# Clinical and Pathological Studies of Slowly Progressive Aphasia without Global Dementia

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## Introduction

In 1892, Arnold Pick, Professor of the German University of Prague, wrote a short article in Prager Medizinische Wochenschrift. In his paper, entitled "On the relationship between senile cerebral atrophy and aphasia", Pich described a man who had developed mental deterioration at age 68. When he examined the patient two years after the onset of the disease, the patient was found to have an evident aphasia consisting of severe impairment of speech comprehension, frequent paraphasia of semantic type, relatively spared repetition, and severe alexia and agraphia. The clinical picture of the patient's aphasia is thought to be of aphasia of the transcortical sensory type. The patient died shortly after, and the postmortem examination revealed cerebral atrophy with focal intensification on the temporal lobe. The atrophy was much more prominent on the left cerebral hemisphere than on the right. What Pick insisted upon in this paper was that the study of focal deficit of higher cortical function could be done not only in the focal destructive diseases of the brain such as cerebrovascular diseases, cerebral trauma, or cerebral tumors, but also in the degenerative disorders like the one he reported.

Pick wrote another paper in 1901 on the same subject reporting a woman who had developed aphasia several years after the onset of dementia. She showed markedly impaired speech comprehension, paraphasia, jargon, continuous perseveration of speech and echolalia. The autopsy of the second patient revealed severe cerebral cortical atrophy, especially on the left hemisphere. The most markedly atrophied cortical areas were Operculum, angular gyrus, superior temporal gyrus, inferior frontal gyrus and insula of the left hemisphere, most of which being known as the major components of the speech area. What Pick wanted to show in these papers, was the beautiful clinico-pathological correlation of aphasia with the affected cortices in degenerative diseases, he did not intend to isolate a disease entity at all.

Pick, himself, had never mentioned about any microscopic findings of his cases. Other neuropathologists, however, reported various microscopic abnormalities seen in the circumscribed cerebral atrophy of this type originally reported by Pick(see Tissot, Constantinidis et Richard, 1975). According to these detailed histopathological descriptions, numbers of new cases appeared as autopsy reports, and Pick's name gradually became the eponym of the neuropathological disease entity which shows circumscribed atrophy of the cerebral cortex associated with such microscopical findings as severe neuronal loss, neuronal intracytoplasmic argentophilic inclusion body, nowadays called as Pick body and the presence of Pick cells, swollen chromatolytic cortical neurons. Meantime, Pick's original scientific idea of investigating the degenerative disorders in search of cerebral mechanism of language became almost completely forgotten.

On the other hand, Mesulam isolated, in 1982, a clinical entity of slowly progressive aphasia without global dementia (SPA). Mesulam reported six cases showing slowly progressive aphasia, mainly of anomic type, with insiduous onset. The patients finally became severely aphasic but had not shown any sign of wide-spread dementia at least for seven years. He believed that this syndrome was a disease entity which affects only the left perisylvian cortices. In spite of his strong insistence(Mesulam, 1987), subsequent case reports suggested the nosological heterogeneity of this syndrome(Poeck & Luzzatti, 1988). Several autosy reports revealed various pathological findings, among them Pick's disease has been the most prevalent(for references see Sakurai, 1992). The purpose of the present paper is to report some cases with the clinical pictures compatible with SPA together with the autopsy findings of a case and to discuss the scientific significance of Pick's original idea.

## Clinical description of cases

From the Department of Neurology at the University of Tokyo Hospital, we reported four cases of SPA (Sakurai et al., 1991a, 1991b). The detailed description of a representative case is described below.

Patient 1 began to notice difficulty of word finding in conversation when he was 37 years old. Reading aloud and writing also became gradually difficult. When we examined the patient at age 42, he showed aphasia of anomic type, associated with bucco-facial and ideo-motor apraxias. In spite of these severe neuropsychological deficits, his global intelligence was remarkably well preserved. Figure 1 shows the score profile of the Japanese version of Western Aphasia Battery (J-WAB)(Sugishita et al., 1986) which is compatible with anomic aphasia. Reading and writing subtests of J-WAB confirmed the presence of alexia and agraphia. On the contrary, PIQ in WAIS and the visual memory index in Wechsler Memory Scale-revised (WMS-R) were both within normal range.

MRI of the patint 1 revealed slight but evident atrophy of the left cerebral hemisphere, especially marked on the left inferior temporal gyrus and the adjacent fusiform gyrus (Figure 2). $^{131}$I-IMP SPECT at rest showed hypoperfusion in the left perisylvian cortices, much more wide-spread than expected from the atrophy seen in MRI. IMP SPECT under the activation state during which the patient was asked to repeat the digits did not show significant activation in the hypoperfusion area seen at rest.

The patient is now 46 years old, 9 years after the onset of the disease, nearly completely aphasic. He had to retire from his work several months ago because of the incapacity of verbal communication. Auditory speech comprehension is null and his speech is confined to a few stereotyped expressions like "Ah, yes, yes, yes" or "good". Writing letters, words, or phrases is entirely impossible. He can not even sign his own name. Although reading aloud of the text is totally impossible, he can understand what is written in the text. As he is interested in archeology, he borrows books of archeology from the public library for his own study. He often visit the exhibitions at the archeological gallery of the National Museum in Tokyo. Since he is living in the country, he has to take train for an hour when he visits the Museum or our hospital, but he still has no trouble in reading the time table to take a proper train or to buy proper train tickets and has never lost his way. He has a very good memory, and can precisely remember the date of next visit to the hospital. He does not show any behavioral abnormality and is fully aware of his language disturbance. He has buccofacial apraxia and can not well imitate the gestures shown by the examiner, but has no trouble with using various items in daily use.

Figures 3 to 5 are the profiles of aphasic manifestations in other cases. The type of aphasia is not uniformly of anomic type. Patint 2 is an example of Broca aphasia and Patient 4 case with Wernicke aphasia. We did functional brain imaging by IMP-SPECT or glucose PET in three out of these five patients, the results of which have been reported elsewhere(Sakurai et al., 1991a). Of interest is that the areas of hypometabolism revealed by these functional imaging techniques are more extended than the affected areas expected from either the clinical pictures and MRI. For example, the PET scan image of regional cerebral metabolic ratio of glucose in Patient 3 who showed clinical pictues of anomic aphasia with well preserved general intelligence and memory function revealed widespread hypometabolism affecting the inferior and basal aspects of both temporal lobes.

## Autosy report

Until now, 16 autosied cases of SPA have been reported in the litterature (Table 1)(for complete reference see Sakurai, 1992). The autopsies revealed various types of degenerative diseases, Alzheimer type dementia, Creutzfeldt-Jakob disease, Pick's disease and non-specific focal cerebral atrophy without any pathognomonic histological abnormality. Most of these reported cases, however, do not exactly meet the criteria of SPA proposed by Mesulam in

1987. Cases with Creutzfeldt-Jakob disease(Mandell, Alexander & Carpenter, 1989) developed profound dementia in less than a year and a case of Alzheimer disease also became demented in a year(Pogacar & Williams, 1984). As a consequence, patients with the clinical pictures of SPA without developing wide-spread dementia for at least two years or more are most likely caused either by Pick's disease or by non-specific focal cerebral atrophy. As we experienced an autopsy case of this disease condition, the clinico-pathological findings are going to be reported.

The patient was a right-handed man who developed first signs of dysarthria of cortical type at age 56. At age 59, he had to retire from his job because of the speech disturbance and acalculia. At age 60, or 4 years after the onset of dysarthria, he began to show some difficulties in writing. Neurological examination at that time revealed non-fluent aphasia with markedly distorted articulation and phonemic paraphasia. He also showed bucco-facial apraxia and mild disturbance of swallowing. On the other hand, his writing ability was relatively preserved as compared with the profound impairment of oral speech function. As to the general intelligence, both verbal and performance IQs in WAIS were quite well preserved.

The patient began to show some aggressive behaviors to his wife at age 64, 8 years after the onset of the disease, but his attitude to the medical and paramedical staffs of the hospital seemed unaltered. He became gradually mute and agraphic in a year, and at age 66, he found to be totally demented with marked emotional and behavioral abnormalities. He died of pneumonia at age 66, or 10 years after the first manifestations of aphasic syndrome. The length of aphasic period without global dementia was 8 years.

Autopsy revealed Pick's disease mainly affecting the frontal cortices, which showed marked neuronal loss and gliosis. Several Pick bodies and achromatic neurons (Pick cells) were also seen among the surviving neurons. Besides, fascia dentata of hippocampus was loaded with Pick bodies, although the number of neurons seemed to be normally preserved.

The inferior extremity of precentral gyrus and the adjacent portion of the inferior frontal gyrus showed very severe atrophy. There was an interesting topographical distribution of the degenerative changes in these areas. The area 4 of the precentral gyrus which is totally buried in the central sulcus at the face region was almost intact with well preserved giant cells of Betz, while the area 6 which covers the surface of the precentral gyrus was very severely depopulated, few surviving neurons were found under the microscope. The area 44 or the posterior portion of the so-called Broca area was clearly affected but much less affected than the area 6, and the area 45 or the anterior portion of the Broca area was only mildly affected.

This topographical distribution of the degenerative process seems to imply that the area 6 was the first to be affected by the disease process in this patient and the areas 44 and 45 were affected much later. On the other hand, the primary motor cortex, area 4, was still unaffected. This chronological sequence of the degenerative process corresponds with the progression of the aphasic syndrome in the patient. During the initial four years, cortical anarthria without any writing disturbance was the dominant speech pathology, and then the patient developed full clinical pictures of Broca aphasia with evident agraphia. Consequently, the involvement of area 6 which was supposed to be affected at first, might be correlated with the initial clinical picture of cortical anarthria and the extension of the degenerative process to the entire Broca area seems to be responsible for the full-brown Broca aphasia.

## Discussion

This type of clinico-pathological correlation based upon the cortical cytoarchitecture can be accomplished only from the post-mortem study of degenerative disease. Focal destructive lesions, such as cerebro-vascular diseases, trauma or neoplasms, do not discriminate the cytoarchitectural boundary of a single gyrus. Recent anatomical studies of cortical anarthria based upon the focal destructive lesions revealed that the involvement of the precentral gyrus is responsible for producing the clinical picture of this syndrome, but not a single report could have mentioned the differential involvement of area 4 and area 6 of the precentral gyrus. The

present autopsy case of Pick's disease which clearly discriminates the cytoarchitectural difference of a single cerebral gyrus gives us very valuable informations with regard to the functional organization of the speech area. As Pick predicted more than a century ago, aphasia caused by degenerative disorder shows us a fruitful field of scientific research on the cerebral mechanism of language.

Many new research techniques have become available for us to investigate the neural mechanism underlying the language function. As compared with these newly developed areas of research, the classical clinico-pathological correlation study of the language dysfunction might appear somewhat old-fashioned and out of mode, but it must be emphasized that it is still one of the best ways to make the precise functional map of human cerebral cortex.

## Conclusion

The real scientific aim of Arnold Pick's reports on the disease condition which have been named after him was not to isolate a disease entity but to insist upon the possibility of clinico-pathological studies of aphasia in the cerebral degenerations. Slowly progressive aphasia without global dementia (SPA), a clinical syndrome recently reported and studied by Mesulam, is a typical example of the pathological conditions upon which Pick had casted the lights. Although the etiological causes of SPA are not unique, the post-mortem studies of this particular syndrome can make it possible to clarify the anatomo-pathological correlation of the human higher brain function at the level of cerebral cortical cytoarchitecture.

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**Table 1: Autopsied cases of slowly progressive aphasia without global dementia**

| Reporter | Year of report | Sex | Age at onset | Type of aphasia | Duration of aphasia without dementia | Total duration of illness | Pathology |
|---|---|---|---|---|---|---|---|
| Wechsler | 1982 | M | 65 | Wernicke | 1 Ys | 6 Ys | Pick |
| Pogacar | 1984 | M | 56 | Fluent | 1 Ys | 6 Ys | Alzheimer |
| Holland | 1985 | M | 66 | Global | 12 Ys? | 12 Ys | Pick |
| Shuttleworth | 1985 | M | 64 | Non-fluent | 5 Ms | 11 Ms | C-J-D |
| MGH CPC | 1986 | F | 67 | Anomic | > 4 YS | 12 Ys | Pick |
| Mehler | 1987 | M | 54 | Global | 3 Ys | 7 Ys | non-specific |
| Kirshner case 1 | 1987 | M | 56 | Wernicke | ? | 10 Ys | non-specific |
| Kirshner case 2 | 1987 | M | 58 | Anomic | ? | 4 Ys | non-specific |
| Mandell | 1989 | M | 61 | Wernicke | 1 Y | 2 Ys | C-J-D |
| Graff-Radford | 1990 | M | 56 | Anomic | 5.5 Ys | 5.5 Ys | Pick |
| Green case 4 | 1990 | M | 57 | ? | 4 Ys | 8 Ys | non-specific |
| Green case 8 | 1990 | M | 71 | ? | 4 Ys | 4 Ys | Alzheimer |
| Lippa | 1991 | M | 66 | TCM | 3 Ys | 3 Ys | Achromasia |
| Snowden case 2 | 1992 | M | 62 | Non-fluent | ? | 9 Ys | non-specific |
| Snowden case 4 | 1992 | M | 63 | Non-fluent | ? | 8 Ys | non-specific |
| Snowden case 7 | 1992 | F | 58 | Fluent | ? | 5 Ys | non-specific |
| Present case | 1993 | M | 56 | Anarthria | 8 Ys | 10 Ys | Pick |

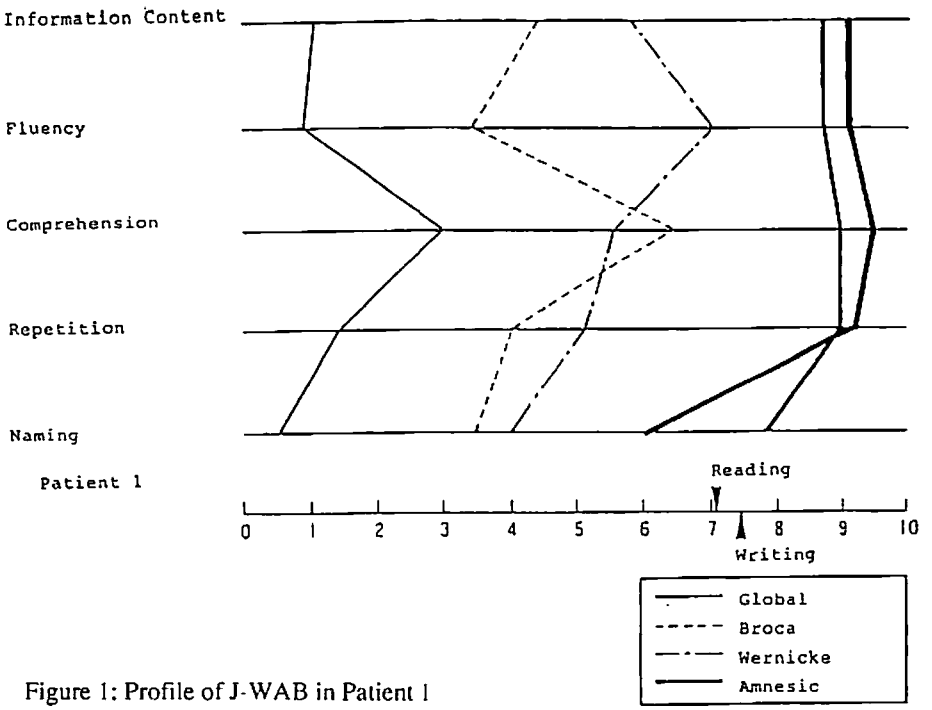


Figure 1: Profile of J-WAB in Patient 1

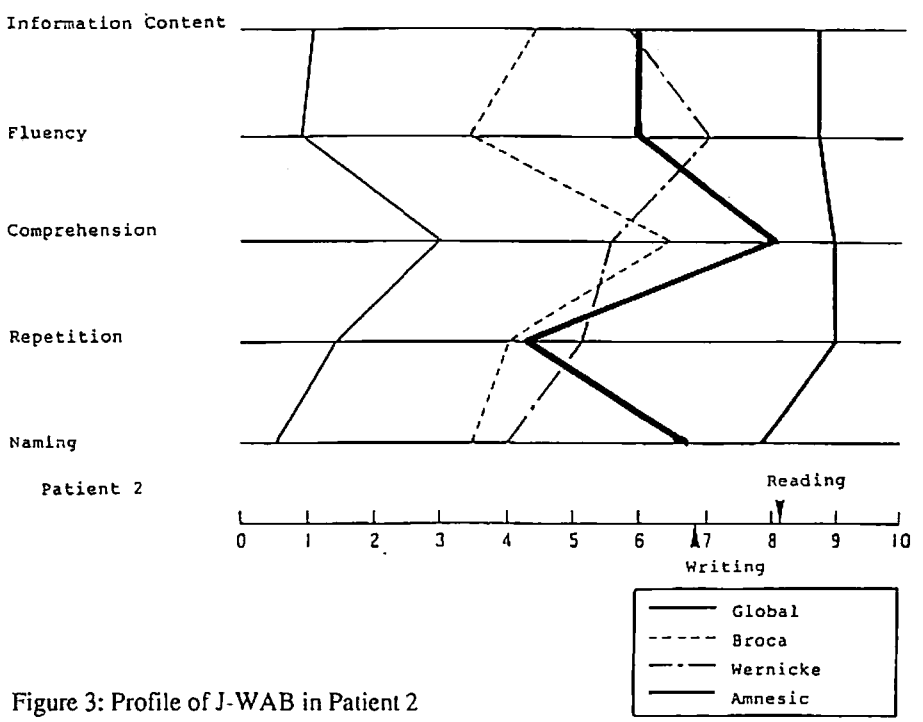


Figure 3: Profile of J-WAB in Patient 2

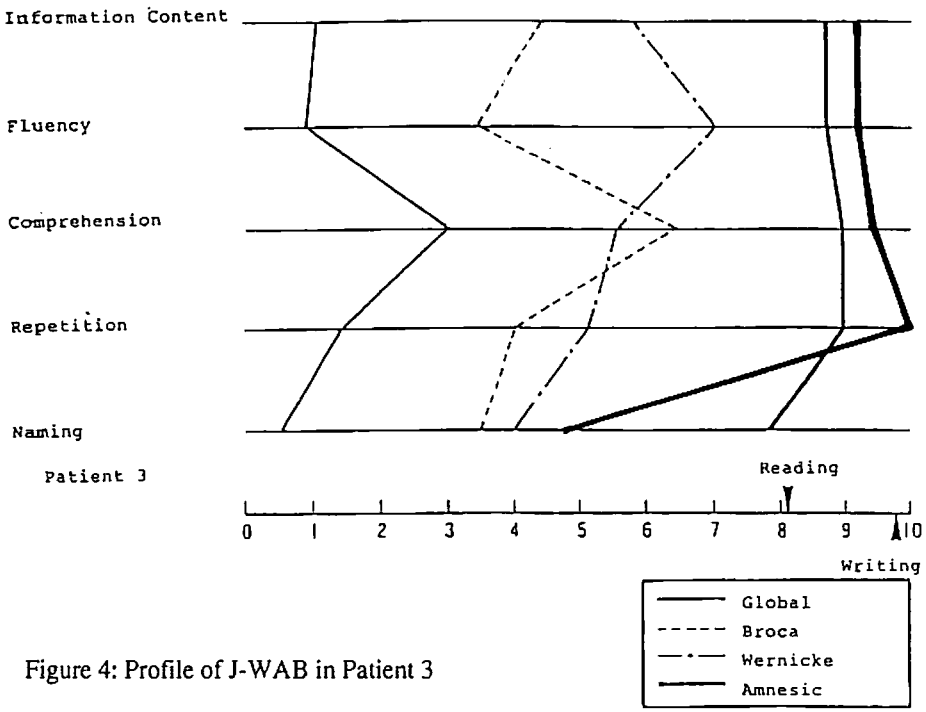


Figure 4: Profile of J-WAB in Patient 3

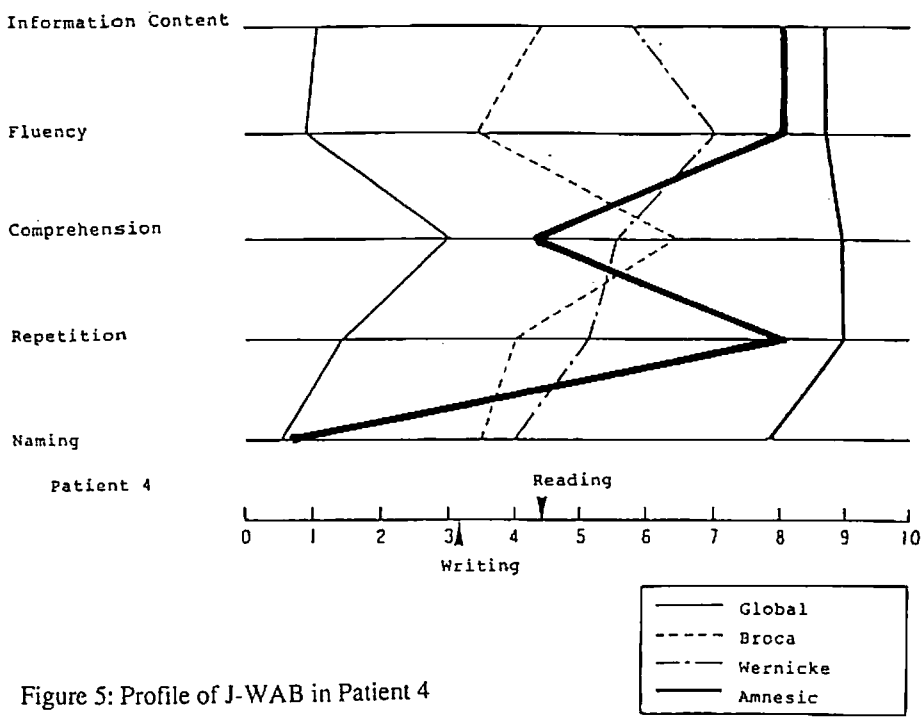


Figure 5: Profile of J-WAB in Patient 4

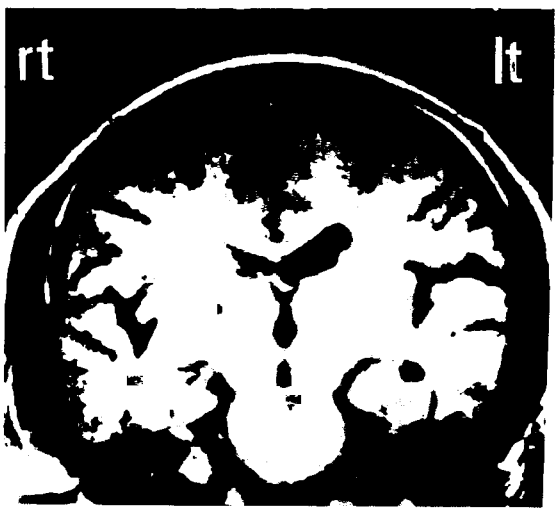


Figure 2: Brain MRI (T1-weighted image) in Patient 1 showing atrophy of the left inferior temporal gyrus and the adjacent fusiform gyrus