

The NLRP3 neuroinflammasome is a common cause of cognitive impairment in AD, stroke, and certain pathogens. The action of DDS demonstrates that the inhibition (control) of NLRP3 is a new target for therapeutics.

4. Discussion

4.1. The Alzheimer’s continuum (A + T + (N) +) (D)

For clinical research, the Alzheimer's continuum (A + T + (N) +) was selected based on biomarkers. Before AD progressed, biomarkers were changed. Therefore, clinical symptoms and biomarkers were separated from AD diagnosis, and AD was defined only by changes in biomarkers [7]. The AD criteria biologically classify cognitive impairments separately as symptoms/signs caused by these diseases. AD problems may include the following: depression, apathy, social withdrawal, mood swings, distrust in others, irritability and aggressiveness, changes in sleeping habits, wandering, loss of inhibitions, and delusions, such as believing something has been stolen [25]. As of mid-2019, several AD drugs were available worldwide: donepezil, galantamine, rivastigmine and memantine [26]. Aripiprazole, olanzapine, risperidone, quetiapine, haloperidol, selective serotonin reuptake inhibitors, and carbamazepine are used to control the psychiatric symptoms associated with dementia [27-32]. However, it was challenging to differentiate whether AAD caused symptoms because of the Korea Dementia Act and the health insurance system. Biomarker (D) can be used as a biomarker to distinguish the symptoms caused by AAD. Since the side effects of AAD have been reported [33, 34], it is necessary to record the biomarker (D).

The FDA warned that dementia-related antipsychotic drugs increase mortality. The boxed warning reads as follows: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death [33]. More recent studies from many countries confirm that antipsychotic drugs should not be prescribed for dementia patients, as they significantly increase the risk of seizures and all-cause mortality [34]. Therefore, to distinguish the symptoms caused by AAD or AD, it is necessary to stop taking AAD and observe clinical progress. In this study, when acetylcholine precursor was administered to the patient, the patient state changed to NCS 6 stage. Medical staff must label the AAD as a biomarker (D) and monitor the patient's condition for changes.
4.2. DDS as the preventive of AD and Aβ neurotoxicity

In the first review [35], DDS was a therapeutic, preventive agent in AD, according to reports [36-38]. However, in the second review [39], DDS was not a therapeutic, preventive agent in AD [38, 40]. There were different interpretations of the commonly cited 'Decreased Aβ and Increased Abnormal Tau Deposition in the Brain of Aged Patients with Leprosy'. It has been reported that amyloid-beta protein (Aβ) depositions were significantly lower in the temporal cortex and hippocampal formation of aged HD and that patients with T-type leprosy (who did not take DDS) exhibited slightly more Aβ deposition than L-type leprosy. The brains of HD show high abnormal tau deposition in neurons and neural threads despite the low levels of Aβ deposition [38]. *Mycobacterium leprae*, which induces leprosy, was assumed to cause a low incidence of AD in HD [41]. However, the next researchers hypothesized a null hypothesis because the Aβ removal function of DDS and the dementia reduction by *M. leprae* are irrelevant [1].

The inflammasome competitor model of DDS shows a reaction pattern that is a typical molecular model of electronic clouds. Therefore, in vitro or in vivo, it can show pathological findings that can be this or that. The autopsy findings of leprosy's brain pathology of the sanatorium in Japan are sometimes like this and sometimes like that. The pathologic findings in the previous review are consistent with those of a typical inflammasome competitor. An alternative way science can help us prevent or treat AD is to use an inflammasome competitor and reduce the prevalence rate.

The molecular properties of DDSs, including electron density and its Laplacian delocalization index, have been elucidated to shed light on the chemical bonding and atomic and molecular details [42, 43]. The redox properties of DDS are dependent on amine and sulfone moieties explain the oxidation mechanism of DDS by electron transfer. The aniline ring is the nucleophilic moiety conferring potential biological properties via a redox mechanism, mainly electron transfer or oxidation for DDS–NHOH formation [44]. We can understand the various neuropathological findings of HD, including its mysterious sensory manifestations [45].

DDS regulates NLRP3 inflammasome activators and a common signaling pathway of SARS-CoV-2 inflammasome activators in the medulla oblongata [46]. It acts through the same competitive therapeutic mechanism to counter the progression of MCI to AD. Korean HD on Sorokdo (an island for HD patients) continues to take DDS throughout their lives. This drug appears to have a preventive effect against AD, according to the study of HD patients who have lived only all their lives [47].

4.3. Neuroimmunity & neuroprotection for Stroke patients

Hypertension causes blood-brain barrier breakdown by mechanisms involving inflammation, oxidative stress, and circulating vasoactive molecules. It exposes neurons to cytotoxic molecules, leading to neuronal loss, cognitive decline, and impaired recovery from ischemia [48]. Active treatment for elevated blood pressure can decrease perfusion at the cerebral infarction area, thus extending the cerebral infarction area [49]. However, there is no evidence that high blood pressure that develops after a stroke indicates Stroke's severity or is intended to provide collateral blood flow to maintain blood flow to the
ischemia area (penumbra) [49-51]. Instead, in 2004, there was a report that patients with stroke had a high mortality rate when hospitalized with high or low blood pressure [51]. There are only reviews reporting that starting treatment for severe hypertension within a few hours of stroke onset can cause a decrease in cerebral blood flow and may be problematic [52]. There is no medical evidence that neglecting high blood pressure can increase a patient's survival rate. However, it has been reported that the stress of being admitted to the hospital is the main factor causing high blood pressure in stroke patients [50].

Markedly low RBC cholesterol and markedly high RBC lipoperoxides may pathologically aggravate cerebral hemorrhage patients and lead to oxidative and lipoperoxidation damage [53]. These factors are positively correlated with erythrocyte deformability [54]. Considering that there are disturbances in the function of erythrocyte membranes and free radicals in acute cerebral infarction, erythrocyte deformity and membrane Na+-K+-ATPase activity in acute cerebral infarction patients were lower than those in healthy persons [55, 56]. Antioxidants such as DDS attenuate microvascular changes in the early phase of experimental pneumococcal meningitis [57]. DDS increases the viability of brain cells in acute stroke. Clinical trials were already conducted in 2013, and statistics were significant [58]. In 2014, an analysis was published that was very effective and economical in treating acute ischemic stroke patients [59]. In 2016, MRI results were published to compensate for functional loss after brain cell damage [60]. Additionally, studies have been reported to protect brain cells and increase viability in various experiments [61]. In particular, the paper that DDS increased Parkin's concentration in old rats was a study that was precisely consistent with the patient (Supplement_7.pdf (page 1-4, Koh) (online suppl. 7 [4])) in the Seoul cohort, who improved Parkinson's symptoms [62].

Astrocytes play a crucial role in regulating homeostasis within the CNS. Furthermore, hypoxia-induced changes in pathological conditions associated with the immune response and manipulation of mitochondrial function and metabolism are mediated. The transcriptomic profile of astrocytes in an in vitro study was used to perform a detailed characterization of hypoxia-induced changes. Analysis of the significant differentially expressed transcripts identified an increase in immune response pathways, dysregulation of signaling pathways, and metabolism, including glycolysis [63]. After administering DDS at 7 pm on 15 September and 18:53 on 16 September, the patient recovered consciousness. Except for taking DDS, the patient's treatment did not change but improved to stable states of infective endocarditis. DDS also reduced doxorubicin's cardiac toxicity due to its production of free radicals and inflammatory cytokines [64].

DDS has already been used as a substitute for colchicine. The specific targeting of NLRP3 itself or up-/downstream factors of the NLRP3 inflammasome by the DDS may be responsible for its observed preventive effects on MCI [1], functioning as a competitor for the SARS-CoV-2 inflammasome [14].

5. Conclusions
DDS is a neuro-inflammasome competitor. By prescribing this drug for neuroinflammation and brain survival, the incidence of AD can be reduced by more than two-thirds [1-3]. Early AD and stroke can be treated with DDS in the same manner as MCI when (A), (T), (N), and (D) are recorded as biomarkers. Trials need to be carried out from middle age (over 40 years old) in parallel, not sequentially, using adaptive trial designs optimized for speed and tested in different populations so that we can ultimately protect everyone.

**Abbreviations**

AD, Alzheimer disease;

AMPK, 5′-adenosine monophosphate-activated protein kinase;

DDS, 4,4′-diaminodiphenyl sulfone (dapsone);

LL, lepromatous leprosy;

MADDS, monoacetyldapsone;

PD, Parkinson's disease;

NLRP3, NACHT, LRR and PYD domain-containing protein 3;

MCI, mild cognitive impairment;

MPO, myeloperoxidase;

TLR, Toll-like receptor

**Declarations**

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Soon Joe (09-12-1931 ~ 03-01-2021) contributed to developing treatment methods for MCI & AD and SARS-CoV-2 ARDS. So naming is Soon, Joe's treatment [46]. Dapsone is used to prevent, treat AD or COVID-19 ARDS. Chang-Soon Koh (20-04-1932 ~ 06-08-2012) participated as a cofounding researcher. He was the physician to the President of South Korea. He took DDS from 27-12-2010 to 06-07-2011 and reported that DDS could also be used to manage Parkinson's disease.

**Statement of Ethics**

This study was based on FDA guidelines in accordance with the World Medical Association Declaration of Helsinki. The subjects (or their parents or guardians) provided written informed consent. We
administered medicines in compliance with medical and pharmacy laws with the informed consent of the patient.

**Conflicts of Interest**

The authors have no conflicts of interest to declare.

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**Author Contributions**

J.L. designed and performed this study and wrote the manuscript. C.J.L., J.P., and S.C. analyzed the symptoms of intractable AD and the use of AAD (D). S.J.L. examined cerebral infarct patients and wrote Supplements 1 and 2.

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Tables

Due to technical limitations, Tables 1 and 2 are only available as a download in the supplemental files section

Supplemental Data

The Supplemental 1 file is not available with this version of the preprint.

Figures
Figure 1

The ranges of SSC, NIA-AA, and NIA-AA + (D) were indicated using a radial chart. The range of SSC was expressed as the NIA-AA standard, and NIA-AA + (D) was expressed as the NIA-AA standard when deteriorated due to (D). The management standard for Alzheimer's disease will be further expanded if the NIA-AA standard includes (D).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

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