THE HISTOLOGIC CHANGES OF THE SYMPATHETIC GANGLIA IN JAPANESE B ENCEPHALITIS*

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INTRODUCTION

The changes of the central nervous system in Japanese B encephalitis is the common subject which were studied by many investigators, and some authors in particular have contributed their findings as good as the previous reports about the type which prevailed in the summer of 1948. But in my opinion the observations about the peripheral nervous system, above all the sympathetic nervous system, are still unsatisfactory. From this point of view Ohnuma's reports of 5 necropsies only are cited in the literature. On the other hand, even in the case of encephalitis lethargica in Europe the number of such date is small, in spite of an abundance of the reports regarding the changes of the sympathetic nervous system in other diseases. Furthermore those cases were mentioned as one of acute infective diseases in general and then could not be gone into details.

Under such consideration I wished to extend this type of work. By microscopic examination on the Ganglion cerv. sup., Ggl. stell., and Ggl. coel. which were derived from 37 corpses (they all showed the usual type of Japanese encephalitis. 35** of them died in 1948 and 2 in 1949), I obtained some findings similar to the changes in the central nervous system. I reflected on them comparing with the process and the symptoms of this disease.

FINDINGS ON THE TYPICAL CASES

I divided the cases into three groups according to the length of disease process and picked up two cases for each group. (See Table 1. concerning the other cases.)

- (a) Stage of degeneration: Where chiefly the nerve cells degenerate.
 - (b) Stage of reaction: Where occurs the glial reaction against the degenerative changes of nerve cells.
 - (c) Stage of cicatrix: Where the injured nerve cells disappear and the glial cicatrices are formed out of the increased glia cells.
- (1) The first stage of degeneration.

§ Case 2. 5 y. ♀ 3 days

Inspection of sections shows a remarkable swelling of the majority of the nerve cells. Some cells are ambiguous in outline or in their dendrites. Some cells have a

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** 27 of them at the Komagome Hospital.

vacuole in their protoplasms. In Nissl-preparation such cells exhibit the acute and severe changes, but we can still see few delicate granules regarded as pathological (which I intend to treat fully later on). Slight proliferation of the capsular cells is not followed by neuronophagia or the formation of the glial cicatrix. Proliferation of the interstitial glia cells can not be found, either.

These situations are in a word a sudden and violent suffering of nerve cells and it means that any reaction against those pathologic conditions doesn't yet go into operation.

§ Case 3. 27 y. ♂ 4 days (Fig. 1)

The swelling involves the majority of nerve cells and frequently we can see the cell without nucleus, so the situation corresponds to Nissl's "Schwere Zellerkrankung." The heavy-injured cells are already collapsed and nothing remains in the lumen of the capsule but occasionally amorphous materials which look like irregular masses or network, namely shadows of cells existing there at one time are seen, but the glial cicatrix can not be found. The size of the pathologic granules reaches that of nucleolus, particularly I found one which was as large as an erythrocyte. Slight proliferation of the capsular cells and the interstitial glia cells is noted. Nerve fibers have disappeared as groups at the region where the nerve cells had degenerated disappeared. In such region the black-stained fibrous network which are evidently visible in the surrounding tissues can be scarcely found and only few fibers which are stained light-brown thinly distributed.

In brief the most dominant changes in this case are degeneration of the nerve cells and destruction of the cell bodies following it.

(2) The second stage: stage of reaction

§ Case 11 63 y. ♂ 5 days

The number of the swollen nerve cells is fairly large but not so many as those in the preceding two cases. We recognize the disappearance of nerve cells and the glial cicatrix here and there. In Nissl-preparations some cells exhibit the aggregated gross granules in their protoplasms or the destruction of cell bodies succeeded the acute changes. The scattered pink-stained spots mean the vestiges of nerve cells (metachromatism). The capsular cells have proliferated and bored into the injured cells, namely neuronophagia is noted. Proliferation of the interstitial glia cells is slight. Aggregating granularly they make a mass around the degenerated nerve cell, and including the microglia they become so-called neuroglial nodules. But these changes are not accompanied by cell-infiltration.

In this case the reaction against the degeneration of nerve cells must be recognized as characteristic and the scene of neuronophagia as well as the formation of glial cicatrices begin to be visible.

§ Case 16 7 y. ♂ 6 days (Fig. 2, Fig. 3)

Evidently the degeneration of the nerve cells occurs. A few cells are found with extraordinarily many patches of brown pigment. In Nissl-preparations we can see chromatolysis in varying degrees. But the acute changes are relatively few. The remarkable disappearance of the nerve cells causes their distribution to be rare here and there. Swelling and proliferation of the capsular cells are remarkable, too.

Everywhere we can see neuronophagia and the glial cicatrices and there the patches of

brown pigment are frequently taken in by the glia cells. The interstitial glia cells proliferate diffusely. Adding to this there are the neuroglial nodules. The endothelium of the blood vessels swelling. Hyperemia and the perivascular round cell infiltration are of high degree. The fine network of the nerve fibres has disappeared everywhere, particularly to a large extent about the neuroglial nodules. In such region the bundles of the nerve fibers are cut off or pushed out, so they are running in various curves.

In a word, this case indicated such phase as follows—the heavy degenerated nerve cells had already been destroyed and subsequently the remarkable cell infiltration or proliferation of the glia cells appeared as a reaction.

(3) The third stage: stage of cicatrix

§ Case 27 11 y. ♂ 7 days (Fig. 4)

Some nerve cells show the regressive changes but the swollen one are on the decrease. In Nissl-preparations we can see the sub-acute alteration. The number of the abnormal cells which have many patches of brown pigment is extraordinarily great considering the age of this patient. These cells are usually in atrophy. The numerous pathologic granules smaller than a nucleolus are noticed. The capsular cells have proliferated; neuronophagia, and the glial cicatrix can very frequently be seen. The interstitial glia cells also proliferate diffusely, including the microglia among them. In brief, the disappearance of the nerve cells and the formation of the many glial cicatrices are the most significant in this case.

§ Case 36 8 y. ♂ 14 days (Fig. 6)

The swelling of the nerve cells is not observable. There are groups of cells having many patches of brown pigment. The pathologic granules are all very delicate. The capsular cells are rarely taking part in phagocytic process. We see remarkable proliferation of the interstitial glia cells and many glial cicatrices. Occasionally there are masses of glia cells. We surmise that they will be completed in future as so many neuroglial nodules. In addition to these findings, hyperemia and the perivascular round cell infiltration are worth noting.

(Nearly the same findings were seen in Case 37. But I omitted it from Table 1, because the duration of the disease were unknown in that case.)

DISCUSSION

The relation of the histologic findings to the duration of the disease (See Table 2.)

In cases where the patient died within four days from pathogenesis (in the stage of degeneration) seven out of nine cases (77.8%) showed the existence of many swollen nerve cells. On the other hand, there are no such changes shown in ten cases where the patient died more than seven days later from pathogenesis (in the stage of cicatrix). Throughout these cases we can see only a few swollen nerve cells.

In this stage, however, there are seven cases (70%) which showed a great number of glial cicatrices, while only a few cicatrices or disappearance of the nerve cells can be seen in the seven cases out of nine (77.8%) in the former stage of degeneration.

To sum up, common change in the initial stage is swelling of the nerve cells, and any positive reactions, for example destruction of them, formation of the glial cicatrices, proliferation of the glia cells etc., are still in the cradle, but we can say, in process of time, the swollen nerve cells gradually go to rack and ruin and the latter appearances as mentioned above begin to take place of the former. Next, in the initial stage the changes of every cell are much the same in the same visual field, and in process of time they begin to exhibit a wide range of variation in manner and in degré.

We can see even the normal cells in the later stage. The variability of resistance of every cell against the pathogen would be the cause which showed the difference as above indicated. I consider that some cells died out, some cells moved into the subacute, and some cells revived according to their resistibility, in process of time.

Of course I grant the existence of an exceptional case, but I suppose its cause the influence of the complex factors, for example, the individual diathesis, the virulence of the pathogen, the disturbance of the central nervous system attacked by the same pathogen, etc.

Table 2

Changes	Stage	Stage of degeneration		Stage of reaction		Stage of cicatrix	
Swollen nerve cells	+++ ++	77.8%	(7/9)	35.3%	(6/17)	0%	(0/10)
	+ ±	22.2%	(2/9)	64.7%	(11/17)	100%	(10/10)
Disapp. n. c. and glial cicatrix	+++ ++	22.2%	(2/9)	70.6%	(12/17)	70%	(7/10)
	+ ± -	77.8%	(7/9)	29.4%	(5/17)	30%	(3/10)
Prolif. of capsul. cell	+++ ++	33.3%	(3/9)	23.5%	(4/17)	20%	(2/10)
	+ ±	66.7%	(6/9)	76.5%	(13/17)	80%	(8/10)
Prolif. of glia cell	+++ ++	22.2%	(2/9)	23.5%	(4/17)	50%	(5/10)
	+ ± -	77.8%	(7/9)	76.5%	(13/17)	50%	(5/10)

Special observation

The nerve cells; First, the nucleus and the cytoplasm swell up remarkably, Nissl's bodies go into solution, and sometimes the nucleus with the nucleolus melts away, in a word, the acute and severe changes occur. Soon the nucleus and the cytoplasm go into atrophy, or Nissl's bodies are aggregated like the gross granules. In some cases of children the increase of brown pigment is pathological over the standard of its age. Many delicate vacuoles begin to appear, so the protoplasm looks like a mass of foams. Occasionally a greater vacuole pushes aside the protoplasm and the nucleus, and lets the cell assume an appearance like a signetring. Those vacuoles reacted negative to fat stains (Sudan III) in fifteen cases without exception. Ohnuma (1), Terplan (2), Beattie and Dickson (3), don't allow the presence of fat in such occasion, too.

The pathologic granules would be just the same as those which Suzuki (4), and Ohnuma (1) recognized in lyssa, Japanese encephalitis, and several other diseases. Those granules are stained eosinophil by the haematoxylin-eosin staining, or Mallory's or Mann's method, and on the other hand fuchsinophil by Alzheimer's method, and lastly react positive to the fibrin-staining. Their size varies from that of very fine mitochondria to that of

an erythrocyte. In configuration they look like a rain-drop or assume an oval outline, and it is surrounded by a narrow clear space of protoplasm, and sometimes differentiates in two portions, viz. the larger granule is dark stained granularly in the peripheral portion but homogeneous hyaline in the central portion.

They are distributed in the protoplasm at random, even in the perinuclear zone, or in the dendritic processes. They also appear in the cells whose nuclei are free from notable changes. But the presence of such granules is not a peculiar accompaniment of lyssa or Japanese encephalitis. That fact was already pointed out by Luktsch (5) and Ohnuma, and I also corroborated it in several other diseases. When these granules are seen in varying sizes and particularly include the ones which are larger than a nucleolus among them, of course situation must be regarded as pathological. However, if those are all very delicate and thinly distributed, we could not determine what amount of the sense of the word "PATHOLOGIC" is suitable to this case, without more careful scrutiny.

The capsular cells and the interstitial glia cells; It is the capsular cells that first of all react against the degeneration of nerve cells. They swell, proliferate, and often surround the nerve cells doubly or triply. They are arranged radially or falcately and invade into the lumen, encroach the degenerated nerve cell, thus exhibit the scene of neuronophagia.

Many investigators described that it was only the capsular cells to do neuronophagia, but Beattie and Dickson insisted that other phagocytes took part in it. As for me, the

Fig. 7. Illustration of changes of nerve cell and capsular cells

microglia were taking part in it. Where the nerve cells disappeared by neuronophagia, commonly the glial cicatrices are formed out of the increased capsular cells which are aggregated centripetally, like a flower. In the cytoplasm of such glia cells, there are frequently the patches of brown pigment. Probably they were once in the nerve cells, and were taken into these glia cells through the phagocytic process.

Repeated examinations could not show a presence of hemosiderin, which according to Kongo (6) can be found rarely in the central nervous system in this disease.

The interstitial glia cells proliferate perivascularly or diffusely. In nine cases the neuroglial nodules, which we know exist commonly in the central nervous system in this disease, could be recognized. These nodules have been formed mainly around the perished nerve cell. The constituent elements are a good few microglia and some free cells, besides the increased capsular cells and the interstitial glia cells. We can distinctly discern those masses of cells as a nodule from the surrounding. The "Knötchen" so-called by Staemmler (7) and Terplan (2) differs from this neuroglial nodule, because it corresponds to the glial cicatrix which were already mentioned. Ohnuma's reports upon this disease don't touch this nodule. I examined circ. 100 cases of other diseases but after all could not find such nodule, either. Accordingly this finding may be characteristic of this disease—Japanese B encephalitis. By Holzer's method, the proliferation of the glia fibres was not evident.

Blood vessels and cell infiltration; The endothelial cells of the vessels show swelling and often hyperemia. The remarkable cell infiltration are seen particularly on the wall of the vessels and in the perivascular area. They are usually round cells, rarely the polynuclear leucocytes. These cell infiltration, however, is not a common phenomenon. They were found in twelve cases, where mostly the situation had already entered the second stage.

The nerve fibers; Fibrolysis of the neurofibrils in such injured cells as I mentioned above were described by many authors but there are few reports concerning the extracellular nerve fibers.

By Cajal's method the disappearance of the fine fibrous network between the nerve cells is visible even in Case 3. Furthermore, I saw that the nerve fibers disappeared as groups to a large extent where the glial cicatrix crowded together or the glial nodules lay, and that the bundles of fibers were cut off or pushed out by the nodule and showing the curved running there, in Case 7, 16, 27, 30, and 36. Abrikossoff (8), too, remarked that the massive cell-infiltration could divide the bundles of the nerve fibers. But we have no definite knowledge whether the degeneration of fiber themselves gave rise to such phenomena, or was caused by the degeneration of the cell body to which the fiber belonged.

Alteration of the Ggl. coeliacum; I observed it in eight cases. The changes are much the same as that of the cervical ganglia but very slight in degree. Especially, there are scarcely any glial reactions. Abrikossoff, Staemmler, and Ohnuma are also aware of the fact that the changes of the Ggl. coel. are slight in comparison with that of the cervical ganglia in several diseases.

Complications

Some cases were accompanied by certain acute diseases, but they alone can not make such remarkable changes histologically according to the literatures and my experiences. I consider the influence of the complications is not a very important factor.

Relationship to the clinical symptoms.

It is quite difficult to distinguish the symptoms which have the origin in the autonomic nervous system from the symptoms which have the other origins, for we must observe the complex, severe, and changing symptoms within a very short period. Anyhow such symptoms as the Table 1 were noted as a result of the inspection in our department.

In this disease Nagasawa (9) also pointed out the disharmony of the autonomic nervous system. But the central nervous system are injured too and its influence must be taken into account. The question whether the above mentioned histologic changes stimulate, or suppress the function of the autonomic nervous system, or the question how the variation of irritability of the peripheral organ is, are quite difficult to determine. But it is in the nature of things that such remarkable morphological changes should bring some or other disorders of function. They should be at least one of the causes which made the autonomic nervous system disharmonic.

According to Blanke (10), the salivation observed in encephalitis lethargica is caused by the hindrance of the center of the autonomic nervous system. As the salivary gland and lacrimal gland work under the direct control of the cervical ganglion, I consider the changes of that ganglion are to be much valued as a cause of salivation and lachrimation in this disease.

Comparison with encephalitis lethargica (so-called A type):

In a retrospect of the literature concerning acute encephalitis or encephalitis lethargica, I see Staemmler's description. He recognized the degeneration of the sympathetic nerve cells in one of the two cases and in another inflammatory changes, but he rather emphasized the changes in streptococcensepsis, so I presume the changes which he observed in encephalitis lethargica were not fairly remarkable.

Furthermore he said that the findings were quite normal in three cases of Parkinson's disease which followed the chronic encephalitis.

Brünning and Stahl (11) found no changes either. Terplan described that there were slight inflammatory changes in three cases out of four but, roughly speaking, the situation might be regarded as normal. Sala (5) is aware of the degenerative alteration in the Ggl. ciliare

Consequently I suppose the alteration of the sympathetic ganglia in A-type would be relatively slight, in comparison with Japanese B encephalitis which showed the remarkable changes in forty-two cases (my thirty-seven cases and Ohnuma's five cases).

CONCLUSION

1. In 37 corpses of Japanese B encephalitis, the histologic inspection showed slight

changes in the Ggl. coel. and remarkable changes similar to that of the central nervous system in the Ggl. cerv. sup. and Ggl. stell. Particularly many neuroglial nodules and remarkable proliferation of the glia cells are characteristic of this disease. The alteration of the nerve fibers were recongnized too.

2. The pathologic granules were found in some cases, but they are not peculiar to this disease.

3. The findings showed gradual transition parallel to the length of disease process. We can divide it in three stages;

- (a) Stage of degeneration.....where chiefly the nerve cells degenerate.
- (b) Stage of reaction.....where occurs the glial reaction against the degenerative changes of nerve cells.
- (c) Stage of cicatrix.....where the injured nerve cells disappear and the glial cicatrices are formed out of the increased glia cells.

4. These sympathetic ganglia as well as the other region are one of the favorite locations of Japanese B encephalitis.

5. Sequently these findings give an information to explain the disharmony of the autonomic nervous system in this disease.

6. The changes in the sympathetic ganglia in Japanese B encephalitis appear to be more intensive than that of encephalitis lethargica (A type).

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EXPLANATION OF THE PLATES

Fig. 1. Case 3, 27y. ♂ 4 days
Ggl. stell. Nissl-preparation.
The nerve cells are swelling. The nucleus remains its vestige. Destruction of Nissl-bodies here and there. Slight proliferation of the capsular cells.

Fig. 2. Case 16, 7y. ♂ 6 days
Ggl. stell. H.E. staining.
Proliferation of the capsular cells.
Diffuse proliferation of the interstitial glia cells with round cell infiltration

Fig. 3. Case 16, 7y. ♂ 6 days
Ggl. stell. Cajal's method.
Proliferation of the glia cells.
Disruption or disappearance of the bundles of nerve fibers.

Fig. 4. Case 27, 11y. ♂ 7 days
Ggl. cerv. sup. H.E. staining
Proliferation of the capsular cells.
Neuronophagia is worth noting.

Fig. 5. Case 39, 7y. ♂ 8 days
Ggl. cerv. sup. H.E. staining
Neuroglial nodule.

Fig. 6. Case 36, 8y. ♂ 14 days
Ggl. stell. H.E. staining
The vestiges of the nerve cells are transmutated into the glial cicatrices by proliferation of the capsular cells.