

The Preventive and Treatment of the Neuro-Inflammasome in Sorokdo National Hospital

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Abstract

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

Method: The Seoul study analyzed AD, and anti-AD drugs (AADs) in the Sorokdo National Hospital's EDI database archived from January 2005 to June 2020 through the ICD-9 and -10 codes.

Result: DDS acts as a neuro-inflammasome competitor; this effect can be inferred by comparing the prevalence of AD in patients who have been prescribed DDS and those who have not.

Conclusion: This study suggests the use of neuro-inflammasome therapy as a preventive and therapeutic method for AD.

1. Introduction

In 1992, an AD research team published a method of preventing and treating human AD dementia with DDS, its didextrose sulfonate derivative, and other closely related sulfones (sulfetrone and thiazolsulfone)¹⁻³.

However, further investigations did not detect any differences in AD prevalence among HD patients treated with DDS and failed to demonstrate that it had any protective effects against A β neurotoxicity⁴.

There have been various claims in autopsy findings and AD interpretations in HD patients⁵⁻⁸. Population studies varied in their specific neuropathological findings, but all observed some abnormal neuropathology characteristic of AD despite DDS treatment.

The Sorokdo National Hospital was established in May 1916 to treat leprosy. The Seoul study originated from the Seoul Longitudinal Study of Aging⁹ had published a prospective observational study of patients diagnosed with MCI from February 2008 to December 2019¹⁰. The Seoul study analyzed the causes of low AD prevalence in Hansen's disease (HD) patients.

We have also analyzed infectious respiratory diseases of HD at Sorokdo National Hospital¹¹. The Korean Hansen Welfare Association reported that HD patients had no known outbreaks of four respiratory infectious diseases (SARS-CoV (2002), influenza A virus subtype H1N1 (2009), MERS (2015), and SARS-CoV-2 (2020)) between 2002 and 2020.^{6,12}

DDS initially approved for leprosy, has potent antimicrobial effects, even at a small dose¹³. The present study suggests that DDS is also a neuro-inflammasome competitor.

2. Results

From 2010 to June 2020, the diagnosis of patients with MCI and AD in Korea increased dramatically (Table 1).

Table 1
Numbers of drug prescriptions for dementia patients in Korea from 2010 to 2019

Year	Total billed quantity of drugs	Total amount billed for drugs (won/(dollar))	Total number of patients
2010	56,258,246	122,334,391,105/ (109,447,004.94)	257,385
2011	72,339,833	149,904,875,429/ (134,113,060.88)	319,327
2012	88,533,271	156,600,063,024/ (140,102,940.12)	376,126
2013	106,422,008	179,065,839,181/ (160,202,046.28)	435,538
2014	127,120,294	209,303,038,969/ (187,253,891.03)	497,676
2015	154,734,543	240,625,672,304/ (215,276,823.70)	562,844
2016	181,226,560	268,559,437,589/ (240,267,890.56)	627,823
2017	207,303,641	297,265,306,699/ (265,949,723.52)	692,531
2018	234,480,000	331,349,269,816/ (296,443,092.12)	767,282
2019	261,621,750	367,097,909,500/ (328,425,770.98)	839,413
(Currency data provided by Morningstar on 07 February, 12:58 AM UTC)			

We analyzed AD in HD patients at Sorokdo National Hospital. The HD patients in Sorokdo National Hospital have lived only on Sorokdo (an island for HD patients) all their lives. Korean HD patients continue to take DDS throughout their lives. Based on the relative prevalence of AD in patients who have

been prescribed DDS and those who have not, this drug appears to have a preventive effect against AD (Table 2) (Fig. 1).

Table 2
The relation between DDS and AD in the Sorokdo National Hospital from January 2005 to June 2020

Year	AD(+)			AD(-)			P-value*
	DDS (+)	DDS (-)	Total	DDS (+)	DDS (-)	Total	
2005	18	19	37	290	417	707	.3583
2006	20	37	57	302	363	665	.1324
2007	22	51	73	317	332	649	.0024**
2008	22	58	80	310	312	622	.00028**
2009	19	66	85	300	283	583	<.00001**
2010	25	82	107	270	286	556	<.00001**
2011	35	98	133	255	268	523	<.00001**
2012	39	135	174	238	241	479	<.00001**
2013	34	172	206	195	248	443	<.00001**
2014	25	190	215	172	236	408	<.00001**
2015	26	242	268	167	168	335	<.00001**
2016	33	255	288	154	149	303	<.00001**
2017	37	268	305	143	115	258	<.00001**
2018	45	292	337	132	87	219	<.00001**
2019	46	334	380	114	40	154	<.00001**
2020	32	352	384	109	4	113	<.00001**

*The relation between DDS and AD each year was analyzed using the chi-square test. A P-value < 0.05 was considered significant. ** indicates a P-value < 0.05.

It shows that DDS's action as a neuro-inflammasome competitor¹² can be conjectured by comparing the AD prevalence in HD patients who have been prescribed DDS and those who have not. Thus, DDS appears to be a neuro-inflammasome competitor.

3. Discussion

Because of the Dementia Management Act in Korea, the Sorokdo National Hospital strengthened the diagnosis of dementia for HD. Since 2010, Korean medical staff have conducted neuropsychiatric examinations and diagnosed patients with AD.

For HD patients, doctors perform standard treatment according to AD diagnosis and test results. They strengthened the prescription of AADs and discontinued DDS in patients with inactive leprosy. As a result, it became possible to separate the group taking DDS from the group not taking DDS in among AD patients. As a long-term study of HD patients living in Sorok Island for 15 years, the relationship between AD and dapsonsone is clear. If any study reflects populations who have been prescribed and then discontinued to take dapsonsone in the statistical data, the effects of dapsonsone as an inflammasome competitor are mixed in the pathology findings⁴⁻⁸.

DDS readily passes through the blood-brain barrier (BBB)

The results of many epidemiologic studies and limited clinical evidence suggest that NSAIDs should delay the onset and hinder AD's progression. The results of long-term clinical trials were negative. Still, these drugs affect the periphery of the inflammatory reaction¹⁴. The components of the neurovascular unit harmoniously working influence the BBB's properties. The brain capillary phenotypes have differences in a lack of fenestration and low pinocytotic activity. They mostly have the presence of tight junctions with low permeability between cells. Since most central nervous system (CNS) diseases are caused by inflammation and oxidative stress, the efficiency of drugs acting on CNS is essential¹⁵.

Although we cannot completely understand the role of microglia in neurological diseases, we can summarize beneficial or harmful phenomena: beneficial, with the role of microglia as housekeeping phagocytes for maintaining tissue homeostasis, or dangerous, with the role of microglia determining a pro-inflammatory state that results in synaptic dysfunction and elevated secretion of potentially neurotoxic cytokines¹⁶. DDS passes through the BBB, and high-dose sulfadiazine results in an effective CSF concentration in humans¹⁷.

DDS appears to have more significant anti-inflammatory effects than NSAIDs. Moreover, DDS does not have the side effects of NSAIDs, such as gastrointestinal disorders; therefore, it is possible to administer adequate doses of DDS (100–300 mg/day) while monitoring other side effects.

DDS in neuroinflammatory foci

The NLRP3 inflammasome in the CNS can be activated in both healthy and pathologic states. As developments in the inflammasome field have uncovered molecular mechanisms, inflammasomes contribute to a broad range of neurological disorders. They are associated with specific mutations in inflammasome genes and diseases modulated by inflammasome activators¹⁸. NLRP3 inflammasomes are cytosolic protein complexes that initiate inflammatory responses through caspase activation by infectious or host stimuli. When specific NLRP3 inflammasome was inhibited in organotypic cerebellar cultures, it effectively reduced axonal damage in a lipopolysaccharide-induced neuroinflammation model.

The roles of IL1B and the NLRP3 inflammasome are crucial as prognostic biomarkers and potential therapeutic targets in patients with primary progressive multiple sclerosis¹⁹. The NLRP3 inflammasome in the CNS is the most abundant and is an essential contributor to neuroinflammation in a broad range of neuronal disorders. By the most extensively investigated inflammasome, it is known that the downregulation of inflammasome activity increases phagocytosis in astrocytes by the release of the chemokine CCL3 (C-C motif ligand 3)²⁰.

DDS had anticonvulsive effects in the amygdaloid inflammation model of epilepsy²¹. DDS prevents neuronal damage induced by glutamate agonists. Usually, glutamate excitotoxicity is implicated in damage after rat brain ischaemia²². DDS suppressed the mRNA expression of TNF- α and significantly decreased the level of TNF- α in the culture supernatant²³. DDS showed a remarkable ability to reduce damage markers through antioxidant, anti-inflammatory, and anti-apoptotic effects²⁴. DDS restored the parkin level and prevented age-dependent dopaminergic neuronal loss and transcriptionally activated parkin via protein kinase RNA-like endoplasmic reticulum kinase-activating transcription factor 4 (ATF4)²⁵.

DDS is a neuro-inflammasome competitor in AD

Neurotoxicity, aggregation, and free radical formation are initiated by the methionine (Met) residue at position 35 in the A β C-terminal domain^{26,27}. Two-electron oxidation of bicarbonate is mediated by hydrogen peroxide after the generation of peroxymonocarbonate (HCO₄⁻). The bicarbonate/carbon dioxide pair stimulated One-electron oxidations. Carbonate radical anions (CO₃^{•-}) mediate one-electron reactions to promote one-electron oxidation to efficiently oxidize thioether sulfur of the Met residue to sulfur radical cations (MetS^{•+})²⁸. DDS has a structure that can competitively reduce the positively charged sulfur radical production rate because it has a similar structure to methionine sulfoxide.

SERP1 is a γ -secretase activator that stimulates A β generation in cells experiencing endoplasmic reticulum (ER) stress, such as diabetes (an inflammatory condition in cells)²⁹. Although low-density lipoprotein receptor-related protein 1 (LRP1) controls the endocytosis and subsequent spread of tau³⁰, it is essential to identify a mechanism that blocks tau production. Considering the structure of DDS and the allosteric regulation of the molecular unit, DDS can be presumed to preserve cells by decreasing neutrophils' inflammatory response.

DDS can regulate the production of hypochlorous acid. This response is associated with myeloperoxidase, a kind of reductase enzyme, and reduces inflammatory reactions¹⁰. DDS in the sandwich test disk showed myeloperoxidase-inhibitor activity in the whole saliva from subjects with periodontal disease. AD is associated with heme-bound A β peptides' peroxidase activity, affecting neurotransmitters' oxidative degradation, such as serotonin. DDS12 inhibited myeloperoxidase activity.

DDS may regulate NLRP3 inflammasome activators and a common signalling pathway. However, the specific NLRP3 target may act through a competitive therapeutic mechanism to counter the progression

of MCI to AD. Our work corroborates a finding reported in 1994: antibodies could inhibit this activation against complement receptors in the nanomolar range. DDS and indomethacin are weakly inhibitory (10^{-4} M range) therapeutic agents in AD³.

4. Methods

The Bioethics Committee, a central institution designated by the Ministry of Health and Welfare, approved the observational study of patients ethically based on FDA guidelines following the World Medical Association Declaration of Helsinki. (P01-202007-22-006) We carried out all methods following relevant ethical guidelines, regulations.

4.1. The medical records of the EDI database of the Sorokdo National Hospital, archived from January 2005 to June 2020

Korea's Dementia Management Act came into effect on 05 February 2012. Act amended it No. 15649, 12 June 2018. The purposes of this Act are to mitigate personal pain and damage from dementia; to lighten its burden on society, and to help enhance national health by establishing and implementing a comprehensive policy on the prevention of dementia, protection of and support for dementia patients, and research for the eradication of dementia.

According to the Official Information Disclosure Act in Korea, the Seoul study analyzed AD and anti-Alzheimer's disease drug (AAD) use in Hansen subjects. We searched all medical records of the National Health Insurance Service (NHIS) in Korea and the Sorokdo National Hospital from the time when the Korean government computerized the International Classification of Diseases (ICD)-9 code and Electronic Data Interchange (EDI). We connected to the medical record database of the Sorokdo National Hospital and archived it from January 2005 to June 2020. With the ICD-9 and -10 codes, we then analyzed medical data on the correlation between DDS and AD. We used the software programs Object-Relational DBMS and SPSS. According to the Official Information Disclosure Act in Korea, we also requested and analyzed the entire ICD 9 and 10 code data (from 2010 to 2019) of AD and AAD from the Health Insurance Review & Assessment system.

4.2. Korean Standard Classification of Diseases (KCD) disease code for "Alzheimer's disease."

The National Agency approved this study for Management of Life-sustaining Treatment, which certified that the life-sustaining treatments were managed properly (Korea National Institute for Bioethics Policy (KoNIBP) approval number P01-202007-22-006).

(1) Mental and behavioural disorders, F00-F09, G30

[F00 code Dementia in Alzheimer's disease (G30.+)]

[F01 code Vascular dementia]

[F02 code Dementia in other diseases classified elsewhere]

[F03 code Unspecified dementia]

[F04 code Organic amnesic syndrome, not induced by alcohol and other psychoactive substances]

[F05 code - Delirium, not induced by alcohol and other psychoactive substances]

[F06 code - Other mental disorders due to brain damage and dysfunction and to physical disease]

[F07 code - Personality and behavioural disorders due to brain disease, damage and dysfunction]

[F09 code - Unspecified organic or symptomatic mental disorder]

[G30 Alzheimer's disease]

(2) For symptomatic relief of Alzheimer's disease

First Group: For symptomatic relief of Alzheimer's disease

[donepezil hydrochloride]

148603ATB 148602ATD 148602ATB 148601ATD 148601ATB 643401ATD 643402ATD

[rivastigmine]

224501ACH 224503ACH 224504ACH 224505ACH 224506CPC 224507CPC 224508CPC

[galantamine]

385203ACR 385203ATR 385204ACR 385204ATR 385205ACR 385205ATR

[N-methyl-D-aspartate (NMDA) receptor antagonist]

190031ALQ 190001ATB 190003ATD 190004ATB 190004ATD

Second Group: For psychologic symptoms of Alzheimer's disease

[haloperidol]

167903ATB 167904ATB 167905ATB 167906ATB 167908ATB 167908ATB 168030BIJ

[Risperidone]

224201ATB 224201ATD 224202ATB 224202ATD 224203ATB 224204ATB 224205BIJ 224206BIJ

[Quetiapine]

378601ATB 378602ATB 378603ATB 378604ATB 378605ATB 378605ATR 378606ATR 378607ATR
378608ATR 378608ATR 378610ATB

[Olanzapine]

204001ATB 204001ATD 204002ATB 204002ATD 204004ATB 204005ATB

[Aripiprazole]

451501ATB 451501ATD 451502ATB 451502ATD 451503ATB 451504ATB 451505ATB 451506BIJ
451507BIJ

[Oxcarbazepine]

206330ASS 206301ATB 206302ATB 206303ATB

[fluvoxamine]

162501ATB 162502ATB

[Escitalopram]

474801ATB 474802ATB 474803ATB 474804ATB

[Trazodone]

242901ACH 242901ATB 242902ATB 242903ATR

[sertraline]

227001ATB 227002ATB 227003ATB

[Escitalopram]

474801ATB 474802ATB 474803ATB 474804ATB

[Fluoxetine]

161501ACH 161501ATB 161502ACH 161502ATB 161502ATD

Declarations

Data availability

According to the Official Information Disclosure Act in Korea, it is possible to provide public access to a dataset based on the linkage of data from nationwide public registries. Access to the National Health Insurance Service (NHIS) in Korea and the Sorokdo National Hospital and the Health Insurance Review & Assessment system's registry data can be granted to individual researchers only upon seeking approval according to the Official Information Disclosure Act in Korea the National Agency for Data Protection. We, therefore, cannot place the dataset in a public repository. However, pooling of aggregated data is possible and would be of interest to the research group.

Acknowledgements

Soon Joe (09-12-1931 ~ 03-01-2021) contributed to making treatment method for MCI & AD, SARS-CoV-2 ARDS. So naming is Soon, Joe's treatment³¹. Dapsone may also be used to prevent, treat AD and COVID-19 ARDS^{12,31}.

Author contributions

JL designed and performed this study and wrote the manuscript. CJL analyzed the medical data statistically and examined the HD patients with MCI and AD in Sorokdo National Hospital. JP analyzed intractable AD symptoms and the use of the AAD (D). SJL analyzed the MCI patient.

Competing interests

The author(s) declare no competing interests.

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Figures

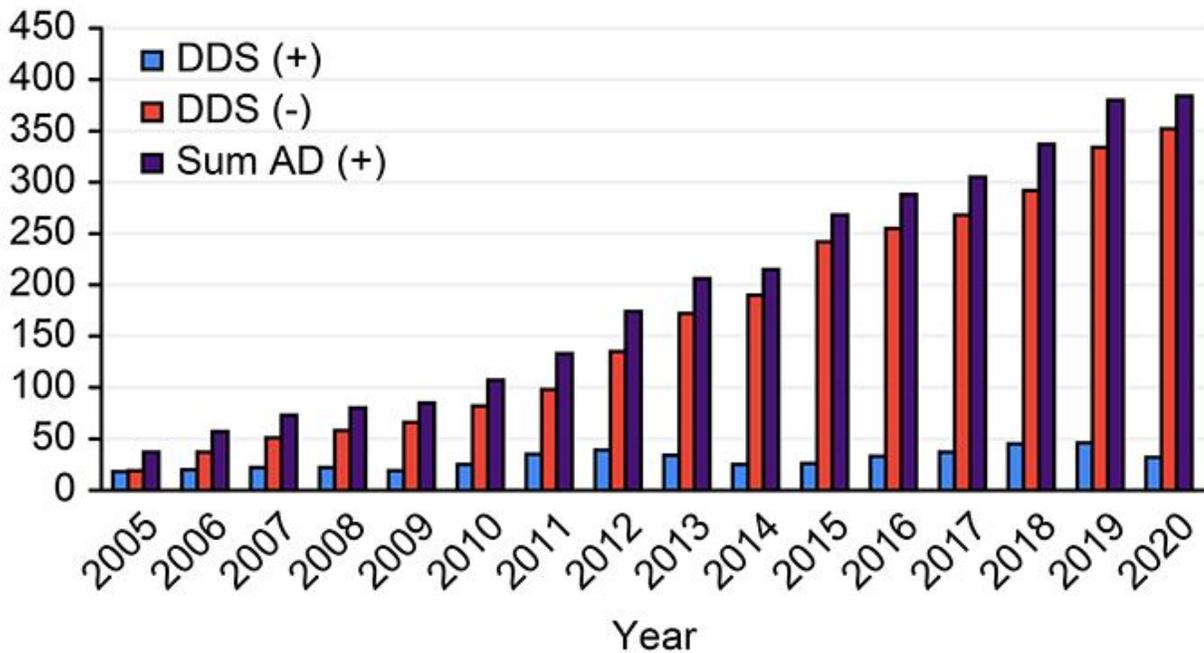
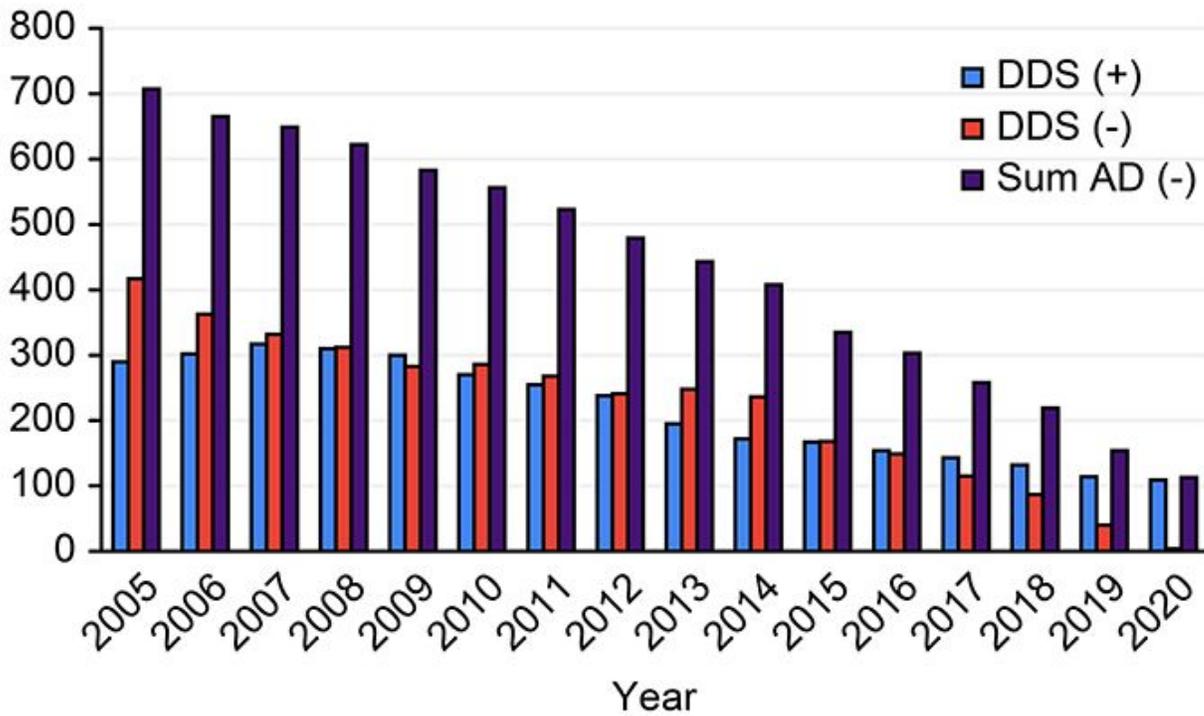


Figure 1

AD in Hansen's disease patients at Sorokdo National Hospital in Korea. The relevant Korean Standard Classification of Diseases (KCD) codes of the International Classification of Diseases (ICD-9, 10) are F00-F99 (mental and behavioural disorders), G30 (Alzheimer's disease), and DDS (140501ATB). The data are archived from January 2005 to June 2020. The graph suggests that DDS acts as a neuro-inflammasome

competitor, given the differential prevalence of AD in patients who have been prescribed DDS and those who have not.

Supplementary Files

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