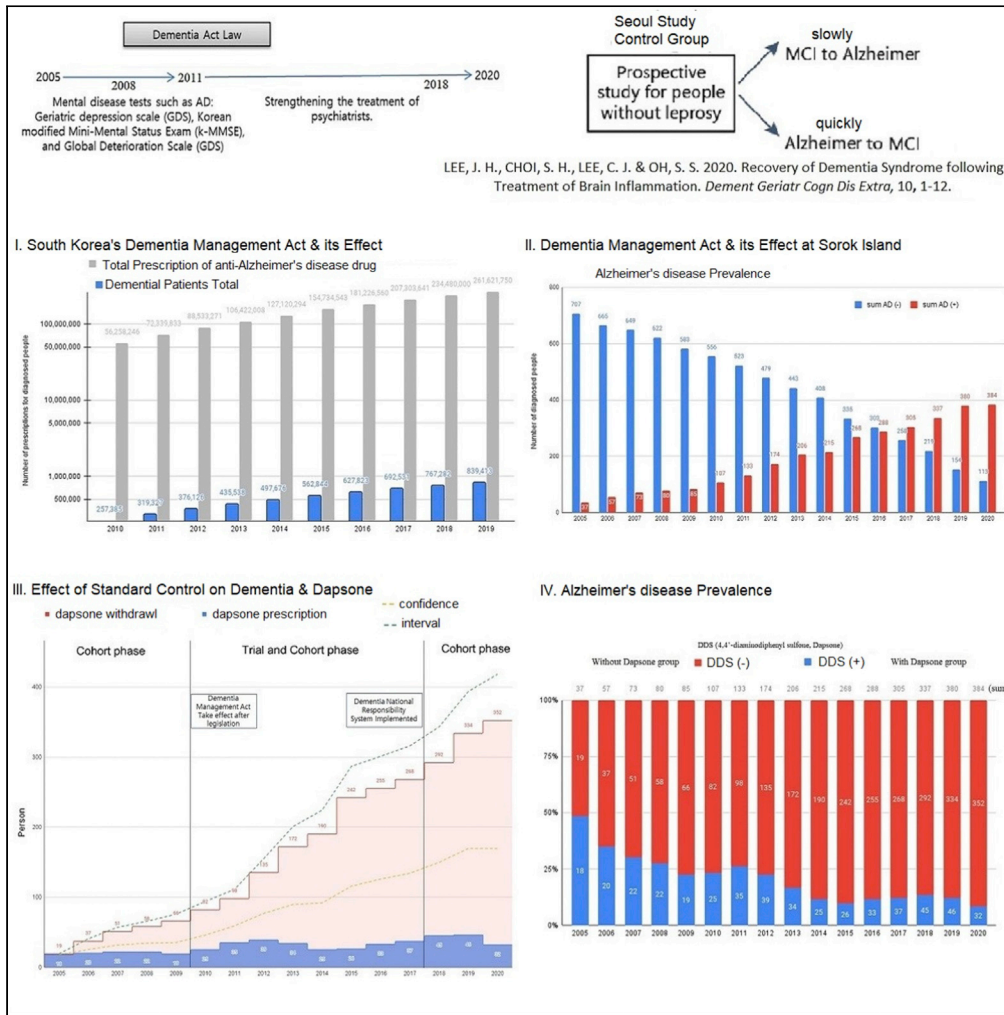## Article

Dapsone is an anticatalysis for Alzheimer's disease exacerbation

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Highlights

Brain inflammation generally accelerates neurodegeneration

Dementia Management Act separates dapsone-taking groups at Sorok Island

The analysis of all from 2005 to 2020 was evaluated based on a p value of 0.05

Dapsone is a preventive therapeutic option for exacerbated Alzheimer's disease

Article

Dapsone is an anticatalysis for Alzheimer's disease exacerbation

Jong Hoon Lee,[1,6,*] Badar Kanwar,[2] Chul Joong Lee,[3] Consolato Sergi,[4] and Michael D. Coleman[5]

SUMMARY

Brain inflammation generally accelerates neurodegeneration. Alzheimer's disease (AD) triggers an innate immune response by activating a cytosolic DNA sensor cyclic-GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) signaling pathway. Our study investigated patients with leprosy and AD. They were treated with dapsone (4,4′-diaminodiphenyl sulfone, DDS) as a neuroinflammasome competitor and cGAS/STING pathway inhibitor. Four groups were defined: Treatment (T) 1: DDS prescribed AD diagnosed, T 2: DDS prescribed AD undiagnosed, T 3 DDS unprescribed AD diagnosed, and T 4: DDS unprescribed AD undiagnosed. Dapsone effects on AD can be clearly distinguished according to dapsone presence or absence. T1:T3 proved that the incidence of AD was significantly reduced by dapsone. T2:T3 proved that the prevalence of AD was significantly high without dapsone. T1:T4 proved that the prevalence decreased when taking dapsone. Our study demonstrates that dapsone can prevent AD exacerbation and may represent a preventive therapeutic option for exacerbated AD.

INTRODUCTION

Alzheimer's disease (AD) is an irreversible, progressive, and incurable brain disorder that impacts memory, cognition, behavior, and personality. It becomes severe before noticeable symptoms appear and cannot be cured by any medicines and therapies. Neuropsychiatric symptoms (NPS) may be highly variable during AD and are considered core AD features rather than merely risk factors for its development (Loeffler, 2021; Lee, 2022). The prevalence rates for NPS in AD patients are apathy (49%), depression (42%), aggression (40%), anxiety (39%), sleep disorder (39%), irritability (36%), appetite disorder (34%), aberrant motor behavior (32%), delusion (31%), disinhibition (17%), hallucination (16%), and euphoria (7%) (Loeffler, 2021; Lee, 2022). Diverse clinical factors reflect the differential involvement of a common core temporoparietal and frontal network that is vulnerable to AD progression (Warren et al., 2012), which is associated with individual genetic influences.

Host-derived oligomerized β-amyloid (Aβ), and tau molecules trigger Nod-like receptor family pyrin domain-containing protein 3 (NLRP3) signaling, and the activation of the chronic NLRP3 inflammasome drives tau pathology, which also causes cognitive decline and AD (Ising et al., 2019; Milner et al., 2021; Trudler et al., 2021). According to Flores et al.'s report (Flores et al., 2021), the sequential activation of a nucleotide-binding oligomerization domain, a leucine-rich repeat and a pyrin domain-containing protein 1 (NLRP 1) inflammasome, caspase-1, and caspase-6 are all implicated in primary human neuron cultures and AD neurodegeneration. In addition, NLRP1, Caspase-1, or Caspase-6 are involved in AD-related cognitive impairment, inflammation, and amyloidogenesis in the AD transgenic mouse model (Flores et al., 2021).

Cytosolic DNA sensor cyclic-GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) signaling is strongly linked to the pathogenesis of CNS diseases, which are highlighted by neuroinflammation-driven disease progression (Fengjuan et al., 2021). Innate immune recognition is mediated by a vast array of germline-encoded innate immune receptors. Pattern recognition receptors and inflammasomes are a distinct class of intracellularly expressed pattern recognition receptors that recognize nucleic acids and mediate proinflammatory responses. The cGAS-STING axis has been identified as a significant nucleic acid recognition pathway, and the cGAS-STING-lysosomal cell death-NLRP3 pathway will ameliorate pathology in inflammatory conditions associated with cytosolic DNA sensing (Gaidt et al., 2017).

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Table 1. Incidence of probable dementia by treatment group from January 2005 to June 2020

Year	DDS (+)[a]	DDS (−)[b]	AD[c] (+) Total	DDS (+)	DDS (−)	AD(−) Total	P-value[d]
2005	18	19	37	290	417	707	0.3583
2006	20	37	57	302	363	665	0.1324
2007	22	51	73	317	332	649	0.0024[e]
2008	22	58	80	310	312	622	0.00028[e]
2009	19	66	85	300	283	583	<0.00001[e]
2010	25	82	107	270	286	556	<0.00001[e]
2011	35	98	133	255	268	523	<0.00001[e]
2012	39	135	174	238	241	479	<0.00001[e]
2013	34	172	206	195	248	443	<0.00001[e]
2014	25	190	215	172	236	408	<0.00001[e]
2015	26	242	268	167	168	335	<0.00001[e]
2016	33	255	288	154	149	303	<0.00001[e]
2017	37	268	305	143	115	258	<0.00001[e]
2018	45	292	337	132	87	219	<0.00001[e]
2019	46	334	380	114	40	154	<0.00001[e]
2020	32	352	384	109	4	113	<0.00001[e]
Sum	478	2651		3468	3549		
Mean	29.88	165.69		216.75	221.81		
SD[f]	9.03	112.31		76.04	117.71		
95% CI[g]	0.81[29.06–30.69]	4.28[161.41–169.96]		2.53[214.22–219.28]	3.87[217.94–225.69]		
Chi-square	252.58						
p value	<0.00001						
The value of R[h]	r(15) = 0.74, p < 0.01. moderately correlated			r(15) = 0.92, p < 0.00001. strongly correlated			

[a]DDS prescription (+) group.
[b]non-prescription (−)group.
[c]Alzheimer's Disease (AD) patients.
[d]The relation between DDS and Alzheimer's Disease each year was analyzed using the chi-square test. A p-value < 0.05 was considered significant.
[e]indicates a p-value < 0.05.
[f]Standard Deviation (SD).
[g]Confident Interval (CI).
[h]Pearson Correlation Coefficient.

Polyglutamine binding protein 1 (PQBP1) triggers an innate immune response by activating the cGAS-STING pathway and is needed for sensing-tau to induce nuclear translocation of nuclear factor κB (NF-κB). In addition, PQBP1 shows an intracellular receptor in the cGAS-STING pathway for cDNA of human immunodeficiency virus (HIV) and the transmissible neurodegenerative disease protein tau (Jin et al., 2021). Dapsone (4,4′-diaminodiphenyl sulfone, DDS) has been linked to an impact on the regulation of NLRP3, which activates mild cognitive impairment (MCI), AD, and SARS-CoV-2-associated acute respiratory distress syndrome (ARDS) (Namba et al., 1992; McGeer et al., 1992, 1994; Lee et al., 2020b, 2021; Kanwar et al., 2021, 2022).

When we treated microglia with pathological tau with hyperphosphorylation and aggregation-containing neuronal media, exosomes, or paired-helical filaments from the human tauopathy brain, we observed interleukin-1β (IL-1β) activation, which is dependent on NLRP3, ASC, and caspase-1 (Jiang et al., 2021). The pathological tau burden coexists with elevated IL-1β and ASC in autopsy brains of human tauopathies (Jiang et al., 2021). Reduced ubiquitin-proteasome system activity has been found in patients affected by AD and its malfunction plays a significant role in Aβ accumulation (Bellia et al., 2021).

Now we focus on the study analyzing the medical records of Sorokdo National Hospital from 2005 to 2020 based on the control group initiated from 1962 to 2005 (Anthony, 2019). This study analyzed
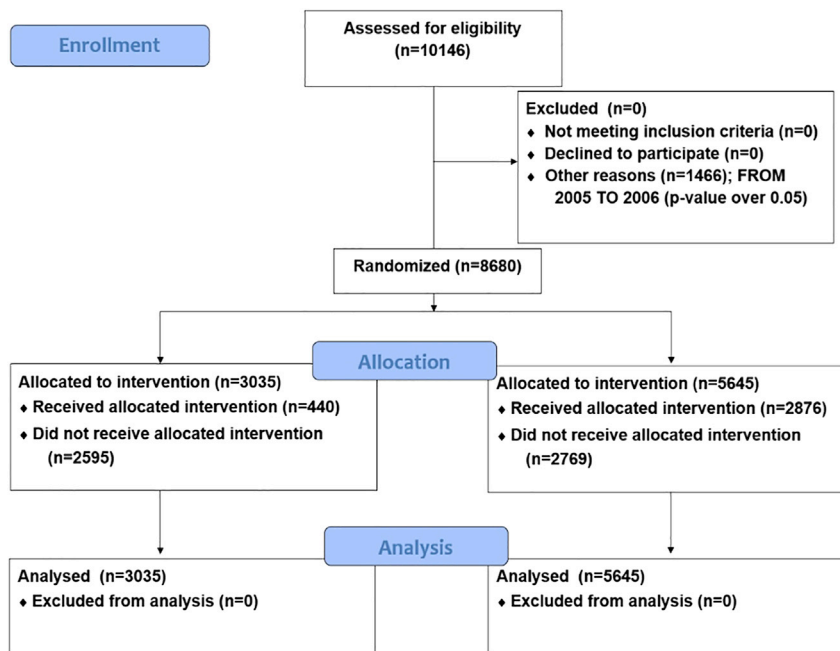
Figure 1. Participant flow of clinical cohort study in the sorokdo national hospital

clinical AD prevalence in leprosy (Hansen's disease HD) patients and inflammasome activity in Sorok Island.

RESULTS

According to the DMA, the medical staff of Sorokdo National Hospital started the diagnosis and treatment of dementia for all HD patients on Sorok Island. As a result, AAD was started for patients diagnosed with dementia, and doctors stopped prescribing dapsone for inactive HD patients. Thus, the two groups were divided clearly. AD (+) subjects (Sum (S) = 3129, Mean (M) = 195.56, Standard Deviation (SD) = 119.15; 95% Confident Interval (CI), 191.39–199.74) consisted of DDS (+) (S = 478, M = 29.88, SD = 9.03; 95% CI, 29.06–30.69) and DDS (−) (S = 2651, M = 165.69, SD = 112.31; 95% CI, 161.41–169.96). AD (−) subjects (S = 7017, M = 438.56, SD = 190.18; 95% CI, 434.11–443.01) consisted of DDS (+) (S = 3468, M = 216.75, SD = 76.04; 95% CI, 214.22–219.28) and DDS (−) (S = 3549, M = 221.81, SD = 117.71; 95% CI, 217.94–225.69) (Table 1) (Figure 1).

Based on the prevalence of AD in patients who have been prescribed and those who have not, dapsone has a preventive effect against AD. AD-diagnosed (+) subjects increased in the DDS (−) group from January 2005 to June 2020 (Figure 2).

Outcome measures with the p-values between treatment groups

The AD (+/−) group was arranged based on the DDS prescription/non-prescription (+/−) group from 2005 to 2020. The relation between DDS and AD each year was analyzed using the chi-square test. The p-value was significant from 2007 to 2020 when the p-value was considered significant at < 0.05 (Table 2).

For the variables DDS (+) and DDS (−) in AD (+) patients, we calculated Pearson's r (Pearson's correlation coefficient) to examine whether they were correlated. The value of R is 0.7406. This is a moderate positive correlation, which means there is a tendency for high X variable scores to go with high Y variable scores (and vice versa). The p-value is 0.001033. The result is significant at p < 0.05. For the variables DDS (+) and DDS (−) in AD (−) patients, we calculated Pearson's r to examine whether they were correlated. The value of R is 0.9233. This is a strong positive correlation, which means that high X variable scores have high Y variable scores (and vice versa). The p-Value is <0.00001. The result is significant at p < 0.05 (Tables S1, S2, S1-1, S2-1).
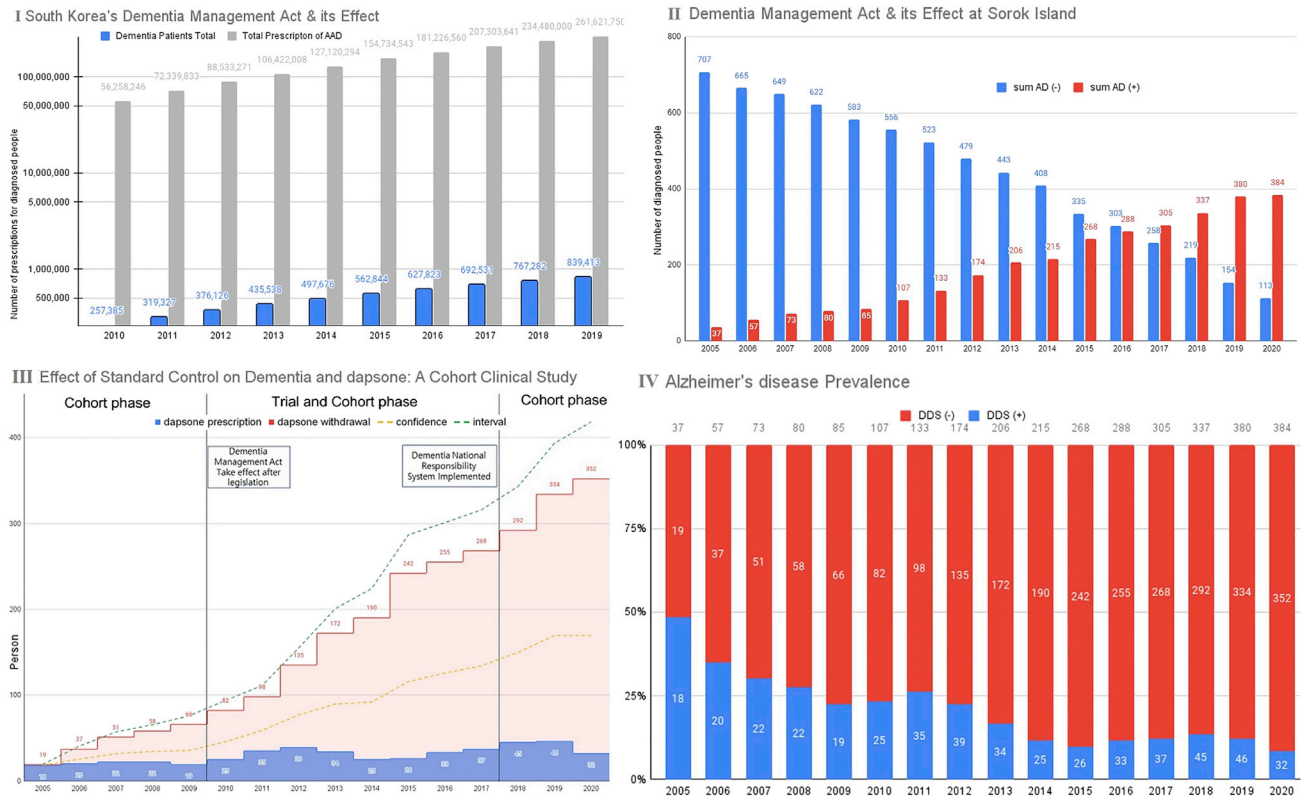
Figure 2. A cohort clinical study for effect of standard control on dementia and dapsone

The Dementia Management Act (DMA) had a significant influence on the diagnosis and treatment of dementia. I. DMA increased the diagnosis of patients with MCI or AD by 3.26 times. In addition, anti-Alzheimer's disease drug (AAD) prescriptions increased 4.65-fold in South Korea from 2010 to June 2019. Thus, through rapid diagnosis and prescription changes over ten years, it is possible to monitor how AAD affects dementia. II. The number of AD-diagnosed (+) HD patients shows an increasing tendency, and the number of AD-nondiagnosed (−) HD patients shows a decreasing tendency. Over 15 years, the number of AD patients increased from 37 to 380. Therefore, the suspension of dapsone by DMA itself needs to be considered an AD trial. III. We classified three phases in Sorok Island. First, based on 2010, when DMA was enacted, and second, 2018, when the dementia national responsibility system was implemented. Therefore, diagnosis and treatment for dementia by DMA were performed. Finally, we decided to analyze this cohort as a type of randomized controlled trial. IV. There is an AD prevalence graph from 2005 to 2020 between the DDS prescription (+) group; HD patients take DDS and the DDS non-prescription (−) group; HD patients do not take DDS. This graph shows a clear relationship between significantly fewer HD patients developing AD in the trial group who regularly took DDS.

The values of f and p were calculated using an ANOVA calculator. Four groups were defined for the T-test: Treatment (T) 1: DDS (+) AD (+), T 2: DDS (+) AD (−), T 3: DDS (−) AD (+), and T 4: DDS (−) AD (−). The f-ratio value is 58.43. The p value is <0.00001 in the one-way repeated measures. The f-ratio value is 77,90, and the p value is <0.00001. The results are all significant at $p < 0.05$ (Tables S4-1, S4-2). However, there were caveats to post hoc Tukey's honestly significant difference. The pairwise comparisons (T1:T2, T1:T3, T1:T4, T2:T3, T2:T4, and T3:T4) were applicable except for T2:T4 (Table S4-3).

t-test

We used the data normalization technique to analyze AD prevalence and the DDS (+)/(−) group from January 2007 to June 2020. T-tests were calculated with the one-way repeated-measures ANOVA calculator. T1 (M = 0.18, SD = 0.074):T2 (M = 0.55, SD = 0.14) in the group taking Dapsone also demonstrated that the group with AD and the group without AD was distinguished. The *t*-value is −8.73 and the p value is <0.00001. (significant at $p < 0.05$) (Table S4-4 and Figure S3)

T3 (M = 0.18, SD = 0.074):T4 (M = 0.55, SD = 0.14) in the group not taking dapsone also demonstrated that the group with AD and without AD was distinguished. The *t*-value is −8.73 and the p value is <0.00001. (significant at $p < 0.05$) (Table S4-5 and Figure S4)

Table 2. T-test table for Alzheimer's Disease prevalence and DDS prescription rates

Year	T1: DDS(+)/ AD(+)total	T2: DDS(+)/ AD (−)total	T3: DDS(−)/ AD (+)total	T4: DDS(−)/ AD(−)total
2007	0.3014	0.4884	0.6986	0.5116
2008	0.2750	0.4984	0.7250	0.5016
2009	0.2235	0.5146	0.7765	0.4854
2010	0.2336	0.4856	0.7664	0.5144
2011	0.2632	0.4876	0.7368	0.5124
2012	0.2241	0.4969	0.7759	0.5031
2013	0.1650	0.4402	0.8350	0.5598
2014	0.1163	0.4216	0.8837	0.5784
2015	0.0970	0.4985	0.9030	0.5015
2016	0.1146	0.5083	0.8854	0.4917
2017	0.1213	0.5543	0.8787	0.4457
2018	0.1335	0.6027	0.8665	0.3973
2019	0.1211	0.7403	0.8789	0.2597
2020	0.0833	0.9646	0.9167	0.0354

The f-ratio value is 77.90945. The p-value is <.00001. The result is significant at $p < .05$.

The National Dementia Responsibility System of South Korea separated the group taking Dapsone from 2011 to 2020. T1:T2 and T3:T4 explain that a cohort has been created in which its effects on AD can be clearly distinguished according to its presence or absence.

The participants with T1 were compared to T3. The T1:T3 test proved that the incidence of AD was significantly reduced by dapsone. The t-value is −23.1, p value is <0.00001. (significant at $p < 0.05$) (Tables S4-6 and Figure S5)

The participants with T2 were compared to T3. The T2:T3 test proved that the prevalence of AD was significantly high without dapsone, and the proportion of HD patients without AD was increased with dapsone. The t-value is −6.38, p value is <0.00001. (significant at $p < 0.05$) (Table S4-7 and Figure S6)

The participants with T1 were compared to T4. This demonstrates that HD patients also develop AD, but the prevalence decreased when taking dapsone. Fewer people do not develop AD without taking dapsone. The t-value is −6.38. The p value is <0.00001. (significant at $p < 0.05$) (Table S4-8 and Figure S7) The T1:T4 test and the T2:T3 test demonstrate a causal relationship in which the presence or absence of DDS determines the onset of AD. (Figure 3)

The T1:T3 tests demonstrate that the incidence of AD is significantly reduced in the presence of dapsone among AD patients. The T2:T3 test showed that the prevalence of AD is significantly high without dapsone, and the proportion of HD patients without AD is increased with dapsone. AD is increased in the absence of dapsone. Our study has demonstrated that dapsone has the potential to prevent AD.

DISCUSSION

Sorok Island was established in May 1916 to quarantine leprosy patients during the colonial period. The public health report filed on Jun 04, 1946, succinctly stated that they would increase the capacity of Sorokdo Leper Colony to 8,000–9,000 and make it the largest leprosarium in the world (Kim, 2012; Jane, 2010). Since diagnosis, the island has been home to HD sufferers for their whole lives. This study is a cohort study with more than 100 years of history.

Sorokdo National Hospital administers the main medicine according to the standard therapy specified in the Hansen project guidelines of the Korea Centers for Disease Control and Prevention based on the World Health Organization (WHO) recommendations for the treatment and prevention of recurrence of
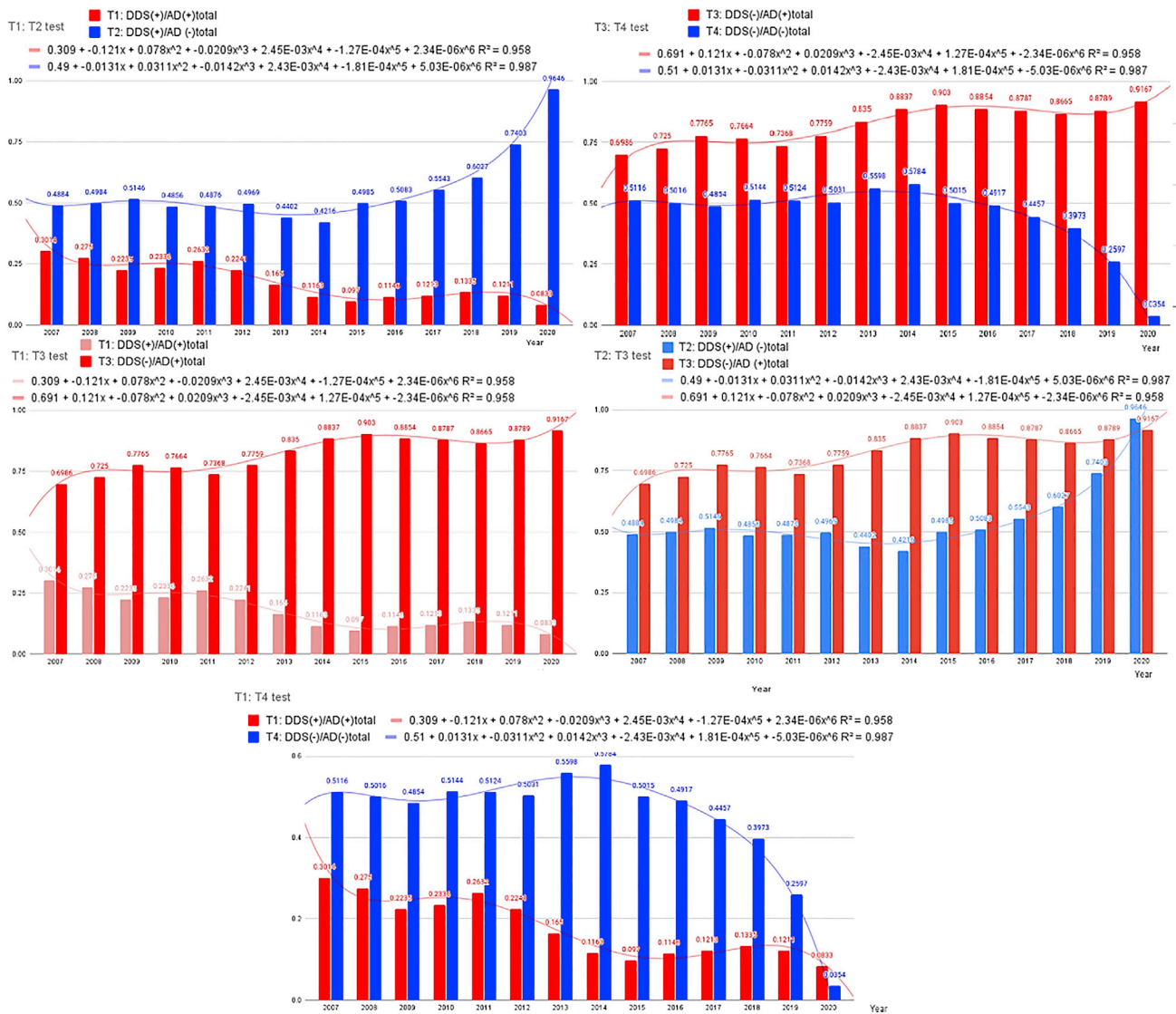
Figure 3. T-test results for Alzheimer's disease prevalence and DDS prescription rates

We used the data normalization technique to analyze Alzheimer's disease (AD) prevalence and the DDS prescription (+)/non-prescription (−) group from January 2007 to June 2020 as T1: DDS(+)/AD(+), T2: DDS(+)/AD (−), T3: DDS(−)/AD (+), and T4: DDS(−)/AD(−). The participants with T1 (M = 0.1766, SD = 0.074) were compared to those with T2 (M = 0.5501, SD = 0.1421). T1:T2 in the group taking Dapsone also demonstrated that the group with AD and the group without AD were distinguished. We compared T3 (M = 0.1766, SD = 0.074) and T4 (M = 0.5501, SD = 0.1421). T3:T4 in the group not taking Dapsone also demonstrated that the group with AD and without AD was distinguished. The participants with T1 (M = 0.1766, SD = 0.074) were compared to those with T3 (M = 0.1766, SD = 0.074). The T1:T3 test proved that the incidence of AD was significantly reduced by dapsone. The participants with T2 disease (M = 0.5501, SD = 0.1421) were compared to those with T3 disease (M = 0.1766, SD = 0.074). The T2:T3 test proved that the prevalence of AD is significantly high without dapsone, and the proportion of HD patients without AD is increased with dapsone. The participants with T1 (M = 0.1766, SD = 0.074) were compared to T4 (M = 0.5501, SD = 0.1421). The T1:T4 test demonstrated that the trend was similar for patients with DDS (+)/AD (+) and DDS (−)/AD (−). This demonstrates that HD patients also develop AD but at a significantly lower rate when taking dapsone. Fewer people who do not develop AD without taking dapsone suggest that there is a clear distinction between the group taking dapsone and the group not taking dapsone.

HD (Table 3). If the test result of leprosy patients turns inactive or keeps inactive, they are not taking leprosy drugs.

From 2008, the medical staff of Sorokdo National Hospital at Sorok Island performed standard treatment according to AD symptoms and neuropsychiatric examination results for leprosy patients. They supported the prescription of AADs and discontinued dapsone in patients with inactive leprosy. As a result,

Table 3. Standard prescription for leprosy chemotherapy at Dermatology Department in Sorokdo National Hospital

Leprosy patient[a]	active patient		inactive patient	
Bacteria load condition	Rich	Low	Rich	low
Dapsone (DDS)	100mg daily	100mg daily	100mg daily	100mg daily
Rifampicin (RMP)	600 mg daily, 600 mg once a month after 3 to 12 months administration	600 mg daily for 3 months	600 mg once a month	600 mg once a month
Clofazimine (Lamprene, B663)	50 mg daily plus 300 mg once a month	50 mg daily	50 mg daily	–
dosing period	two additional years after switching to inactive	add six months after two years of dosing	two years	six months

[a]Reproduced from: Department of Dermatology of Sorokdo National Hospital. Standard prescription for leprosy chemotherapy, translated 2022 March. web: http://www.sorokdo.go.kr/sorokdo/html/content.do?menu_cd=02_03_03&depth=ms.

it became possible to separate the group taking dapsone from the group not taking dapsone among AD patients for fifteen years (Figure 3. T1:T2, T3:T4 test). Thus, the relationship between AD and dapsone became clear. In the event that studies did not distinguish groups who had been prescribed from the other groups discontinued taking dapsone then the effects of dapsone as an inflammasome competitor are mixed or concealed in the autopsy findings, similar to previous confusing pathologic reports (McGeer et al., 1992, 1994; Namba et al., 1992; Kimura and Goto, 1993; Chui et al., 1994; Goto et al., 1995; Endoh et al., 1999).

Normally, healthy neurovascular tissue promotes the integrity of the blood-brain barrier (BBB). The brain microvessel capillary phenotypes have differences in a lack of fenestration and low pinocytotic activity. They mostly have tight junctions with low permeability between cells. Because many central nervous system (CNS) diseases are strongly linked with local inflammation and oxidative stress, the efficiency of drugs acting on the CNS: in drug penetration through the BBB and treating them is essential (Miller, 2010). Dapsone passes through the BBB results in an effective CSF concentration in humans (Nau et al., 2010). The results of many epidemiologic studies and limited clinical evidence suggest that NSAIDs should delay the onset and hinder AD progression (Breitner et al., 1995; Anthony et al., 2000). Chronic activation of cGAS by self-DNA leads to severe autoimmune diseases for which no effective treatment is available yet. Activation of cGAS signaling requires its deacetylation, but acetylation inhibits cGAS activation and that the enforced acetylation of cGAS by aspirin robustly suppresses self-DNA-induced autoimmunity. Aspirin has therapeutic potential to treat SLE by acetylating cGAS, and acetylation suppresses cGAS activity. Acetylation by aspirin inhibits cGAS-mediated interferon production and alleviates DNA-induced autoimmunity in Aicardi-Goutières syndrome patient cells (Dai et al., 2019) (Elkon, 2019).

However, the results of long-term clinical trials with aspirin were negative. NSAIDs affect the periphery of the inflammatory reaction (McGeer and McGeer, 2002). Thus, dapsone appears to have more significant anti-inflammatory effects than NSAIDs. Dapsone can regulate the production of hypochlorous acid, which is associated with myeloperoxidase, a peroxidase that forms reactive species that form hypochlorous acid, which is part of the neutrophilic response to bacterial invasion. DDS may regulate NLRP3 inflammasome activators and a common signaling pathway (Lee et al., 2020a). According to a report on the neuroinflammasome treatments and AAD side effects, neuroinflammasomes without dapsone were exacerbated for two years from MCI to AD, and then dapsone has shown a capacity to revert AD to MCI from Nov 28, 2018, to Jan 18, 2019. Dapsone may have achieved this through a competitive therapeutic mechanism to counter the progression of MCI to AD (Lee et al., 2020b, 2021). This study explains that dapsone acts to inhibit the neuroinflammasome and ubiquitination stochastically by the flow of electrons (Lee et al., 2020a; Kanwar et al., 2021). (Figure 4)

Lee et al. reported the observed preventive treatment effects, functioning as an inflammasome competitor for pandemic viral inflammasomes. A total of 2186 people (1152 males, 1034 females) and the average age was 83.7 years (M 84, IQR 76.8–91.2, SD 10.8, 95% CI: 0.45, 83.6–84.5) from 2005 to 2020 on Oct 27, 2020. They compared leprosy patients with viral respiratory diseases (VRDs) after prescribing dapsone to standard treatment from 2005 to 2020. The 3022 VRD participants who received the dapsone intervention
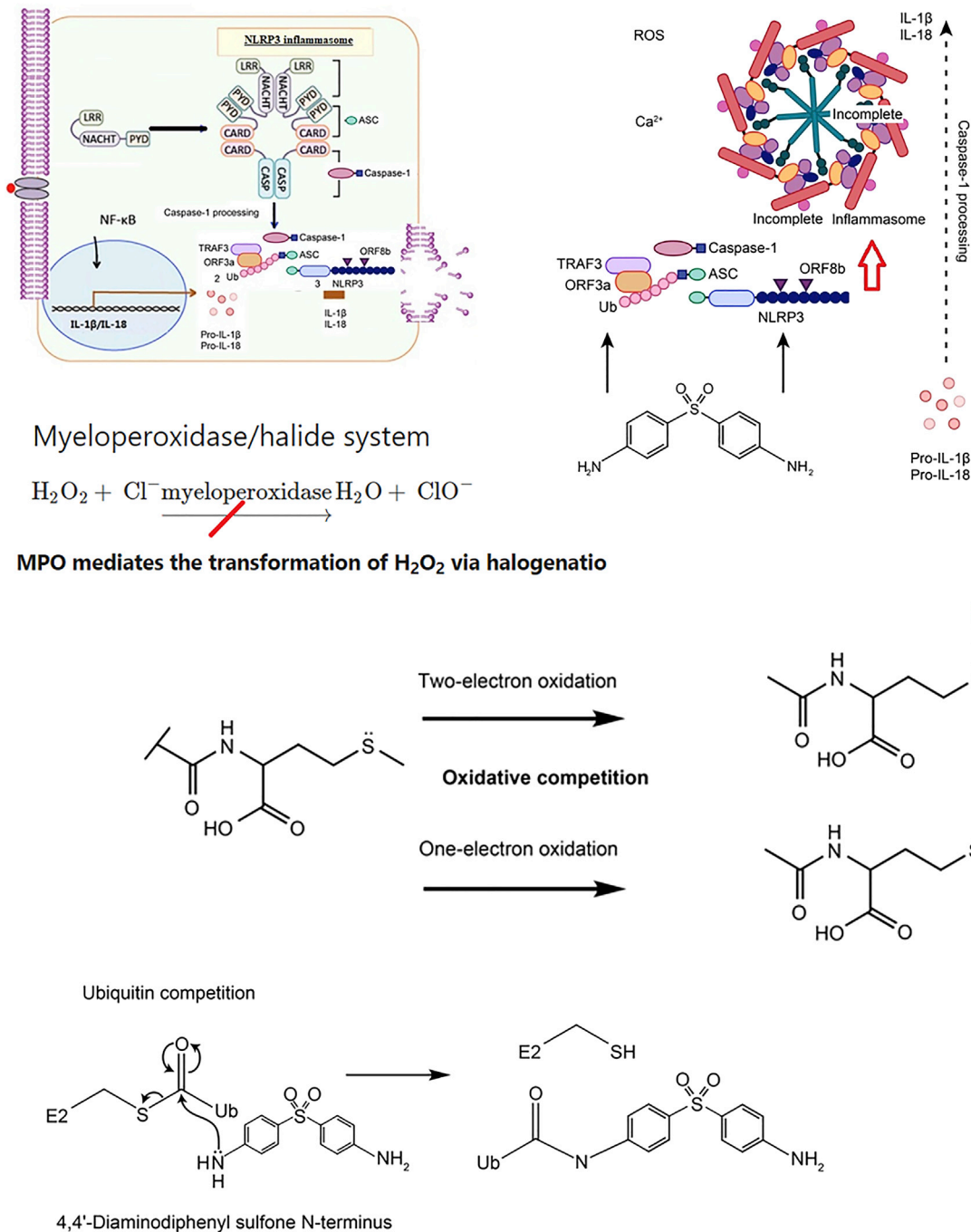
Figure 4. Anticatalysis schematic diagram: blocking of the neuroinflammasome by Dapsone(Lee et al., 2020a)

Dapsone is a myeloperoxidase inhibitor. Myeloperoxidase is a kind of oxidoreductase that catalyzes the chemical reaction of the following response: $H_2O_2+Cl^- = H_2O + OCl^-$. Dapsone binds to myeloperoxidase and regulates the production of hypochlorite, thereby reducing the inflammatory response of cells. Dapsone inhibits radical one-electron oxidation by oxidative competition. The methionine (Met) residue at position 35 in the Aβ C-terminal domain is critical for neurotoxicity, aggregation, and free radical formation initiated by the peptide (Enache and Oliveira-Brett, 2017). The bicarbonate/carbon dioxide pair cannot stimulate one-electron oxidation mediated by a radical carbonate anion ($CO_3^{\cdot-}$), which efficiently oxidizes the thioether sulfur of the Met residue to sulfoxide. Instead, $CO_3^{\cdot-}$ causes the one-electron oxidation of methionine residue to sulfur radical cation ($MetS^{\cdot+}$) (Francioso et al., 2020). Dapsone has nucleophilic properties. Nucleophilic properties of dapsone compete with NLRP3. ORF8b activates NLRP3 through direct interaction of the leucine-rich repeat domain of NLRP3. Nucleophilic properties of DDS compete with NLRP3. DDS binds to the AT-rich region of the minor groove of DNA. The nucleophilic properties of dapsone also compete with those of ubiquitin. Dapsone can compete with the ubiquitination cascade. Cysteine thiols and hydroxyls on serines, threonines, leucines, and tyrosines could also potentially be ubiquitinated by an identical mechanism.

(M = 201, SD = 34) compared to the 3961 VRD participants in the control group (M = 264, SD = 84) demonstrated significantly better peak flow scores, t(28) = −2.7, p = 0.01 (Jong-Hoon et al., 2021). Dapsone acts like PQBP1 in the cGAS-STING pathway for cDNA of HIV and the transmissible neurodegenerative disease protein tau (Jin et al., 2021). Dapsone can compete with the ubiquitination cascade. The identical mechanisms can potentially ubiquitinate cysteine thiols and hydroxyls on serines, threonines, leucines, and tyrosines (Lee et al., 2020a; De Cesare et al., 2021). Dapsone noncovalently binds/interacts with the minor groove of DNA so that it might inhibit STING gene expression directly.

According to our study results, we considered a common impact of dapsone on inflammasome-driven diseases. Kanwar et al. administered standard treatment plus dapsone for coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS) patients in the intensive care unit (ICU) from Dec 21 to Dec 29 2020. The case-control study in ICU is symmetrical (22/22). The mortality rates at the ARDS onset stage were 0 (5.9)% and 40%, respectively. The 17 participants (M = 1.7, SD = 2.63) received the dapsone intervention compared to the 20 participants (M = 2.8, SD = 3.79) in the control group at the ARDS onset stage. The chi-square statistic is 5.81. (p value is 0.016, significant at p < 0.05).

Thus, continuous preventive anticatalysis treatments are needed to treat AD over ten years. The appropriate observation period for dementia seems to be more than ten years regarding our study results. This study overcomes the diverse limitations of previous five-year-observational studies. A more large-scale preceding cohort study is also necessary for the elderly (Khattak et al., 2021).

This study indicates that dapsone is a valid preventive therapeutic for exacerbated AD.

Limitations of the study

The paradoxical limitation of this study is that it was conducted in an isolated island area. Therefore, a large-scale population survey study is required to derive universal research results later, in which study dapsone should be prescribed as preventive medicine for dementia, and it may also be key to perform in open countries and have at least a 10-year observation period.

STAR★METHODS

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- ADDITIONAL RESOURCES

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2022.104274.

in February 1962 and Sister Margaritha Pissarek entered Sorok Island in October 1967. They treated the control group of this study for 40 years with dedication, free of charge, and we decided to call this AD study 'Marianne and Margaritha treatment'. JL's older sister, Young Soo Lee, a genius painter and designer, who has shown improvement in cognitive function in dementia for 10 years even after undergoing cerebral hemorrhage, CPR, and two surgeries, who have been the constant motivation for this study and the thesis. Six hours before we heard from the editorial office, we heard that she had passed away. She repainted her pictures and read books.

AUTHOR CONTRIBUTIONS

Conceptualization, J.L.; Methodology, J.L.; Investigation, B.K., C.J.L, and J.L.; Resources, C.J.L. and J.L.; Data Curation, J.L.; Writing – Original Draft, J.L.; Writing – Review & Editing, C.S. and M.D.C.; Visualization, J.L.; Supervision, B.K., C.J.L, C.S., and M.D.C.; Project Administration, J.L.

DECLARATION OF INTEREST

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Sorok Island_Population_Demography-Lee, Jong-hoon (2022), "Basic Cohort Study: Dapsone is an anticatalysis for Alzheimer's disease exacerbation", Mendeley Data, V2, https://doi.org/10.17632/bt6h5trpg9.2	Seoul National University College of Medicine	disclosure_7,511,041_Sorok Island_Population_Demography.xlsx
Sorok Island_Cohort-Lee, Jong-hoon (2022), "Basic Cohort Study: Dapsone is an anticatalysis for Alzheimer's disease exacerbation", Mendeley Data, V2, https://doi.org/10.17632/bt6h5trpg9.2	Seoul National University College of Medicine	disclosure 693,119_Sorok Island_Cohort.xlsx
Software and Algorithms		
Effect Size Calculator for T-TestOne-Way ANOVA Calculator for Independent MeasuresT-Test Calculator for 2 Independent MeansT-Test Calculator for 2 Dependent MeansPearson Correlation Coefficient CalculatorPost hoc Tukey honestly significant difference (HSD)	SPSS FROM SocSciStatistics.Com	https://www.socscistatistics.com/tests/

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Jong Hoon Lee (science@research.re.kr)

Materials availability

This study did not generate new unique reagents.

Data and code availability

We presented the data through the pooling of aggregated data (Reserved https://data.mendeley.com/datasets/bt6h5trpg9/2, https://doi.org/10.17632/bt6h5trpg9.2). Any additional information required to re-analyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAIL

Population demography

HD patients have lived on Sorok Island for a lifetime. According to the request for disclosure of health checkup information from 2005 to 2020 on Oct 27, 2020, a total of 2186 people (1152 males, 1034 females) resided there, and the average age was 83.7 years (median (M) 84, interquartile range (IQR) 76.8–91.2, standard deviation (SD) 10.8, 95% confidence interval (CI): 0.45, 83.6–84.5) (Figures S1 and S2).

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 patient's informed consent.

The National Agency approved this study for the Management of Life-sustaining Treatment, which certified that life-sustaining treatments were managed properly (Korea National Institute for Bioethics Policy (KoNIBP) approval number P01-202007-22-006). The KoNIBP approved the observational study of patients ethically based on FDA guidelines following the World Medical Association Declaration of Helsinki. Therefore, we carried out all methods following relevant ethical guidelines and regulations and reported the study results. Sorokdo National Hospital provided the necessary information in accordance with Article 13 of the "Act on Information Disclosure of Public Institutions". Sorokdo National Hospital obtained

informed consent from all participants or, if participants were under 18, from a parent and/or legal guardian.

METHOD DETAILS

Study design

In the 1990s, a Japanese epidemiological survey of HD patients revealed dementia in leprosy patients. McGeer et al. detected the low prevalence of AD (McGeer et al., 1992, 1994). Furthermore, a neuropathological case series of leprosy patients noticed the absence of senile plaques. They showed high abnormal tau deposition in neurons and neural threads despite low levels of Aβ deposition (Chui et al., 1994). However, similar studies the following year showed no difference in discovering senile plaques between the patient and control groups (Namba et al., 1992; Kimura and Goto, 1993; Goto et al., 1995). Therefore, we hypothesized that the lack of an effect of antileprosy drugs in preventing AD and Aβ neurotoxicity (Endoh et al., 1999) should be a null hypothesis (Lee et al., 2020b; Kanwar et al., 2021). A pilot cohort study on dapsone was conducted from 2008 to 2020 and demonstrated recovery from AD to MCI (Lee et al., 2020b, 2021). Therefore, we expanded to HD patients taking dapsone continuously for decades on Sorok Island.

Eligibility criteria

According to the Dementia Management Act, all Hansen subjects on Sorok Island are registered and treated at Sorokdo National Hospital. For this study, we analyzed all leprosy patients who could study the relationship between AD and dapsone. The cohort consisted of AD patients, dapsone, and anti-Alzheimer's disease drug (AAD) users in all Hansen subjects according to South Korea's Official Information Disclosure Act. We searched all medical records of the Sorokdo National Hospital and the National Health Insurance Service (NHIS) in South Korea from 2005 when the Korean government computerized the International Classification of Diseases (ICD) codes and Electronic Data Interchange (EDI). We connected 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 dapsone and AD.

Study setting

ICD code of Korean diseases and medicines

(1) Mental and behavioral 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 behavioral 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] 148,603ATB 148602ATD 148602ATB 148601ATD 148601ATB 643401ATD 643402ATD, [rivastigmine] 224,501ACH 224503ACH 224504ACH 224505ACH 224506CPC 224507CPC 224508CPC, [galantamine] 385,203ACR 385203ATR 385204ACR 385204ATR 385205ACR 385205ATR, [N-methyl-D-aspartate (NMDA) receptor antagonist] 190,031ALQ 190001ATB 190003ATD 190004ATB 190004ATD

Second group: for psychologic symptoms of Alzheimer's disease

[haloperidol] 167,903ATB 167904ATB 167905ATB 167906ATB 167908ATB 167908ATB 168030BIJ, [Risperidone] 224,201ATB 224201ATD 224202ATB 224202ATD 224203ATB 224204ATB 224205BIJ 224206BIJ, [Quetiapine] 378,601ATB 378602ATB 378603ATB 378604ATB 378605ATB 378605ATR 378606ATR 378607ATR 378608ATR 378608ATR 378610ATB, [Olanzapine] 204,001ATB 204001ATD 204002ATB 204002ATD 204004ATB 204005ATB, [Aripiprazole] 451,501ATB 451501ATD 451502ATB 451502ATD 451503ATB 451504ATB 451505ATB 451506BIJ 451507BIJ, [Oxcarbazepine] 206,330ASS 206301ATB

206302ATB 206303ATB, [Fluvoxamine] 162,501ATB 162502ATB, [Escitalopram] 474,801ATB 474802ATB 474803ATB 474804ATB, [Trazodone] 242,901ACH 242901ATB 242902ATB 242903ATR, [Sertraline] 227,001ATB 227002ATB 227003ATB, [Escitalopram] 474,801ATB 474802ATB 474803ATB 474804ATB, [Fluoxetine] 161,501ACH 161501ATB 161502ACH 161502ATB 161502ATD

Complete blinded study

We classified three phases in Sorok Island. First, based on 2011, when the Dementia Management Act (DMA) was enacted, and second, 2018, when the dementia national responsibility system was implemented. Therefore, DMA was enacted to diagnose and treat all HD subjects. In particular, HD patients on Sorok Island were diagnosed and treated without exception. Doctors treated leprosy and Alzheimer's disease, and HD patients were treated, while no one knew about Dapson's relationship to AD. In addition, they were all in complete-blinded states. Therefore, we investigated this cohort study with the randomized controlled trial methodology.

Interventions

The 'War against Dementia' and the First National Dementia Plan was announced in 2008 (Lee, 2019), the DMA came into effect on Aug 04, 2011, and it was amended on Jun 12, 2018 (Korea Legislation Research Institute, 2018). According to the DMA, the medical staff of Sorokdo National Hospital started a full investigation in 2010 for the treatment of dementia for all HD patients on Sorok Island. As a result, AAD was started for patients diagnosed with AD, and doctors stopped prescribing dapsone for inactive HD patients. They have followed up for dementia. DMA administered dapsone to the trial group. A Hansen's bacteria test is performed once every 6 months for positive outcomes and once a year for negative outcomes according to Wade's skin smear test method in 1952. An antibody test (ELISA), an auxiliary means of diagnosing healed HD, is also conducted in parallel. As for health examination, various pathological tests such as biochemical, immunological, hematological, and blood bank tests are carried out following transfusion, and neuropsychiatric studies performed in Sorkodo National Hospital.

Outcomes

From 2005 to 2020, significance was evaluated based on a p value of 0.05 in the DDS (+) subgroup and the DDS (−) subgroup of the AD (+) group and AD (−) group. An effects analysis from 2007 to 2020 was conducted as valid data (Table 1, Table 2).

Outcome assessment

Effect Size Calculator for T-Test, Pearson's R (Pearson's Correlation Coefficient), One-Way Repeated Measures ANOVA Calculator and Post Hoc Tukey honestly significant difference (HSD) were applied. A significant T-test was performed among the T1: DDS(+)/AD(+), T2: DDS(+)/AD(−), T3: DDS(−)/AD(+), and T4: DDS(−)/AD(−) groups (Tables S1, S2, S4, and Figure 3).

QUANTIFICATION AND STATISTICAL ANALYSIS

We used the software programs Object-Relational DBMS (Oracle Database) and Google spreadsheet (Google Sheets) with SPSS (SPSS FROM SocSciStatistics.Com). According to the Official Information Disclosure Act in Korea, we also requested and analysed the entire ICD-10 code data of AD and AAD from the NHIS. Leprosy patients with AD were analysed with AAD drugs.

ADDITIONAL RESOURCES

We will continue to disclose the medical records of Sorokdo National Hospital in accordance with Article 13 of the "Act on Information Disclosure of Public Institutions to form a prospective cohort for observation and analysis over the next 10 years.