CORTICAL CEREBELLAR ATROPHY OF GRANULAR TYPE IN JAPANESE CATTLE

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INTRODUCTION

There is an endemic disease of unknown cause, so-called "Kiriyoi* disease", in mountainous districts of Chugoku, western Honshu, which has been known mainly to affect young Japanese cattle during grazing in spring. There seems to be no definition on the concept of the said disease other than unilateral or vague explanations because of the imperfectness of pathological studies made in the past.*11,12,20,22 & 28 In the literature, emphasis seems to be laid on the role played by such things as geographical conditions and seasonal-meteorological influence particularly coldness in terms of the outbreak. In addition, the present authors understand that as characteristic symptoms somnolence, coma, rotation of the ocular bulbus, etc. were taken up* and hypoglycemia was confirmed.*

The authors (S. Y. & H. S.) have not had opportunity to go into a study of this so-called “Kiriyoi disease” despite of their keen interest in the disease. They have had an opportunity to re-examine, from the general point of view and pathologically, the cases of Japanese cattle regarded as affected with the disease by their owners; the materials had been collected by one of the authors (M. G.) at the site of the outbreak of the disease. Surprisingly, detailed microscopical examination clearly revealed the existence of extensive primary lesion (atrophy) just in the granular layer of the cerebellar cortex which is conspicuously characterized by the degeneration and loss of granule cells, at a high rate in the central nervous system. With interest in the relation between so-called “Kiriyoi disease” and the significance of the degenerative process of the granular

* Kiri means “fog” and Yoi “to be intoxicated”.

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layer in the cerebellar cortex which belongs to a peculiar category in terms of the literature, the present workers have tried to give possible explanations of the said degenerative process from the pathomorphological viewpoint without being swayed by the concept of the disease described under the foregoing references.

Hoping that the present studies made centering around the central nervous system would assist in understanding the reality of so-called "Kiriyoi disease", and on the other hand make some contribution to the future study of neuropathology throughout human being and animals, the authors, taking this opportunity, dare to make public this report despite of the imperfect materials obtained under limited circumstances. The authors further are hoping to have opportunities to conduct thorough pathological investigations of possible occurrences of the disease in Japanese cattle in the future.

**MATERIALS AND METHODS**

**Materials Used for Investigation**

Twelve different central nervous systems, as shown in table 1, were used for the present studies. They were obtained from 16 young Japanese cattle which were collected by one of the authors (M. G.) and were regarded as having suffered "Kiriyoi disease" by owners in Hino-gun, Tottori Prefecture, endemic districts of so-called "Kiriyoi disease", between 1951 and 1958.

Four other cases which did not provide the central nervous system—one each case in

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1951 (No. 1), 1952 (No. 2), 1953 (No. 3) and 1954 (No. 6)—will be taken up in a proposed report “Pathological studies on so-called Kiriyoi disease” by M. Goto, K. Itagaki, O. Yamane, H. Fujihara, Y. Fujimoto, K. Ohshima, H. Satoh and S. Yamagiwa which covers the entire bodies in 16 cases.

Practically all of the twelve cases shown in table 1 were found as corpses by the owners in mountainous pastures. No clinical symptoms are available. It, however, can be imagined that there was approximately one-half to two and a half days between the appearance of symptoms and death judging from various circumstances.

The majority of corpses were autopsied 15~30 hours after death because of the delay in discovering the corpses and geographical conditions except No. 9 which was autopsied relatively soon after slaughter.

The cervical spinal cord and brain were obtained simultaneously; in case No. 9 the lumbar cord was also taken out. However, in cases Nos. 4 and 5 (cases sent for verification) only a part of the central nervous system was obtained. The obtained central nervous systems were preserved in 10% formalin solution without loss of original shape.

Methods of Investigation

Upon making exterior and interior observations macroscopically on the nervous system preserved in formalin solution, the authors conducted histological investigations on frontal sections obtained from several portions of the telencephalon, diencephalon, mesencephalon and rhombencephalon and cross sections obtained from the spinal cord; in the cerebellum frontal sections were obtained from several portions about in parallel with primary sulcus; and similar sections were obtained from several portions of the posterior part of the brain stem.

In the histological investigations use was made of paraffin embedding and H.E. staining on the central nervous system of all cases, celloidin embedding and cresylviolet staining, Spielmeyer’s myelin sheath staining, Bielschowsky’s impregnation method and Sudan III staining on the tissue sections of the cerebellum and posterior part of the brain stem of a large majority of the cases.

RESULTS OF INVESTIGATIONS

Macroscopical Findings

Except Nos. 4 and 5 (cases sent to us for verification) which did not provide the entire central nervous system, the shape and the size of the brain and spinal cord were almost normal and their meninges showed nearly normal conditions in all cases. No abnormality was recognized even on the various cut surfaces of the brain and spinal cord mentioned before.

Microscopical Findings

Outlines The most noteworthy change was the degeneration and the loss of granule cells in diffused granular layers of the cerebellar cortex of all cases except No. 9; it appears that such changes are nearly equivalent to the degree of bilateral localization.
In Nos. 7, 13 and 14, H.-E. staining revealed reddish acidophil granule substances in a constant size in protoplasm of medium sized nerve cells in the area vestibularis of "Bodengrau" of the medulla oblongata (Fig. 24).

A slight hyperemia was noticed in 3 cases (8, 13 & 14), but all other cases rather showed anemic. About half of the cases showed petechiae in the meninges and parenchyma of the brain, which showed mainly in the portions other than cerebellum in the brain; such petechiae are so small in number and slight in degree that they are not worth describing. In some of all cases small blood vessels rarely contained hyaline thrombi.

In No. 13 slight perivascular cell infiltration comprised mainly of lymphocytoid round cells was often noticed in meninges and parenchyma of the prosencephalon; such a cell component often contained neutrophil or eosinophil leucocytes. Such cellular infiltration was also observed in the parenchyma of prosencephalon and cerebellar meninges of No. 16. However this weakness in degree is incomparable to the former. No other changes of the central nervous system was found in any place.

The outlines of visceral changes will be described below in the discussion contained in this report.

Cerebellum Microscopically, it was clearly observed without difficulty that the granular layer of the section preparations of the cerebellum shows decrease and loss of staining in all cases except case No. 9; the degree of such indication seems to be severe in the paleocerebellum (Fig. 1). In some of the cases the authors often encountered portions which did not show staining at all and in other cases showed the decrease of staining limited to the vermis of the cerebellum (Nos. 8 & 15).

By means of microscopy various degenerative features or the loss of granule cells of the granular layer of the section preparations of the cerebellum shows decrease and loss of staining in all cases except No. 9 (Fig. 5). Therefore, the "Lichtung" of various degrees of the granular layer becomes apparent depending on the process in granule cells. The desolation in the granular layer is thoroughly limited according to the process of granule cells, and Golgi's cells and others are relatively well maintained without having suffered damage. Contrary to what happened in the granular layer, there were no changes in the Purkinje-cell layer, molecular layer, white matter and cerebellar nuclei; their tissue structure seemed to be relatively well maintained (Figs. 2 & 6~19).

Features of the process of desolation shown in different stages between the degeneration and the loss of granule cells can be clearly observed in the reference photographs attached. Quantitative and qualitative difference which appears in the degeneration which is observable in each case and location depends generally on combination of individual characteristic degenerative features of granule cells described below (Figs. 20~23).

1. Pycnosis.
2. Hyperchromatosis of nucleus.
3. Deformation of nucleus.
4. Structure of caryoplasm becomes irregular, and that nucleus itself loses staining conspicuously (ghost appearance); on that occasion, some nuclei have irregularly shaped one which is regarded as remaining nucleus.
5. In many cells which show ghost appearance, a large or small vacuole is formed
nearly in the center of the nucleus and membraneous substance limiting the vacuole in the nucleus is simultaneously observed; in some nuclei, a large number of the similar vacuoles which were formed in the nucleus are enclosed in the reticular structure of the caryoplasm.

6. The central portion of the nucleus remains hyperchromatic caryoplasm of irregular shape and the other nuclear area which shows ghost appearance takes reticular structure.

7. Small vacuole formation is uniformly observed in a deformed nucleus which is remarkably short of caryoplasm (ghost appearance), and which is divided by the reticular structure of the remaining caryoplasm.

8. Disappearance of cell.

Therefore, it can be said, on the basis of macroscopical observation of H–E. stained preparations, that there is one case in which some portion which still retain large numbers of granule cells showing ghost appearance and others with a considerable loss of cells show the decrease of staining to the same extent.

In general, the most severe desolation of the granular layer was confirmed in the palaeocerebellum under microscopy as well as macroscopical observation on stained preparations. On the contrary, the dorso-lateral cerebellar hemisphere seems to show slight degeneration throughout 11 cases in general. There is one case where the difference of the changes is considerably intense as shown in Figs. 16 and 17; Fig. 16 shows scarcely any granule cells but the other (Fig. 17) only shows slight "Lichtung" though remaining individual granule cells show pycnosis. In cases Nos. 8 and 15 where desolation in the palaeocerebellum is nearly limited to the vermis, the hemispheres show very slight changes and only slight pycnosis of granule cells (Figs. 18 & 19). Such indications seem to occur in each one of 11 cases, and in general the degree of changes in hemisphere quantitatively and qualitatively depends on the degree of desolation in the palaeocerebellum.

"Lichtung", though inconstant depending on the degree of desolation of the granular layer, causes loosening of ground substance. The authors, however, have not encountered any case which had completely lost the ground substance.

The section preparations to which impregnation method was applied (Fig. 3) did not show any outstanding change in any cases. Purkinje's cells seemed to be almost normal, and basket cells, baskets and tangential fibers even in case No. 9 did show any recognizable change and were relatively well maintained. Parallel fibers seem to be decreased slightly depending on localization, but it seems that qualitative and quantitative difference can not be detected in any part of the molecular layer of the cerebellar cortex which shows variation on changes of the granular layer; even in comparison with case No. 9 no recognizable difference of the fibers was discovered. Even in the picture of fibers of the granular layer, comparative investigation with microscopy conducted of areas which show the different changes and those in No. 9 did not reveal any obvious change. It seems that Golgi's cells are also relatively well maintained.

It seems that myelin sheath fibers which exist in the cerebellar cortex in preparations stained with myelin sheath stain (Fig. 4) do not always show abnormal appearance. In addition, positive substances were also not found in any portion of the cerebellar cortex in the preparations stained with Sudan III.
Also, no changes were seen in the various stained preparations from the white matter and cerebellar nuclei.

Regardless of the existence of the degenerative process of the granule cells as mentioned above, reactive changes were not observed in any part of 11 cases at all. Besides, there seems to be no disorder in the thickness of each layer of the cerebellar cortex including the granular layer, which may be an important factor not showing abnormality in the macroscopical size and shape of the brain.

DISCUSSION

Cerebellar lesions

The authors would like firstly to lay stress on the peculiar characteristic of the cerebellar lesions found in the 11 cases in terms of histopathology. Very few reports have been made pertaining to such diseases of the central nervous system as the conspicuous degeneration and necrosis occurring only in the granular layer in the entire area of the cerebellum, though their appearances vary depending on the localization. In order to identify the characteristics of such changes, the authors wish to make two or three comments referring to the concept of various cerebellar disorders which are recapitulated by ULE as "Systematische Kleinhirnatrophie."

Studies on the degenerative disorders of the cerebellum of animals have been conducted on the fowl, cat, dog, sheep, cattle and other creatures as follows:

1. Daft lambs and Canadian lambs (cortical cerebellar atrophy) which are fancied as inherited (VAN BOGAERT & INNES, and INNES & MACNAUGHTON), in cases which are not accompanied by macroscopical changes.

2. Familial cerebellar hypoplasia and degeneration of calves of Hereford stock (INNES et al.)

3. Progressive cerebellar atrophy or abiotrophy of a lamb (VAN BOGAERT & INNES).

4. Cerebellar atrophy of Purkinje-cell type of a Fox terrier stock dog (FRAUCHIGER & FANKHAUSER).

5. A case of cerebellar ataxia in dog (TAJIMA & OSHIMA).

6. Hereditary congenital ataxia of Jersey calves mainly accompanied by changes in the white matter of the cerebellum (SAUNDERS et al.).

The changes mentioned above, however, seem to be of different form from what the authors have described in this report. However, the authors' statement is based upon the premise of disregard of whether or not morphogenetical comparison should be made of the lesions in lambs of VAN BOGAERT & INNES, and INNES & MACNAUGHTON with those of the authors, even though the cerebellar disorders in this report may belong to those of extremely acute for the reason that reactive changes are scarcely recognizable and existence of the degenerative
features of granule cells.

According to ULE\textsuperscript{24}, a large portion of relatively rare "Kleinhirnrindennatrophie vom Körnertyp," observed except in amaurotic idiocy, is observed as congenital atrophy. In a case of such type, the neocerebellum is chiefly affected (sometimes diffusely) and congenital atrophy is said to be distinctly appreciable macroscopically. From the point of view of the histological features, the cerebellar disorders forming the subject of this report without doubt belong to cortical cerebellar degeneration (atrophy) of granular type (Körnertyp). It, however, goes without saying that no hasty conclusion should be reached whether or not the lesion belongs to congenital atrophy. The circumstances can be easily understood by reference to the reports of many investigators as briefly described in the following.

Five cases out of juvenile feeble-mindedness reported by ULE\textsuperscript{23} were diagnosed as cases of primary systematic cortical cerebellar atrophy outbroken congenitally or in earliest infancy and their cerebellar disorders are represented by loss of granule cells. Simultaneously, in the molecular layer, "Stachelkugel- and morgensternartige Gebilde" were observed as well as the proliferation of various glial elements in the cortex and white matter of the cerebellum. Even in two other cases which were supposed to belong to the category of cerebral infantile paralysis, cerebellar changes have consisted of atrophy of granular type, and a little of vacuolation or loss of Purkinjes' cells were observed as well as glia-proliferation of the cortex and white matter. As instances of cortical cerebellar atrophy of granular type, furthermore, there can be cited the primary degeneration of the granular layer as an unusual form of familial cerebellar atrophy (Norman) and the cases of familial cerebellar degeneration (Jervis) which are similar to the former.

Furthermore, the degenerative changes of the granular layer of the cerebellar cortex can also be observed in the following cases, viz., experimental poisoning by lead, histamine, indol and cyankali (Williams); thiophen poisoning (Christomanos & Scholz, and Upners); mercury compounds (Hunter & Russel, and Noetzelt), and carbon oxide (Winkelmann) poisoning; etc. In describing such cases of poisoning, the authors find it necessary to take interest in the description by Schrappe pertaining to the cases of acute granule cell changes at the time of intoxication; that is, 3 characteristic forms of the falling ill of granule cells observed in a few cases which were diagnosed clinically as intoxication.

As to the next step, the authors would like to give attention to the report by Leigh & Meyer and to cerebellar disorders in a case of hypoglycemic coma which was referred to by ULE\textsuperscript{23} in his report. It is true that everyone would be more less attracted to the picture contained in ULE's report which shows fresh necrobiosis or necrosis of the granular layer.
To this end, the authors go not overlook the stomach-intestine disturbances frequently existing which were referred to by Leigh & Meyer and the fact that Jakob has observed, in acute intestinal gangrene, findings of the cerebellar cortex coinciding with cases of Leigh & Meyer.

Thus, as mentioned above and as Ule\textsuperscript{23) says, it is understood that the cortical cerebellar atrophy of granular type does not indicate etiological unification of disease; in other words, it is interpreted as an unspecific one. And this fact naturally gives rise to discussion in respect to the cases taken up by the present authors.

From the viewpoints of above mentioned, it can undoubtedly be said that any attempt to find similarity by comparing the report of Schappe and the attached picture of Ule's case of hypoglycemia with the pictures or histological findings of the present 11 cases involves considerable dangerousness. However, it is necessary to add that we have no way to imagine a similarity except by comparing our cases with one or a few possible groups temporarily extracted by referring to 5 groups of primary cortical cerebellar atrophy which were classified pathogenetically by Zülich. When making such comparison, in our cases, one must consider a certain change which may be fancied only on the basis of the histological changes or careful morphogenetical consideration, and a particular by age, and that primary infectious disease is denied as mentioned in latter part of this report, because of lack of clinical data. Some etiological discussion on such a point of view will upon in the latter part of this report.

In any case, the authors would like to lay emphasis on the fact that the cerebellar changes found in 11 case out of 12 young Japanese cattle as mentioned in this report are to be diagnosed as "Cortical cerebellar atrophy of granular type ("Kleinhirnrindenatrophie vom Körnertyp")." And this type may be regarded to belong to so-called "Cerebello-petalale Degenerationstyp." It is also suspected that the stage of its changes may be one of an extremely acute sort from the morphogenetical viewpoint.

Changes in other portions

Setting aside whether or not the disorders of the brain described in this report may belong to the category of system-like cortical cerebellar atrophy, the authors could not find any proof to show systematic changes in the present cases. It, however, is interesting that acidophil granule substances were found in protoplasm of nerve cells in cases Nos. 7, 13 and 14, as the similar substances were confirmed in the tegmentum of the pons in Ule's case No. 1\textsuperscript{21) and in the "Bodengrau" of the medulla oblongata in case No. 1 of bovine malignant catarrh reported by Fujimoto et al.

Relation between so-called "Kiriyoi disease" and cortical cerebellar atrophy
As the present cases represent mortal or slaughtered ones, regarded by owners as "Kiriyoi disease", obtained in the districts with occurrence of so-called "Kiriyoi disease", the authors, accordingly, feel an obligation to add explanation to the relation between the cerebellar disorders which were found in the present cases and the so-called "Kiriyoi disease."

Prior to going into discussions concerned, it seems to the authors that outlines of changes of the visceral organs in the present cases might require explanation in the first place. In the changes of the visceral organs, circulatory disturbances which occurred based upon cardiac insufficiency and anemia had played a main role in all cases including Nos. 1, 2, 3 and 6. In other words, there were observed: congestive edema of the lungs, acute congestion of the spleen, hyperemia, congestion and hemorrhages of the liver, kidneys and heart, hyperemia and hemorrhages of the adrenal glands, interlobular edema, hyperemia and hemorrhages of the thymus, and frequently infectious changes which subsequently occurred. In addition, the features of parenchymatous goiter were noticed in all cases investigated.

Prior to anything else, the fact that on cerebellar disorder was found in case No. 9 (Pr. 488) among the present 12 cases which were all regarded as so-called "Kiriyoi disease" gives rise to discussion as to the significance it has. As regards this, deep consideration will have to be given upon whether or not so-called "Kiriyoi disease" is accompanied or not with cerebellar lesion; in other words, the question is to the fact whether or not "Kiriyoi disease" cases not accompanied by cerebellar lesion are the same as those with cerebellar lesion. In this regard, the authors feel necessity to call attention to the facts that the occurrence of "Kiriyoi disease" has rarely taking place in adult Japanese cattle, in seasons other than spring and in animals stall-raised and that the majority (60~70%) of animals with illness have been enabled to recover by symptomatic treatment, etc.

As for the etiology of the cerebellar disorders in the cases subjected to the present investigation, the authors could only exclude those which do not have possibility as mentioned before. In this sense, the following particulars will have to be excluded from considerations:

1. Primary infectious agents.
2. Aplasia or hypoplasia in view of lack of macroscopical changes in the cerebellum.
3. Senile atrophy.
4. Particular of contracting a carcinoma.

As possible particulars, then, hereditary or familial factors, congenital one, active growth of internal or external toxic factors, etc. may give rise to discussion.
The authors, thinking of it, are of opinion that the facts that hypoglycemia has been confirmed in cases with so-called “Kiriyoi disease” and cattle in mountainous pasture with the occurrence of so-called “Kiriyoi disease” are also in hypoglycemic condition must not be ignored as particulars to be excluded. The authors further wish to say that cautious contemplation must be given without fail to what the features of parenchymatous goiter, hypoglycemia and influence of cold (mentioned in introduction; about 20°C difference in temperature between day and night; the highest temperature 25°C in daytime, the lowest was around 0°C at night) have respectively significance, and to mutual interrelation supposedly created by the said facts.

Without necessity of repeating, it is unsafe to clinically conduct comparative study on the present cases and so-called “Kiriyoi disease” under any conventionally known concept. Possibility that there might have been some cases, among the present ones handled by the authors, with some sort of accompanying symptoms which might coincide with the conspicuous cortical cerebellar disorders is not beyond imagination; the authors would like to avoid discussion on problems pertaining to the cerebellar lesions and the functional localization. What comes into the first question in studying various symptoms which have been reported as concept of “Kiriyoi disease”, is as described above whether or not the cases with such symptoms coincide nosologically with our present cases having cerebellar disorders.

To this end, the authors have to say that no concrete conclusion can be reached on the relation between primary cortical cerebellar atrophy of granular type in this report and so-called “Kiriyoi disease.” The authors, however, are confident in saying that the present studies will establish a significant foundation for the study of so-called “Kiriyoi disease” in the future.

**CONCLUSION**

In connection with primary cortical cerebellar atrophy of granular type found in the central nervous system of 11 cases out of 12 young Japanese cattle, from the morphological viewpoint, discussion is offered on the nature of the lesions and on the relation between the local disease (so-called “Kiriyoi disease” in Japanese cattle) occurring in the area where our cases were obtained and the cerebellar lesions.

The authors with the present work, therefore, are confident of providing a significant foundation for the development of study on so-called “Kiriyoi disease.”


EXPLANATION OF PLATES

Except in Fig. 24, all are section preparations of the cerebella. Fig. 5 shows the cerebellum obtained from a slaughtered case (No. 9).

PLATE I.

Fig. 1. No. 14. Magnified picture of transverse section preparation of the cerebellum. Note decrease of staining of the granular layer in various degree (degeneration and loss of granule cells), which severely took place particularly in vermis. H.-E. (Hematoxylin-Eosin staining). × 2.8. Cf. Fig. 12.

Fig. 2. No. 16. Hemisphere. Outstanding “Lichtung” of the granular layer (degeneration and loss of granule cells). Practically no other changes shown in other tissue structures. Cresylviolet staining. × 63.

Fig. 3. No. 13. Vermis. Remarkable “Lichtung” of the granular layer (degeneration and loss of granule cells). Nerve fibers in the granular layer, tangential fibers, baskets, and cells of Purkinje and Golgi relatively well maintained. Bielschowsky’s impregnation method. × 260. Cf. Fig. 9.

Fig. 4. No. 13. Vermis. Myelinated nerve fibers in the granular layer which shows “Lichtung” are relatively well maintained. Spielmeyer’s myelin sheath staining. × 168. Cf. Fig. 9.

PLATES II—IV.

Figs. 5 (No. 9) and 15 (No. 7) are hemispheres. Figs. 6—14 and 16 (Nos. 15, 8, 10, 13, 11, 16, 14, 4, 5 & 12) are vermis. Fig. 5 is the cerebellar cortex in the case which did not show structural abnormality. Others show various extent of remarkable “Lichtung” of the granular layer (degeneration and loss of granule cells); cells of Purkinje and Golgi are relatively well maintained. All are H.-E.-stained. × 260. Cf. Figs. 1 & 17.

PLATE V.

Fig. 17. No. 12. Hemisphere. Same case as Fig. 16. “Lichtung” of the granular layer in low degree. H.-E. × 260. Cf. Figs. 5 & 16.

Figs. 18 & 19. No. 15. The former is vermis and the latter hemisphere. Degeneration and loss of granule cells (“Lichtung”) of the granular layer differ in degree depending upon localization. Cresylviolet × 168.

Figs. 20—23.

Fig. 20. No. 16. ...... Vermis.
Fig. 21. No. 16. ...... Hemisphere.
Fig. 22. No. 15. ...... Vermis. Cf. Fig. 6.
Fig. 23. No. 13. ...... Vermis. Cf. Fig. 9.

Showing processes of degeneration, in various degree, of nuclei of granule cells, i.e. pycnosis, hyperchromatosis, vacuolation, ghost appearance, etc. H.-E. × 1000.

Fig. 24. No. 13. Medulla oblongata. Nerve cell from vestibular area; the protoplasm packed with reddish acidophil granule substances. H.-E. × 1000.