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Vascular Thrombi and Neuronal Alterations in Human Botulism

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Summary. Pathological study in a case of human botulism showed the presence of minor nerve cell changes and extensive vascular thrombi. The latter occurred chiefly in the central nervous system but occurred in other organs as well. An attempt to put these findings into proper perspective and offer a rational explanation for their frequent occurrence in this syndrome is undertaken. It is suggested that the hemagglutination factor present in botulin may cause changes which play a definite role in the clinical symptomatology. It may account for some observations not explainable by present theories which have limited the action of botulin to the neuromuscular junction.

Zusammenfassung. Die histopathologische Untersuchung eines Falles von Botulismus beim Menschen ergab geringfügige uncharakteristische Nervenzellveränderungen und ausgedehnte rezente Gefäßthromben, die vorzugsweise im ZNS auftraten, aber auch in anderen Parenchymorganen nachweisbar waren. Die Bedeutung dieser Befunde wird erörtert und ihr häufiges Auftreten beim Botulismus zu erklären versucht. Es wird vermutet, daß der im Botulin enthaltene Hämagglutinationsfaktor eine grundlegende Rolle für die klinische Symptomatik und für einige durch die bisher vorliegenden Theorien nicht erklärbare Beobachtungen spielen dürfte.

Key-Words: Botulism — Thrombi — Neuronal alterations — Hemagglutination — Platelet agglutination.

Following the original description of botulism (van Ermengen, 1896a, 1896b, 1897a, 1897b) Marinesco (1897) reported widespread neuronal changes in the experimental animal. Similar changes were prominently reported in almost all the early studies. It was recognized subsequently that these changes were not always present and did not necessarily correlate with the distribution of symptoms. The presence of vascular thrombi was also noted (Ophuls, 1914; Dickson, 1918), but again they were not uniformly present and their explanation not clear. With the recognition that the botulin toxin had its primary effect at the neuromuscular junction, these pathological changes were regarded as being of little significance.

A recent case of botulism which demonstrated these changes is reported and discussed in light of our present knowledge of the action of botulin.

The following pathological studies were performed on a 64-year-old white male. This patient's clinical course has been previously reported in detail (Tyler 1963a).

Five days prior to admission, he had eaten home-jarred mushrooms. Two days later, generalized weakness, ptosis, anarthria, and dysphagia gradually developed.

Neurological examination revealed an alert man with a normal mental status. His pupils were large and reacted poorly to light. There was bilateral ptosis and partial 3rd, 4th and

6th nerve weakness. Bilateral facial, palatal, lingual, and neck weakness were noted. He exhibited marked proximal weakness of upper and lower extremities. He had no sensory loss, and his reflexes were equal.

He was treated with botulin antitoxin. He stabilized after a few days but became weaker and required tracheotomy and respiratory assistance on the sixth hospital day. He died from a sudden cardiac arrest while on the respirator.

A second person who partook of the same food had mild ocular symptoms at 24—48 hours and recovered.

Pathological Findings

The post-mortem examination was performed 6 hours after death. General autopsy revealed severe bilateral bronchopneumonia but no other significant gross findings. The brain appeared normal except for mild congestion of the small vessels over the surface and in the brain stem.

On histological examination, the systemic organs revealed the severe bronchopneumonia already mentioned. The only other histological finding was the presence of thrombi in occasional vessels of many organs.

In the central nervous system, the majority of neurons were quite normal. In the lumbar area, a few neurons showed a tendency of the Nissl substance to clump or showed some powdery change in the central Nissl substance. There were rare degenerating neurons with loss of tinctorial quality, degeneration of Nissl substance, shrinkage, and satellitosis. The thoracic and cervical cord showed essentially the same findings to a lesser degree. In the medulla oblongata, no abnormality was noted.

The Betz cells of the motor strip were normal in all respects. The hippocampal and dentate gyri were completely normal. There was no suggestion of changes such as observed in hypoxia. There were occasionally occluded vessels in the pia over the cortex.

The dentate and central nuclei of the cerebellum appeared unaltered. The molecular layer did not seem to stain as densely as usual, and the number of cells seemed slightly decreased. In many areas there was an erratic and patchy falling out of Purkinje cells and a mild activation of basket cells and Bergmann glia in these areas.

It should be emphasized that these minor changes would not in any way seem to explain the patient's extensive paresis.

In many organs, small veins contained thrombi. These were by far most common in the central nervous system. They were most easily recognized in the brain stem, pons and medulla oblongata, but were also noted in the meninges over the cortex and the cervical cord. They were noted in the diaphragm, pancreas, kidney, adrenal, tongue and lung.

Thrombi were characteristically seen in vessels 2 mm in diameter and less. At early stages, clumping occurred in red blood cells and white blood cells. At more advanced stages, lamination between white blood cells and red blood cells could be made out. Many of the thrombi contained fibrin and agglutinated platelets, which clearly established them as antemortem. Occasionally the whole vessel would seem to be filled by white cells, or more rarely agglutinated platelets. An occasional blood vessel showed some minimal perivascular cell reaction, usually all lymphocytes. In no case was any endothelial reaction or any area of infarction identified in relationship to these occluded vessels. This suggested that the thrombi occurred in the last day and probably in the last 12 hours of life. It was also clear that the neuronal lesions did not have any relation to these vascular lesions and that the two were independent phenomena.

Discussion

Changes in neurons in cases of botulism were first described by Marinesco (1897). It should be noted that in most cases in which these changes were reported the paralysis does not correlate with the neuronal changes in distribution or in magnitude. In our case, for example, the extraocular muscles were severely paralyzed, and there were no histological changes in the respective brain stem nuclei. Neuronal changes of the type noted in our material have frequently been seen as a nonspecific finding under many circumstances, and most neuropatho-

logists consider them post-mortem artifacts. They are described in this report, however, because of recent publications noting that the toxin may have some central, as well as peripheral, effect (Erzina and Mikhailov, 1956b; Mikhailov, 1956c; Tyler, 1963c).

The vascular thrombi noted are identical with those found by Ophuls (1914) and subsequently by Dickson (1918, 1924; Corbus, 1923) both in human and experimental botulism. While it seems clear that they do not develop in every case, they have occurred with sufficient frequency to warrant some explanation.

In our case the patient was beginning to show improvement in his muscular strength, and the series of respiratory and cardiac irregularities occurring in the last 6—8 hours of life were rather unexpected. It seems likely that these delayed phenomena were either the result of, or contributed to, the presence of the vascular thrombi.

The recognition in recent years of a factor in the purified toxin which has hemagglutination properties suggests the possibility that this may lead to agglutination phenomena *in vivo* and be the cause of thrombus formation such as was noted in this case. In this regard, it is interesting to note that Dickson (1918) could not produce vascular thrombi in mice, but only in "larger animals".

These observations raise the question of whether prophylactic anticoagulation should not be considered in some patients with severe botulism in conjunction with the use of antitoxin. We believe it should be used in the seriously ill patient if there are no contraindications.

In our patient a pronounced neuromuscular defect was demonstrated by physiological testing (Tyler, 1963a). Histologically the peripheral nerves, muscles and neuromuscular junctions were all normal (Tyler, 1963b). The pathological findings in the central and peripheral nerve system did not account for the severity of the clinical state. It would seem probable that botulin toxin prevents transmission of nerve impulses to muscles without severely damaging tissue structure.

The central nervous system changes described in this report have frequently been reported in patients with botulism. An attempt is made to relate them to the recently described phenomenon which suggest a central action of the toxin (Tyler, 1963c; Vick, Cinchta and Manthel, 1965) and the hemagglutination factor by Lamanna (1959). Whether this "central action" is related to damage produced by the blood vessel lesions or represents a primary central action of the toxin producing a defect in central neuronal transmission is not clear at the present time.

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