A report on cases of lichen amyloidosis and cases of Alzheimer's disease that responded well to tranilast

- from the verification of the amyloid hypothesis to the eradication of Alzheimer's disease

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Introduction

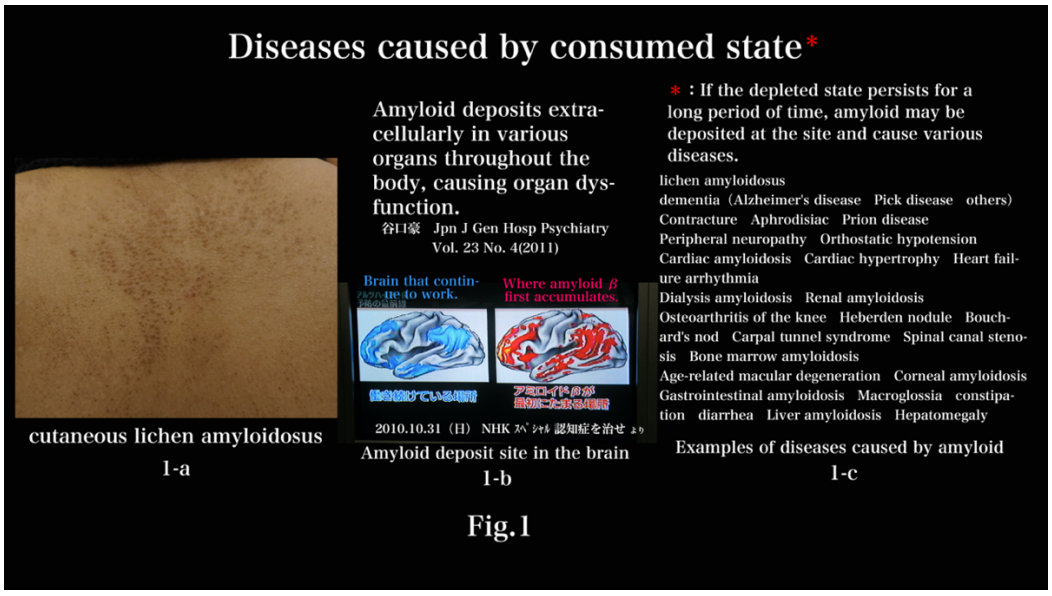
Before 1990, the author, Hideyasu Takata, encountered cases of mild to moderate lichen amyloidosis in patients with atopic dermatitis that responded well to tranilast, a drug for atopic dermatitis, which is considered a debilitating disorder. Lichen amyloidosis is a disease that causes distinctive skin rashes and severe itching at sites affected by atopic dermatitis over a long period. The condition can be easily diagnosed by a dermatologist; however, it is extremely difficult to treat as with other types of amyloidosis.

Since Alzheimer's disease (AD) is also associated with debilitating disorders, the potential of tranilast as an effective treatment for AD through drug repurposing became apparent. Thereafter, tranilast was administered as an additional treatment to patients undergoing outpatient care in our department and to those who were diagnosed with AD and being treated at another medical institution. As a result, clear improvement in cognitive function was achieved in the patients with AD.

Diseases caused by debilitating disorders

A debilitating disorder is chronic, and causes a protein called amyloid, a waste product, to be deposited and to build up at specific sites. [1)] This diminishes the function of cells at the site of deposition, leading to the development of another disease. Specifically, it can cause cardiac amyloidosis, lichen amyloidosis, AD, and other diseases that can affect different parts of the body (Figure 1). The name of the disease differs depending on the site of amyloid deposition (Figure 1-c). It is a well-known fact that there are no cures for any of these diseases, and systemic amyloidosis is designated as an intractable disease in Japan.

Amyloid deposition at a site of persistent atopic dermatitis may cause lichen amyloidosis (Figure 1-a). Amyloid β may start accumulating in the areas of cognition located in the parts of the brain that are constantly active (Figure 1-b[2)]), even 10–20 years before the onset. AD is diagnosed when the symptoms appear.



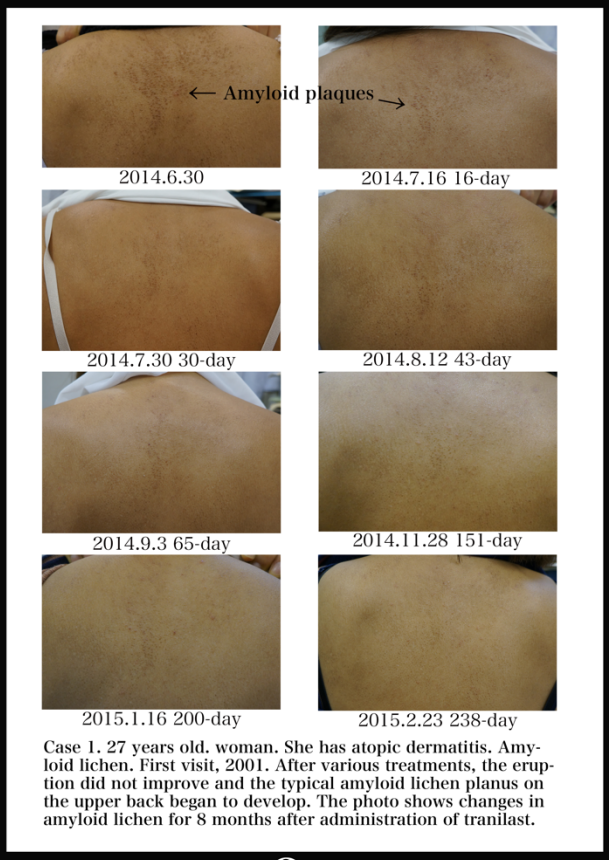
Case Presentation: Lichen amyloidosis (Figure 2)

Case 1: A 27-year-old woman presented with lichen amyloidosis (Figs. 2-a, 2-c, 2-e), which occurred during the treatment of atopic dermatitis. Conventional treatment led to no change in the lichen amyloidosis symptoms. Skin rashes were observed during additional treatment with tranilast at a dose of 300 mg/day.
Figure 2-a shows clinical photographs from the first day of treatment to Day 238. A clear reduction (57%) in the number of amyloid papules was seen at 2 weeks of tranilast treatment. Severe itching also disappeared. The number of amyloid papules continued to decrease through continuous administration of tranilast, and the rate of decrease at Day 238 was 96%.

Case 2: A 23-year-old woman presented with lichen amyloidosis and atopic dermatitis (Figs. 2-b, 2-d, 2-f). Skin rashes were observed during additional treatment with tranilast at a dose of 300 mg/day. Figure 2-b shows clinical photographs from the first day of treatment to Day 486. As with Case 1, the number of amyloid papules clearly decreased, and severe itching disappeared. The reduction rate in the number of amyloid papules was 13% at 4 weeks and 80% on Day 89, indicating a marked improvement. The patient discontinued the treatment at this point. During the follow-up visit on Day 364, the number of amyloid papules had increased to 181 (reduction rate, 25%). The patient resumed treatment thereafter, and the reduction rate in amyloid papules improved to 83% on Day 486.

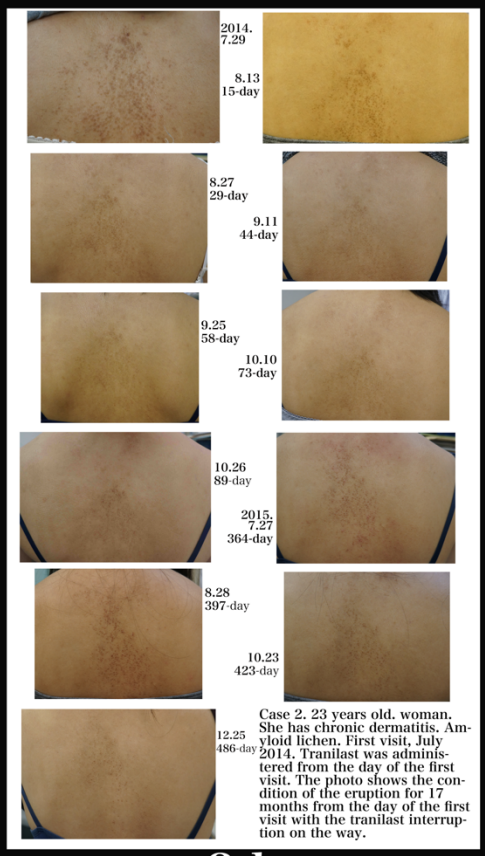
Conventional drugs had failed to reduce amyloid papules. The intended effect of tranilast appeared immediately after the first dose in both cases. Although it took several years for amyloid deposition to occur, the number of papules started to decrease within 2 weeks of the first dose, a surprisingly short period of time. In Case 2, the treatment was interrupted, and the number of amyloid papules increased again; however, they rapidly started to decrease after the resuming tranilast administration.

As the amount of amyloid is considered proportional to the number of amyloid papules, the rate of decrease in the amount of amyloid is considered the same as the reduction in the number of amyloid papules. Thus, the rate of amyloid reduction was 96% in Case 1 and 83% in Case 2. Tranilast is considered effective in reducing amyloid.



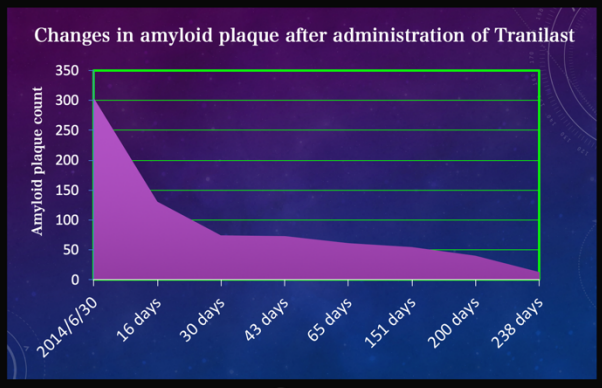
Case 1. 27 years old. woman. She has atopic dermatitis. Amyloid lichen. First visit, 2001. After various treatments, the eruption did not improve and the typical amyloid lichen planus on the upper back began to develop. The photo shows changes in amyloid lichen for 8 months after administration of tranilast.

2-a



Case 2. 23 years old. woman. She has chronic dermatitis. Amyloid lichen. First visit, July 2014. Tranilast was administered from the day of the first visit. The photo shows the condition of the eruption for 17 months from the day of the first visit with the tranilast interruption on the way.

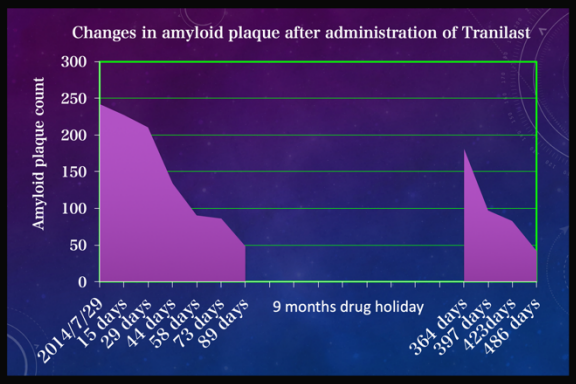
2-b



2-c

Days after administration of Tranilast	Amyloid plaque count (Decrease rate)
2014/6/30	303
16	131 (57%)
30	75 (75%)
43	73 (76%)
65	62 (80%)
151	55 (80%)
200	40 (87%)
238	13 (96%)

2-e



2-d

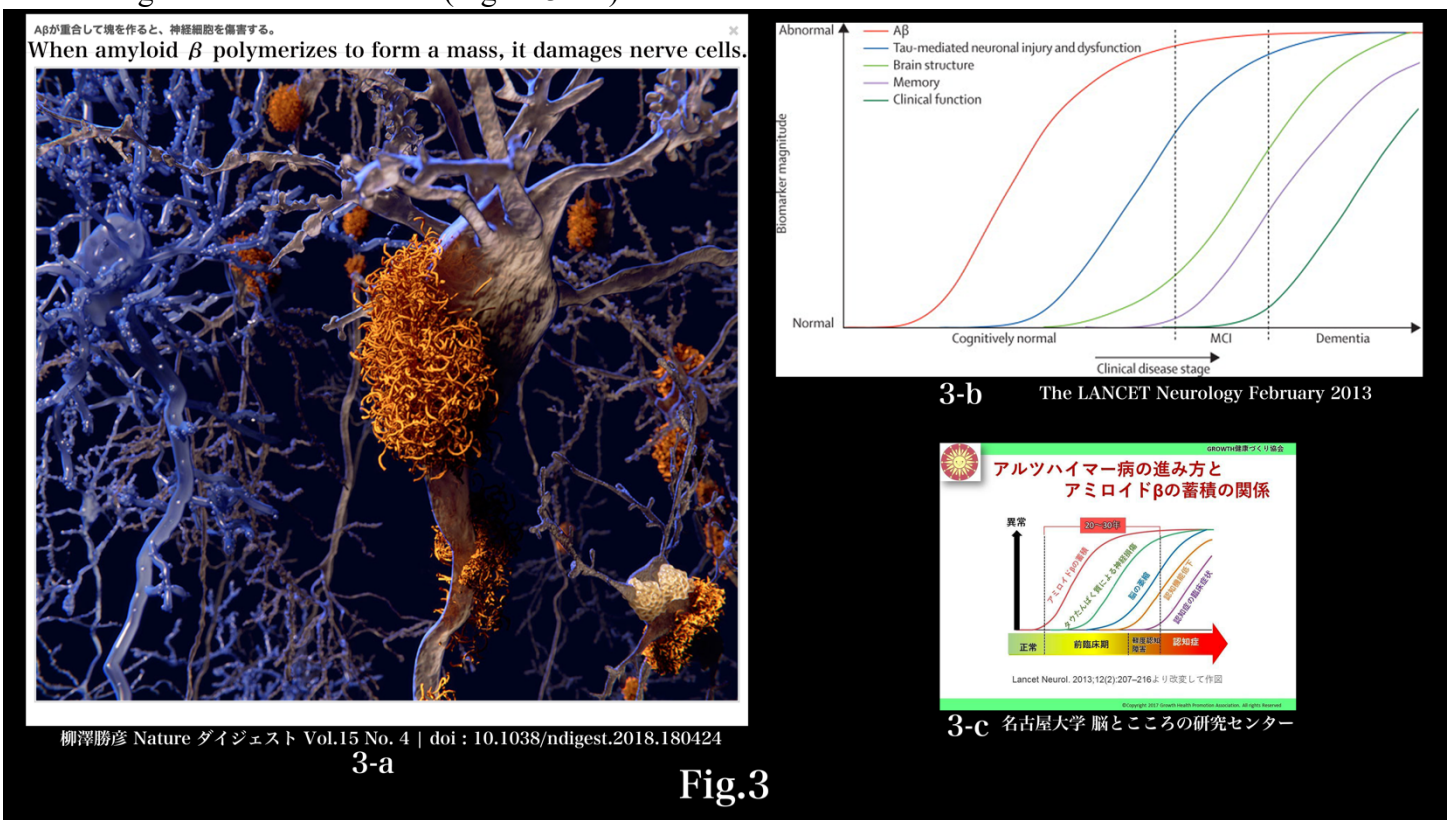
Days after administration of Tranilast	Amyloid plaque count (Decrease rate)
2014/7/29	242
15	227 (6%)
29	210 (13%)
44	134 (45%)
58	90 (63%)
73	86 (64%)
89	48 (80%)
Treatment interruption for 9 months	9ヶ月間治療中断
364	181 (25%)
397	97 (60%)
423	83 (66%)
486	42 (83%)

2-f

Fig.2

Case Presentation: Alzheimer's disease (Figure 4)

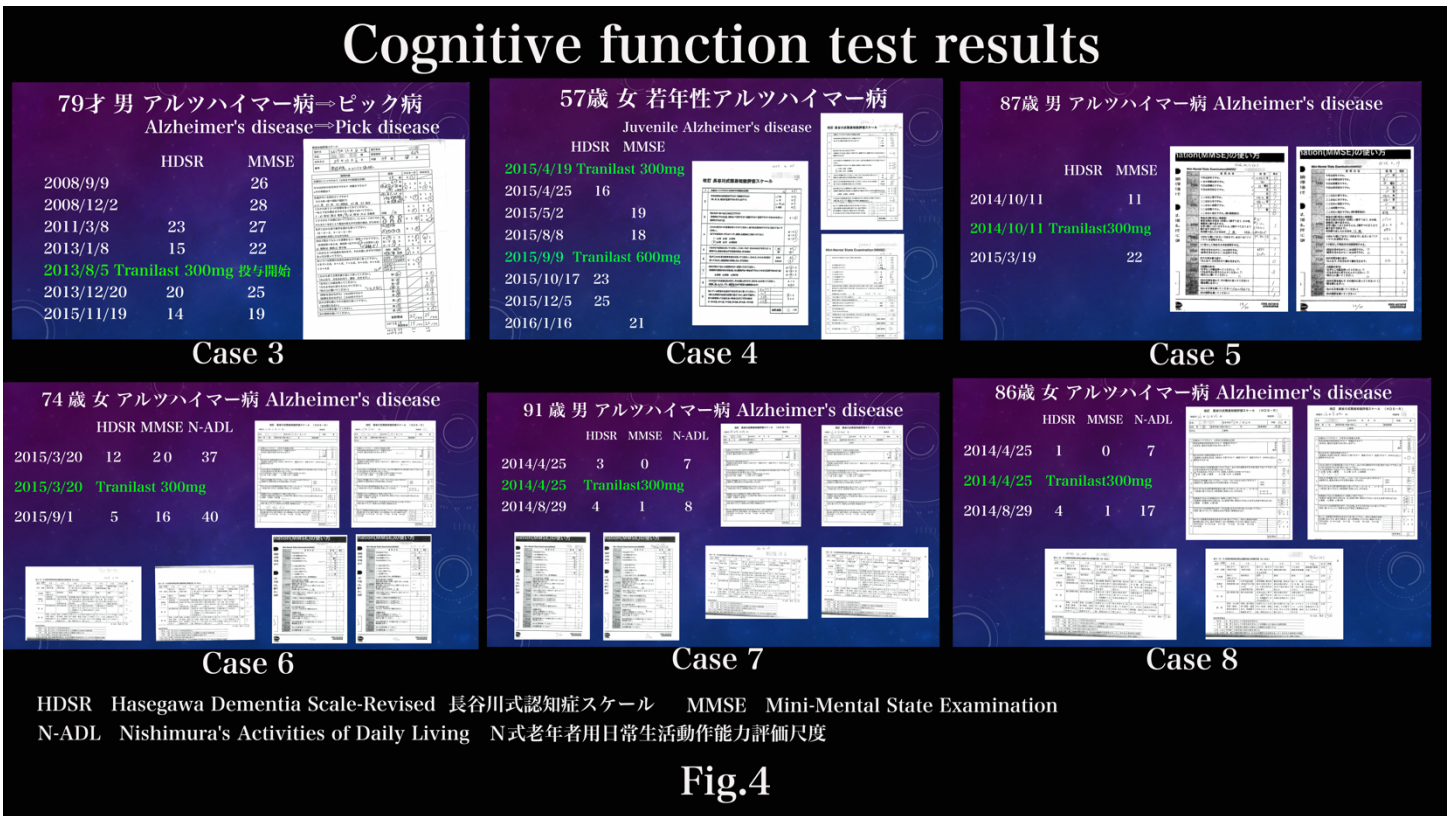
Amyloid β becomes neurotoxic through aggregation in the central nervous system and damages neurons. This leads to cognitive decline and AD (Figure 3-a [3)]).



In 6 patients with AD with no signs of improvement, tranilast was administered in addition to conventional treatment. Cognitive function tests (the Revised Hasegawa's Dementia Scale [HDS-R] and the Mini-Mental State Examination [MMSE]) and Nishimura's Activities of Daily Living of the elderly (N-ADL) were administered by specialists and experienced nurses and were used to evaluate the therapeutic effect (Figure 4).

Cognitive function worsened in Case 8. The remaining five patients (83.3%) showed improvement. Case 3 responded to the treatment and eventually developed Pick's disease concomitantly with AD. The scores improved from 15 to 20 on HDS-R and from 22 to 25 on MMSE. Case 4 was a 57-year-old woman with early-onset AD. Tranilast 300 mg/day was ineffective, so the dose was increased to 600 mg/day. Clear improvement was noted in cognitive function, from 16 to 23 to 25 on HDS-R and from 18 to 21 on MMSE. The onset of action of tranilast appears to be dose dependent. Case 5 was an 86-year-old woman. After tranilast administration, slight improvement was seen in cognitive function, from 1 to 4 on HDS-R and from 0 to 1 on MMSE. Case 6 was a 91-year-old man. His baseline scores were extremely low, but they slightly improved from 3 to 4 on HDS-R and from 0 to 1 on MMSE. Case 7 was an 87-year-old man. His HDS-R score improved from 14 to 22. The intended effect of tranilast was also observed in the elderly patients.

In Cases 5, 6, and 8, N-ADL was used in addition to the cognitive function tests to assess the impact on basic activities of daily living such as "walking, dressing, and bathing." A clear improvement was observed in Case 5 (from 7 to 17) and Case 8 (from 37 to 40). In Case 6, the score changed slightly (from 7 to 8). Tranilast was shown to improve not just cognitive function but also the activities of daily living.



Discussion

The number of cases presented in this report was only eight (two with lichen amyloidosis and six with AD). However, as there is no effective drug for amyloid plaques, it is unlikely that the other drugs taken by the patients influenced the outcomes we observed. Moreover, since cognitive function does not improve with placebo, our findings are considered reliable. Regarding lichen amyloidosis, our experiences with more than 30 cases since the late 1980s were also taken into consideration in addition to the two cases included in this report to conclude that tranilast can reduce amyloid plaques.

Conventional drugs did not promote regeneration of damaged neurons or remove amyloid plaques, thereby failing to improve AD or the results of the cognitive function tests. Based on the outcomes of these six cases and the findings obtained through the treatment of lichen amyloidosis, we will now examine the mechanisms underlying the cognitive improvement. Conventionally, there has been a theory suggesting that a part of the amyloid plaques (amyloid β protein) may directly damage neurons and thus impair cognitive function. If the part of amyloid plaques directly damaging neurons is the only cause of cognitive decline, use of tranilast should not improve cognitive function. However, the outcomes of our study clearly showed cognitive improvement. In addition to the conventional theory, it was proposed that the volume and weight of amyloid plaques induce compression stress on neurons, resulting in cognitive decline. As the stress increases, cognitive function decreases proportionally. The use of tranilast reduced amyloid plaques, which presumably led to decreased compression stress and improved cognitive function.

This study found that tranilast reduced amyloid plaques, thereby decreasing compression stress on neurons and improving cognitive function. Therefore, we can say that this is the first case report in the world to prove the amyloid cascade hypothesis in AD.

Figure 2 shows changes in the amount of amyloid after the first dose of tranilast. At 1–2 months, amyloid papules were reduced by approximately 60%. Researchers say that it could take several to 20 or 30 years from the start of amyloid deposition to the onset of symptoms. In Case 2, amyloid was once reduced by 80%, but the reduction rate went down to 25% after only 9 months of treatment interruption (a 65% increase). We wondered

why amyloid increased over such a short period of time. Because amyloid β has a β-sheet structure, the reason for this was considered as follows: Instead of dissolving amyloid plaques, tranilast may suppress the formation of the plaques by interfering with the β-sheet structure, such as by acting on hydrogen bonds linking β sheets, which extend the plaques and increase their surface area. Amyloid in the extended plaque region not in contact with neurons does not apply compression stress to neurons. We thus inferred that nerve function improves proportionally with decreasing compression stress on neurons. Once tranilast was discontinued, extended amyloid may return to its original plaque form in a short period of time, like a shape-memory alloy, leading to the worsening of lichen amyloidosis and AD.

The seeming reduction of amyloid plaque means going back towards the beginning of the amyloid β accumulation curve in "Figure 3-b , 3-c Association Between AD Progression and Amyloid β Accumulation." [4,5] Therefore, it is strongly suggested that use of tranilast in people at risk of developing AD may be able to prevent the onset.

If the aforementioned mechanism of action is correct, tranilast may also be effective for not just lichen amyloidosis and AD but also other amyloid-related debilitating disorders, such as cardiac amyloidosis and systemic amyloidosis. Tranilast has the potential to play the role of a “game changer” in the treatment of AD.

Regarding the effect of tranilast on amyloid, further investigations and studies by other clinicians and researchers are needed.

Conclusion

Tranilast may be useful in the treatment of lichen amyloidosis, as well as in the treatment, prevention and eradication of AD and other amyloid-related debilitating disorders.

Acknowledgements

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