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Distribution of Alzheimer's Neurofibrillary Changes in the Brain Stem and Hypothalamus of Senile Dementia

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Alzheimer's Neurofibrillary Changes (ANF) have been considered to be distributed mainly in Ammon's horn, subiculum and amygdaloid nucleus in senile dementia (Simchowicz 1911; v. Braunmühl 1957). But little, if any, attention has been paid to NFA in the brain stem and hypothalamus (Herz and Fünfgeld 1928; Hirano 1962; Lindgren 1952), although the occurrence in these areas was not infrequently reported in postencephalitic parkinsonism (Malamud et al. 1950; Greenfield 1953; Hallervorden 1933, 1935) and other diseases (Hirano et al. 1961).

The present study revealed that ANF were widely distributed in the brain stem and hypothalamus of senile dementia as well, and that the distribution showed a marked predilection to a certain group of nuclei such as nucleus dorsalis raphes, nucleus centralis superior Bechterew, etc. This distribution has a striking similarity with that of monoamine containing nerve cells (Dahlström and Fuxe 1964). A functional characteristic of the nuclei is manifested in that some of them are considered to be responsible for rhombencephalic phase of sleep (R.P.S., Jouvet 1962), and that disappearence of R.P.S. was observed in the later stage of senile dementia and Alzheimer's disease (Suzuki and Hirota 1965). Thus, correlation between occurrence of ANF in the brain stem and hypothalamus of senile dementia and regional metabolic and functional characteristics of the particular nuclei will be suspected.

Material and Methods

6 cases of senile dementia were examined. Clinical findings of these cases were briefly summarized in Table 1. All the cases showed a typical clinical course of senile dementia. Histopathologically abundant senile cerebral lesions were confirmed in the cerebrum, although some were complicated with arteriosclerotic lesions.

For the study of ANF in the brain stem and hypothalamus, Bielschowsky silver impregnation and HE preparations were used. All the preparations of both areas were projected to the drawing papers by a photographic enlarger and then the location of ANF were plotted exactly on the corresponding sites of the maps. As the control study 6 cases of arteriosclerotics over 80 years of age and 24 cases of controls over 60 years of age were examined.

Results

ANF which were found in the brain stem and hypothalamus generally tend to take a shape of round form in Bielschowsky preparations (Fig. 1b). The thickened and whirled fibrills looked somewhat brown and glossy. Sometimes few lipofuscin granules were scattered between the fibrills. In HE preparations the degenerated

Table 1. *Clinical Data on Senile Dementia*

Case Number	Sex	Year of Onset	Date of Death	Age at Death	Approximate Duration (Yr.)	Clinical Course
1.	M	1946	1959. 10	68	13	Onset with apathia, then steadily progressive dementia
2.	M	1957	1960. 3	76	3	Progressive dementia, wandering
3.	F	1945	1954. 6	75	9	Wandering, progressive dementia
4.	F	1945	1950. 12	68	5	Forgetfulness and euphoric mood, then progressive dementia
5.	F	1956	1958. 9	90	2	Insomnia and wandering at night, erotic and jealous, progressive dementia, hypertension (200—140)
6.	F	1955	1959. 11	72	4	Wandering, 4 years later under police custody, dementia, hypertension (200 to 120), cancer of mamma

cells were usually filled with the homogeneous or whirled, slightly hematoxyliphilic substance (Fig. 1 a).

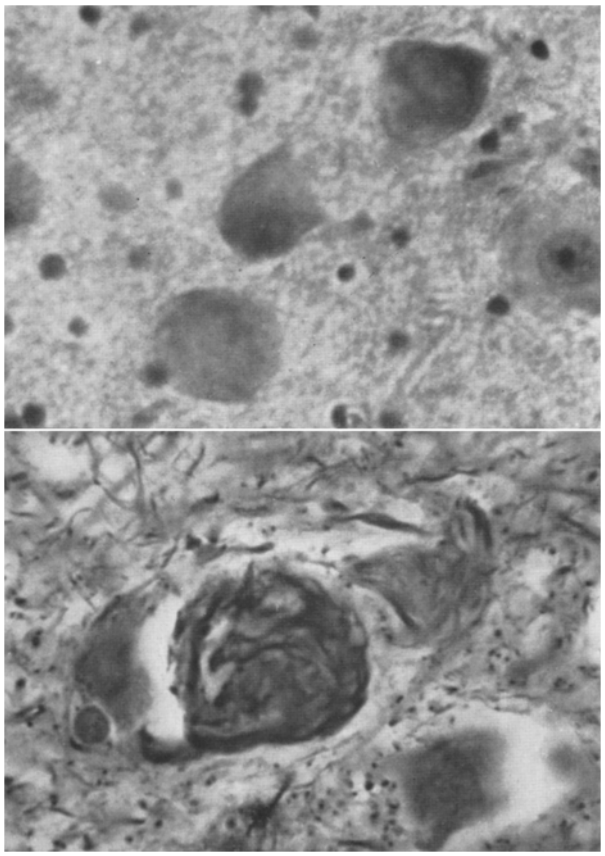

Fig. 1. a ANF in the N. centralis superior. HE stain. ×400. Case 4, 68 year-old, senile dementia. b ANF in the N. dorsalis raphes. Bielschowsky stain. ×700. Case 1, 68 year-old, senile dementia

The distribution of ANF was presented in the diagrams (Figs. 2 and 3). The nuclei in which ANF occurred were shown in Table 2. As was seen in the Figs. 2 and 3, and Table 2, ANF occurred most abundantly and constantly in the nucleus dorsalis raphes and nucleus centralis superior. Sometimes even over half of the remaining nerve cells of these nuclei had ANF. Less frequently encountered were ANF in the nerve cells of nucleus reticularis tegmenti and locus coeruleus. A few

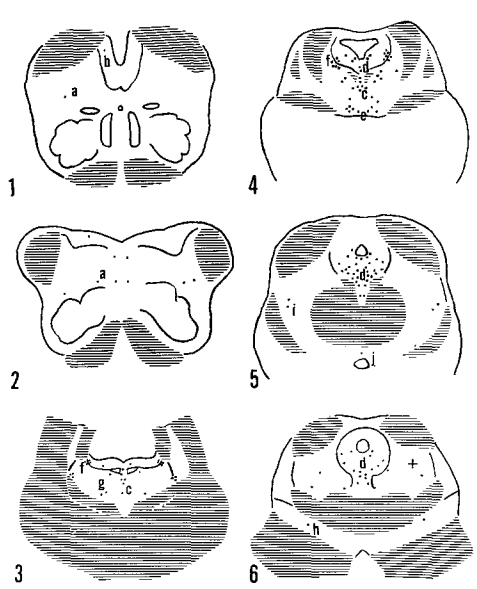

Fig. 2

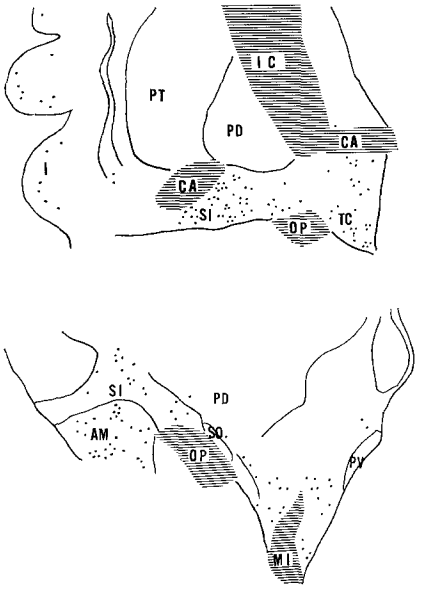

Fig. 3

Fig. 2. Distribution of ANF in the Brain Stem (Senile Dementia). *1* lower medulla oblongata; *2* upper medulla oblongata; *3* lower pons; *4* upper pons; *5* upper pons; *6* lower mesencephalon

Fig. 3. Distribution of ANF in the Hypothalamus (Senile Dementia). *AM* Nucleus amygdalae; *CA* Commissura anterior; *I* Insula; *IC* Capsula Interna; *MI* Fasciculus Mamillo-infundibularis; *OP* Tractus Opticus; *PD* Globus Pallidus; *PT* Putamen; *PV* Nucleus Paraventricularis; *SI* Substantia innominata; *SO* Nucleus supraopticus; *TC* Tuber Cinereum

Table 2. *ANF in Brain Stem and Hypothalamus — Senile Dementia*
3+: Approximately over half; 2+: over $^1/_5$; 1+: below $^1/_5$; 0: none of the nerve cells of the nucleus showed ANF)

Case Number	Brain Stem											Hypothalamus		
	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	*j*	*k*	*l*	*m*	*n*
1	1+	1+	3+	3+	2+	2+	2+	1+	0	3	1+	2+	2+	2+
2	1+	1+	3+	3+	2+	1+	1+	1+	0	0	1+	2+	1+	1+
3	1+	0	2+	2+	1+	1+	1+	1+	1+	0	1+	1+	1+	2+
4	0	0	2+	3+	1+	1+	1+	1+	0	1	1+	2+	2+	2+
5	0	0	2+	3+	1+	1+	1+	1+	0	0	1+	1	0	1+
6	0	0	2+	2+	1+	1+	1+	1+	0	0	0	1+	1+	1+

Abbreviations used in the tables and diagrams. a magnocellular nucleus of reticular formation of medulla; *b* nucleus alae cinereae; *c* nucleus centralis superior; *d* nucleus dorsalis raphé; *e* nucleus reticularis tegmenti; *f* nucleus loci caerulei; *g* reticular formation of pons; *h* substantia nigra; *i* nucleus lemnisci lateralis; *j* nucleus intercruralis; *k* central gray matter of mesencephalon; *l* substantia innominata; *m* nuclei tuberis; *n* nucleus mamillo-infundibularis. · = Alzheimer's neurofibrillary change; × = granulovacuolar body.

were scattered in the central gray matter of mesencephalon, reticular formation of pons, and medulla oblongata. Very few were seen in substantia nigra, nucleus intercruralis, and ala cinerea. None was found in the dentate nucleus, inferior and superior olives.

Of the hypothalamic nuclei, nuclei tuberis, substantia innominata, nucleus mamillo-infundibularis (Fig. 3) got numerous ANF. While unexpectedly none of ANF was found in the nerve cells of corpus mamillare, nucleus paraventricularis and supraopticus.

Contrary to the above, practically no ANF were found in the nuclei of the brain stem and hypothalamus of 6 arteriosclerotics over 80 years of age. Just as well, only a negligible number of ANF was found in other 24 controls of 60 to 79 years of age with the exception of some postencephalitic cases. The quantitative difference between senile dementia and control cases with regard to the occurrence of ANF in the brain stem and hypothalamus was a very marked one.

Comment

Hitherto little attention has been paid to the distribution of ANF in the brain stem and hypothalamus of senile brains. Among the few authors, HERZ and FÜNFGELD suggested a selective nature of distribution of ANF in these areas of Alzheimer's disease. LINDGREN (1952) reported occurrence of ANF in these areas but without comment on the distribution pattern HIRANO (1962) discussed a similar pattern of distribution of ANF i.e. predilection to a certain group of nuclei, between Alzheimer's disease and Parkinsonism-dementia complex.

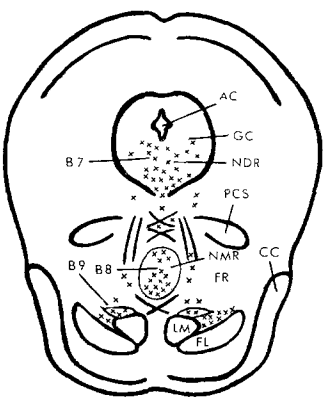

Fig. 4. Distribution of monamine containing nerve cells. Transverse section through the mesencephalon at a level just behind the nucl. interpeduncularis. The 5-HT type cells are indicated as crosses. B 7, substantia grisea centralis, nucl. dorsalis raphes. B 8, nucl. medianus raphe, and cells within the formatio reticularis. B 9, cells within the formatio reticularis mesencephali. *AC* Aqueductus cerebri; *FL* Fasciculus longitudinalis; *FR* Formatio reticularis; *GC* Grisea centralis; *LM* Lemniscus medialis; *NDR* Nucl. dorsalis raphes; *NMR* Nucl. medianus raphe; *CC* Crus cerebri; *PCS* Pedunculus cerebellaris superior. [Cited from A. DAHLSTRÖM and K. FUXE: Acta physiol. scand. **62**, Suppl. 232 (1964)]

According to the present study, ANF were widely distributed in the nuclei of the brain stem and hypothalamus of senile dementia, while in arteriosclerotics and others practically none were found in these areas. The contrast was very marked as far as the ANF in these areas are concerned. In this connection there seemed to be no continuity between physiological ageing and senile dementia.

Physiological functions of the brain stem and hypothalamus are not clear enough. In general they are considered to be autonomous in nature and playing an important part in the central control of attention, consciousness, wakefullness, and sleep. JOUVET (1962) has induced, using electrolytic method in cats, that nucleus reticularis pontis oralis, n. centralis superior and n. raphes are responsible for the R.P.S. On the other hand, SUZUKI et al. (1965) reported that the duration and frequency of R.P.S. reduced especially in the later stage of senile dementia and Alzheimer's disease in contrast with arteriosclerotics and

normal senile. They concluded this phenomenon to depend on the functional decrease of the above mentioned nuclei in the brain stem and speculated that the pathological process of senile dementia and Alzheimer's disease seemed to progress downward from neocortex to brain stem.

It is of great interest that most of the nuclei which tended to get ANF in the brain stem and hypothalamus of senile dementia belong to the monoamine containing nerve cells (DAHLSTRÖM and FUXE 1964, Fig. 4). In fact, striking similarities exist between distribution pattern of ANF and monoamine containing nerve cells in the brain stem. According to them the latter specifically produce and store either DA, NA, or 5-HT and give rise to synaptic terminals where the amines show a tremendous accumulation. N. dorsalis raphes, n. centralis superior and the nucleus of the raphe mesencephali are proved to be 5-HT neurons and send axons to hippocampus and amygdaloid nucleus which are again the well known areas of predilection of ANF in senile dementia. On the contrary, locus coeruleus, substantia nigra, etc. are cells of catecholamine type. In the reticular formation of pons and mesencephalon both types of monoamine containing nerve cells are scattered. In hypothalamus periventricular nuclei within the anterior hypothalamus, n. supraoptics, and paraventricularis are the main sites of monoamine containing nerve cells (CARLSSON 1962).

In addition to the above, most of the nuclei which tended to get ANF, seemed to be characterized by an early accumulation of lipofuscin (OBERSTEINER 1930; MANNEN 1955; SAKAGUCHI 1958), and a high activity of oxidative enzymes in their perikarya (FRIEDE 1962).

Thus, it seems probable that certain regional characteristics in the metabolism and functional activities of the cells involved, in addition to the disease process, may play an important part in provoking ANF.

Summary

Distribution of Alzheimer's Neurofibrillary Changes (ANF) in the brain stem and hypothalamus of 6 cases of senile dementia were examined. ANF were found with marked predilection to a certain group of nuclei in all cases. Among them nucleus dorsalis raphes, nucleus centralis superior were the most severely affected ones. Sometimes even more than half of the remaining nerve cells got ANF. Nucleus reticularis tegmenti, locus coeruleus were next. Periaqueductal gray matter, reticular formation of pons and medulla oblongata, substantia nigra, ala cinerea showed few ANF. Of hypothalamic nuclei, nuclei tuberis, substantia innominata, nucleus mamillo-infundibularis were sites of predilection of ANF.

2 points were discussed:

1. In arteriosclerotics over 80 years of age and other 24 controls practically no ANF were found in the brain stem and hypothalamus. The contrast between senile dementia and arteriosclerotics concerning the occurrence of ANF in these areas was very marked. Thus continuity between physiological ageing and process of senile dementia in the brain is denied as far as the ANF findings in the areas concerned.

2. Predilection of ANF to a certain group of nuclei in the brain stem and hypothalamus. This group of nuclei is supposed to be in a close correlation with the activating system of the brain and playing an important part in bringing about

the rhombencephalic sleep as well as in other central autonomous activities. Most of them are characterized by high content of monoamines, especially 5-HT, in the cytoplasm, an early accumulation of lipofuscin and higher oxidative enzyme activities in the perikaryon. Thus, certain regional characteristics in the metabolism and functions of the cells involved, in addition to the disease process, may play an important part in provoking ANF.

Zusammenfassung

Die Verbreitung der Alzheimerschen Neurofibrillenveränderung (ANF) im Hirnstamm und Hypothalamus wurde in sechs Fällen von seniler Demenz untersucht. In allen Fällen wurde ANF vor allem in einer bestimmten Gruppe von Kernen gefunden. Unter diesen waren der Nucl. dorsalis raphes und der Nucl. centralis superior am schwersten betroffen. Bei einigen Fällen wiesen mehr als die Hälfte der verbliebenen Nervenzellen die ANF auf. Nach diesen beiden Kernen waren der Nucl. reticularis tegmenti und Locus coeruleus am meisten geschädigt. Auch im periaquäduktalen Grau, in der retikulären Formation der Brücke und des verlängerten Marks, in der Subst. nigra und in der Ala cinerea waren einzelne ANF zu finden. In den Hypothalamuskernen tritt die ANF mit Vorliebe in den Nuclei tuberis, in der Subst. innominata und im Nucl. mamillo-infundibularis auf. Wir erörtern folgende zwei Punkte:

1. Bei Patienten mit Arteriosklerose im Alter über 80 Jahren und bei 24 Kontrollfällen konnte man die ANF im Hirnstamm und im Hypothalamus kaum nachweisen. Was die ANF in den genannten Gebieten betrifft, so zeigte sich eine auffällige Verschiedenheit zwischen Arteriosklerose und seniler Demenz. Demnach gibt es, was die ANF der genannten Gehirnteile angeht, keine Kontinuität der Gehirnveränderungen zwischen dem physiologischen Alternsprozeß und dem Prozeß der senilen Demenz.

2. Die ANF treten hauptsächlich in einer bestimmten Gruppe von Kernen des Hirnstamms und des Hypothalamus auf. Man kann annehmen, daß diese Kerngruppe im engen Zusammenhang mit dem aktivierenden System des Gehirns steht und eine wichtige Bedeutung sowohl für den rhombencephalen Schlaf als auch für andere vegetative Leistungen besitzt. Die meisten dieser Kerne sind durch hochgradigen Monoamingehalt (besonders 5-HT) im Cytoplasma, durch frühzeitige Lipofuscinanhäufung und durch hochgradige Aktivität der oxydativen Enzyme im Perikaryon charakterisiert. Der eigentümliche Stoffwechsel und die Funktionen der Nervenzellen bestimmter Regionen dürften in Verbindung mit dem Krankheitsprozeß eine wichtige Rolle bei der Entstehung der ANF spielen.

References

BRAUNMÜHL, A. v.: Alterserkrankungen des Zentralnervensystems. Hdb. spez. path. Anat. Bd. 13/I, S. 337—539. Berlin, Göttingen, Heidelberg: Springer 1957.

CARLSSON, A., B. FALCK, and N.-Å. HILLARP: Cellular localization of brain monoamines. Acta physiol. scand. **56**, Suppl. 196 (1962).

DAHLSTRÖM, A., and K. FUXE: Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta physiol. scand. **62**, Suppl. 232 (1964).

FRIEDE, R. L.: The relation of the formation of lipofuscin to the distribution of oxidative enzymes in the human brain. Acta neuropath. (Berl.) **2**, 113—125 (1962).

Greenfield, J. G., and F. D. Bosanquet: The brain-stem lesions in Parkinsonism. J. Neurol. Neurosurg. Psychiat. **16**, 213—226 (1953).

Hallervorden, J.: Zur Pathogenese des postencephalitischen Parkinsonismus. Klin. Wschr. **12**, 692—695 (1933).

— Anatomische Untersuchungen zur Pathogenese des postencephalitischen Parkinsonismus. Dtsch. Z. Nervenheilk. **136**, 68—77 (1935).

Herz, E., u. E. Fünfgeld: Zur Klinik und Pathologie der Alzheimerschen Krankheit. Arch. Psychiat. Nervenkr. **84**, 633—664 (1928).

Hirano, A., N. Malamud, and L. T. Kurland: Parkinsonism-dementia complex, an endemic disease on the Island of Guam.—II Pathological Features. Brain **84**, 662—679 (1961).

—, and H. M. Zimmermann: Alzheimer's neurofibrillary changes. A topographic study. Arch. Neurol. (Chic.) **17**, 227—242 (1962).

Jouvet, M.: Recherches sur les structures nerveuses et les mécanismes responsables des differentes phases du sommeil physiologique. Arch. ital. Biol. **100**, 125—206 (1962).

Lindgren, A. G. H.: Morbus Alzheimer und Morbus Pick. (By T. Sjögren, H. Sjögren and Lindgren). Part III, p. 119 (1952). The Pathoanatomical Classification of Morbus Alzheimer und Morbus Pick.

Malamud, N., W. Haymaker, and H. Pinkerton: Inclusion encephalitis with a clinicopathologic report of three cases. Amer. J. Path. **26**, 133—153 (1950).

— A. Hirano, and L. T. Kurland: Pathoanatomic changes in amyotrophic lateral sclerosis on guam, Special reference to the occurrence of neurofibrillary changes. Arch. Neurol. (Chic.) **5**, 401—415 (1961).

Mannen, H.: La cytoarchitecture du systeme nerveux central humain regardée au point de vue de la distribution de grain de pigments jaunes contenant de la graise. Acta anat. Nippon. **30**, 151—174 (1955).

Obersteiner, H.: Über das hellgelbe Pigment in den Nervenzellen u. das Vorkommen weiterer fettähnlicher Körper im Z. N. S. Arb.Neurol. Inst. Wien. Heft 10, 245—274 (1930).

Simchowicz, T.: Histologische Studien über die senilen Demenz. Nissls Arbeiten IV, 267—444 (1911).

Suzuki, Y., and I. Hirota: EEG study on senile Dementia. 62th Japan Neuropsychiatric Meeting. 1965.

Sakaguchi, K.: Studies on senile brains-mainly on Alzheimer's neurofibrillary change. Psychiat. Neurol. jap. **60**, 126 (1958).

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