Fig. 3. Microscopic findings of the cerebral cortex of cases 2 (**a-c**) and 6 (**d-f**). **a** Moderate neuronal loss and spongy change in layers II–IIIab of the IT. HE staining. **b** Moderate gliosis in layers II–IIIab of the IT. GFAP immunostaining. **c** Some ubiquitin-positive DNs (arrows) and a few NCIs (arrowheads) in the inferior temporal cortex. Ubiquitin immunostaining. **d** Moderate neuronal loss and spongy change in layers II–IIIab of the superior frontal cortex. HE staining. **e** Moderate gliosis in layers II–IIIab of the superior frontal cortex. GFAP immunostaining. **f** Some ubiquitin-positive NCIs (arrows) without DNs in the superior frontal cortex. Ubiquitin immunostaining.

frontal cortex showing mild neuronal loss demonstrated neuronal loss and gliosis with spongy change in layers II–IIIab (fig. 3d, e).

Compared to neuronal loss between aPiD and D-MND cases, the frontal cortex showed similar neuronal loss, whereas the temporal cortex showed more severe neuronal loss in aPiD cases than in D-MND cases. Neuronal loss was significantly more severe in aPiD cases than in D-MND cases in the temporal pole, AMT, AIT, PMT and PIT (p < 0.05). The hippocampus and amygdala showed similar neuronal loss.

The results of the regional evaluation of ub-positive inclusions (NCIs and DNs) in aPiD and D-MND cases are shown in tables 3 and 4, respectively. Almost all NCIs and DNs were also positive for TDP-43 in both aPiD and D-MND cases. In aPiD cases, the affected temporal cortex usually demonstrated some DNs of curly or spindle shape and a few NCIs of crescent shape in layers II–IIIab

and V–VI (fig. 3c). The frontal and temporal cortex showed a small number of ub-positive NCIs, and the average score ranged from 0.0 to 0.8. In contrast, there were a moderate-to-large number of ub-positive DNs in the frontal and temporal cortex. Their average score ranged from 1.0 to 3.0, and was 2.2 and 3.0 in the cingulate and entorhinal cortex, respectively. The anterior temporal cortex showed a greater number of DNs than the posterior temporal cortex. Compared to the number of DNs with neuronal loss, the number of DNs increased with the degree of neuronal loss in the cortex showing mild-to-moderate neuronal loss, but decreased in the cortex showing severe neuronal loss. In the hippocampus and amygdala, a moderate number of NCIs were found in the dentate gyrus and amygdala, with an average score of 1.8 and 2.6, respectively, and a moderate number of DNs were found in the subiculum and amygdala, with an average score of 1.4 and 1.6, respectively.

Table 2. Regional evaluation of neuronal loss in aPiD and D-MND cases

	SF	OR	CI	PO	AST	PST	AMT	PMT	AIT	PIT	EN	PA	SU	CA1	DE	AM
aPiD																
Case 1	1	2	1	3	2	1	2	2	2	2	2	3	2	2	1	1
Case 2	2	2	2	3	3	1	3	2	3	3	3	3	2	1	1	1
Case 3	2	2	2	3	1	2	2	3	2	3	3	2	2	1	1	2
Case 4	1	1	1	3	1	1	2	2	2	2	2	2	1	1	1	2
Case 5	1	1	2	3	3	3	3	3	3	3	2	2	2	1	1	2
Average	1.4	1.6	1.6	3.0	2.0	1.6	2.4	2.4	2.4	2.6	2.4	2.4	1.5	1.2	1.0	1.4
D-MND																
Case 6	2	2	2	1	1	1	1	1	1	1	2	1	2	1	2	2
Case 7	1	1	1	1	1	1	1	1	1	1	2	2	2	1	1	1
Case 8	2	1	1	2	1	1	1	1	1	1	2	3	2	1	1	1
Case 9	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1
Case 10	1	1	2	1	1	1	1	1	1	1	1	2	2	1	1	1
Average	1.4	1.2	1.6	1.2	1.0	1.0	1.0	1.0	1.0	1.0	1.6	1.5	1.5	1.0	1.2	1.2

0 = Absent; 1 = mild neuronal loss with mild gliosis and spongy change; 2 = moderate neuronal loss with moderate gliosis and spongy change; 3 = severe neuronal loss with rare intact neurons, severe gliosis and spongy change.

SF = Superior temporal cortex; OR = orbital cortex; CI = anterior cingulate cortex; PO = temporal pole; AST = anterior portion of superior temporal cortex; PST = posterior portion of superior temporal cortex; AMT = anterior portion of middle temporal cortex; PMT = posterior portion of middle temporal cortex; AIT = anterior portion of inferior temporal cortex; PIT = posterior portion of inferior temporal cortex; EN = entorhinal cortex; PA = parahippocampal cortex; SU = subiculum of hippocampus; CA1 = CA1 of hippocampus; DE = dentate gyrus of hippocampus; AM = amygdala.

Table 3. Regional evaluation of ub-positive NCIs in aPiD and D-MND cases

	SF	OR	CI	PO	AST	PST	AMT	PMT	AIT	PIT	EN	PA	SU	CA1	DE	AM
aPiD																
Case 1	0	0	0	1	2	0	1	0	1	0	2	1	1	2	1	4
Case 2	0	0	1	0	1	0	0	0	0	0	0	1	0	1	3	3
Case 3	0	0	1	1	0	0	0	1	1	1	0	0	0	0	3	4
Case 4	0	0	0	0	1	0	1	0	1	0	0	1	0	1	1	1
Case 5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Average	0.0	0.0	0.4	0.4	0.8	0.0	0.4	0.2	0.6	0.2	0.4	0.6	0.2	0.8	1.8	2.6
D-MND																
Case 6	1	1	1	1	0	1	1	1	1	1	2	1	1	1	2	1
Case 7	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Case 8	0	0	0	0	0	0	0	0	1	1	2	2	1	1	1	2
Case 9	0	0	0	0	0	0	1	0	1	1	1	1	0	0	1	0
Case 10	2	1	3	2	0	2	1	1	1	1	2	1	1	1	3	3
Average	1.3	0.7	1.3	0.8	0.4	0.8	0.6	0.4	1.0	1.0	1.6	1.2	0.8	0.8	1.6	1.4

(0) = Absent; (1) = ≥1 but <3; (2) = ≥3 but <9; (3) = ≥9. See table 2 for explanation of abbreviations.

In D-MND cases, the affected frontal cortex usually showed some NCIs of crescent shape without DNs in layers II–IIIab (fig. 3f). A small-to-moderate number of NCIs was found in the frontal and temporal cortex, and ranged from 0.4 to 1.6. The number of NCIs was significantly greater in D-MND cases than in aPiD cases in the PIT and entorhinal cortex ($p < 0.05$). In contrast, the number of DNs in the frontal and temporal cortex ranged
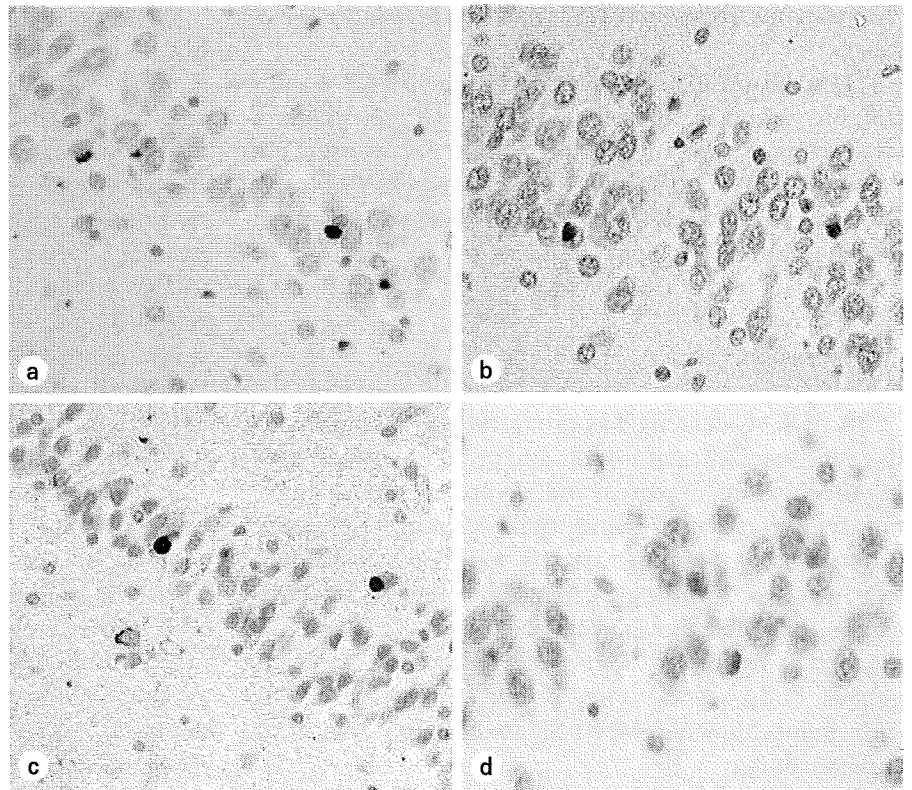
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Fig. 4. Microscopic findings of the dentate gyrus of case 2 (**a, b**) and 6 (**c, d**). **a** Ubiquitin-positive NCIs in the dentate gyrus. Ubiquitin immunostaining. **b** TDP-43-positive NCIs in the dentate gyrus. TDP-43 immunostaining. **c** Ubiquitin-positive NCIs in the dentate gyrus. Ubiquitin immunostaining. **d** TDP-43-positive NCIs in the dentate gyrus. TDP-43 immunostaining.

Table 4. Regional evaluation of ub-positive DNs in aPiD and D-MND cases

	SF	OR	CI	PO	AST	PST	AMT	PMT	AIT	PIT	EN	PA	CA1	SU	DE	AM
aPiD																
Case 1	1	1	1	1	1	1	1	1	1	0	1	1	0	1	0	2
Case 2	1	1	3	1	2	1	2	1	2	1	4	3	0	2	0	1
Case 3	2	1	3	1	2	2	2	2	3	3	4	2	0	2	0	1
Case 4	1	1	2	1	1	1	1	1	1	1	4	1	0	1	0	2
Case 5	2	1	2	1	1	1	1	1	1	1	2	1	0	1	0	2
Average	1.4	1.0	2.2	1.0	1.4	1.2	1.4	1.2	1.6	1.2	3.0	1.6	0.0	1.4	0.0	1.6
D-MND																
Case 6	1	0	1	1	0	1	0	0	0	0	1	0	0	0	0	1
Case 7	0	0	0	1	1	0	1	1	1	2	2	1	1	0	0	2
Case 8	0	0	0	1	0	0	0	0	1	1	2	1	0	0	0	1
Case 9	0	0	1	1	0	0	1	1	1	1	1	0	0	0	0	1
Case 10	1	1	1	1	1	0	1	0	0	0	1	0	0	0	0	1
Average	0.4	0.2	0.6	1.0	0.4	0.2	1.0	0.8	0.6	0.8	1.4	0.4	0.2	0.0	0.0	1.2

(0) = Absent; (1) = ≥ 1 but <3; (2) = ≥ 3 but <9; (3) = ≥ 9. See table 2 for list explanation of abbreviations.

from 0.2 to 1.4 and was significantly smaller than that in aPiD cases, except for the cingulate cortex and PIT ($p < 0.05$). There was no difference in the number of NCIs between the anterior and posterior temporal cortex. The number of NCIs increased with the degree of neuronal loss in the affected cortex. In the hippocampus and amygdala, there were no differences in the number of NCIs or DNs between aPiD and D-MND cases. The dentate gyrus

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showed some ub-positive NCIs in both aPiD and D-MND cases.

These ub-positive NCIs or DNs were all TDP-43-positive but tau-negative (fig. 4a–d). There were neither amyloid β-protein-positive senile plaques nor α-synuclein-positive Lewy bodies in the cerebral cortex of all cases, but there were a small number of tau-positive neurofibrillary tangles in the hippocampal area.

Discussion

SA in SD is described as profound deficit in semantic memory, semantic paraphasia and problems understanding the meaning of words, and SD presents SA as an initial symptom before perceptual skills and nonverbal problem-solving abilities are affected [1]. SA does not result from word-finding difficulty but reflects degraded general knowledge of objects or concepts, and episodic memory is reasonably well-preserved in SD [22]. In the present study, SA was noted on the charts of all 5 aPiD cases before they developed SD with progression of the clinical course.

CT or MRI examination of SD revealed atrophy of the anterior temporal lobe with left-side dominancy [18]. In addition to the anterior temporal lobe, atrophy of the amygdala and anterior hippocampal region was also reported in SD [23]. SPECT or PET study of SD demonstrated hypoperfusion or glucose hypometabolism of the left temporal lobe [17]. Hypometabolism in SD was more focalized compared to Alzheimer's disease with milder semantic impairment, which shows widespread hypometabolism in the left frontal, occipitotemporal and temporoparietal regions [24]. These findings suggest that dysfunction or volume reduction in the anterior left temporal lobe as well as the amygdala and anterior hippocampal region is associated with impairment of semantic processing and causes SA in the early stage of the disease course of SD. In the present study, MRI findings of the 2 aPiD cases shared localized atrophy of the anterior portion of the temporal lobe, followed by the superior temporal to the fusiform gyrus, with unilateral dominancy. However, the parahippocampal gyrus, hippocampus and amygdala were still preserved in the early stage of the disease course of case 1, whereas these regions were already involved in the late stage of the disease course of case 2. These findings suggest that the regions involved in the early stage of the disease course of SD are more restricted to the anterior and inferior portion of the temporal lobe on the side of the dominant hemisphere.

Previous neuropathological studies have reported that SD pathologically corresponds to aPiD [7], and aPiD shows temporal-dominant lobar atrophy with ub-positive, tau-negative inclusions [6, 12]. However, these studies did not clarify the regions responsible for SA as an initial symptom of aPiD, and there have been no reported neuropathological studies concerning the pathomechanism of SA. Meanwhile, similar ub-positive, tau-negative inclusions are also found in the MND type of FTD corresponding to D-MND [9], lacking SA, and these inclusions are positive for TDP-43 common to the 2 disorders [16]. Both aPiD and D-MND are therefore included in TDP-43 proteinopathy as well as FTLD-U. However, the distribution of ub- and TDP-43-positive inclusions is different between the 2 disorders, and NCIs and DNs are predominant in D-MND and aPiD, respectively [13, 16].

In the present study, we investigated the degree of neuronal loss as well as the number of ub-positive NCIs and DNs in the cerebral cortex, hippocampus and amygdala of aPiD and D-MND to clarify the regions responsible for SA in SD. Consequently, the frontal cortex revealed mild neuronal loss in both aPiD and D-MND, and there was no significant difference between the 2 disorders. In contrast, the temporal cortex showed moderate to severe neuronal loss in aPiD but mild neuronal loss in D-MND. The temporal pole, AMT, PMT, AIT, PIT and entorhinal cortex showed significantly more severe neuronal loss in aPiD than in D-MND. In aPiD, neuronal loss in the temporal pole was the most severe throughout the cerebral cortex, and the anterior temporal cortex tended to show more severe neuronal loss than the posterior temporal cortex. The number of ub-positive NCIs showed no significant difference in all regions between the 2 disorders, whereas the number of ub-positive DNs was significantly greater in almost all regions in aPiD than in D-MND. The degree of neuronal loss was not always parallel to the number of ub-positive DNs in aPiD, because the number of DNs increases with the degree of neuronal loss in the cortex with mild-to-moderate neuronal loss, but decreases in the cortex with severe neuronal loss. These findings suggest that the region involved in the earliest stage of the disease course in the cerebral cortex of aPiD is the temporal pole, followed by the anterior portion of the MT and IT, on the side of the dominant hemisphere.

Previous structural and functional imaging studies of SD have highlighted the abnormality of the anterior and inferior portions of the temporal cortex [22, 25]. In the present study, AMT and AIT showed significantly more severe neuronal loss and a greater number of DNs in aPiD than in D-MND. The function of these regions has been

investigated by PET. The MT participates in visual word processing and stored knowledge about patterns of visual motion using objects [26, 27], while the IT is associated with the function of name processing [28]. The MT is also known to participate in the memory system [22], and therefore degeneration of the IT and MT may cause aphasia encompassing amnesia, namely amnestic aphasia, which was noted in the early stage of the disease course in aPiD.

The hippocampus and amygdala have also been reported to show gray matter reduction in SD [2]. In the present study, neuronal loss in these regions was mild in both aPiD and D-MND. There was also no difference in the number of NCIs or DNs between the 2 disorders. The hippocampus and the entorhinal cortex are closely concerned with the memory system [29, 30], while the amygdala is known to modulate memory, attention and perception according to emotion processing [31, 32]. Degeneration of the hippocampus and amygdala may have more amnesic influence in SD, namely amnesia, as noted in aPiD. Therefore, the pathomechanism of SA in SD may be directly concerned with degeneration of the temporal pole and indirectly with that of the anterior portion of the MT and IT, although function of the temporal pole has been not evident.

In the present study, we neuropathologically investigated aPiD and D-MND cases with and without SA, respectively, and attempted to clarify the regions responsible for SA in the early stage of the disease course of SD. In conclusion, we suggest that degeneration of the temporal pole is most likely to participate in the pathomechanism of SA. Future studies are needed to collaborate the neuroimaging and neuropathological studies of SD, because it is difficult to demonstrate the developmental process of SA using only neuropathological studies.

Acknowledgements

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