Neuropathological findings in primary brainstem lesions compared to *secondary insults*

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In severe head injury, macroscopic findings with multiple lesions involving the hemispheres, the basal ganglia or the diencephalon may also include lesions of the brainstem and the cerebellum. This pattern will easily lead to the conclusion that damage of the brainstem in these cases may be a secondary lesion based on increased intracranial pressure and temporal herniation caused by the primary damage to the hemispheres, the basal ganglia and the diencephalon. Only in the case that the main lesions are found in the posterior fossa, including the caudal brainstem from the mesencephalon to the medulla oblongata, does this pattern indicate a local injury of the brainstem. A primary lesion of the brainstem, however, will not only comprise such a localized pattern of injury. Frequently, the histology in the generalized pattern of brain injury as mentioned initially will also exhibit signs of a primary *injury* of the brainstem.

However, the macroscopic aspect of a brainstem with nearly normal aspects and / or small petechial hemorrhages may also microscopically exhibit signs of a primary *injury* of brainstem tissue. To judge primary and secondary influences a thorough microscopic investigation is necessary, in order to recognize the pattern of macroscopic and microscopic changes not only in the brainstem but also in the other parts of the brain.

Figure 1 and 2 present a summary of events and factors which may be helpful to decide the primary or the secondary character of the brainstem lesions. Some relevant points are discussed in the following pages.

Primary Brainstem Lesions

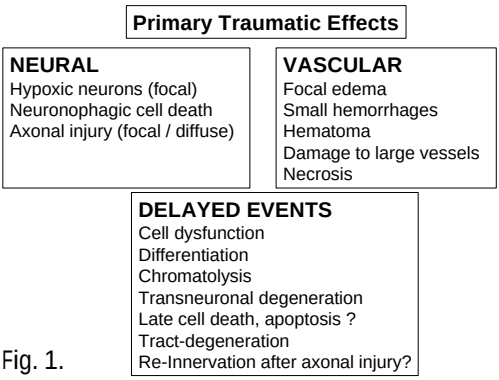

Fig. 1.

The group of changes which can be found in the *neural* structures include *hypoxic neurons* and *neuronophagic cell death*. These changes will be

Secondary Brainstem Lesions

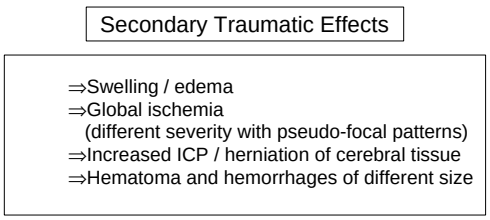

Fig. 2.

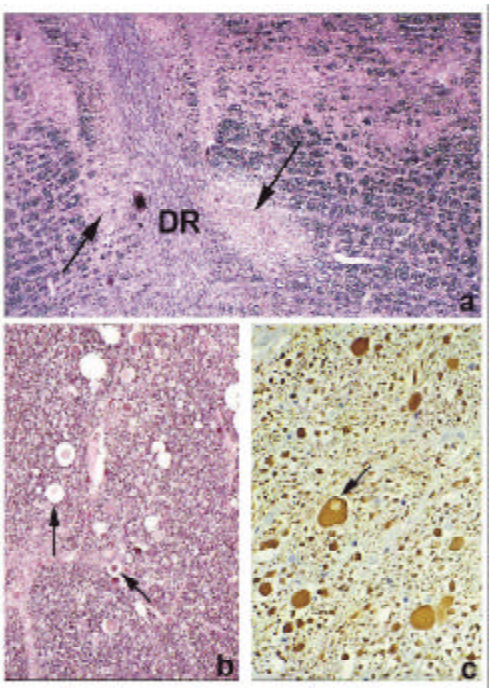

Fig. 3. A: Bilateral foci (←) situated close to the raphe dorsalis (DR) 10 days after trauma in a 22 year old male. There is a central small artery in the lesions exhibiting iron depots in the vessel wall and the surrounding tissue. The whole area of the foci is filled with eosinophilic and argyrophilic bulbs on nerve fibers as a proof of axonal injury. B: Axonal swelling and bulbs from a larger focus (←). The involved nerve fibers are cut in horizontal direction. Sudanblack B, 700x. C: Similar region stained by neurofilament, 700x

focal and different from those in generalized hypoxia. In the latter, *sensitivity* to hypoxia plays an important role with regard to the time cascade of hypoxic events in different brain regions. As an example of this, the inferior olive should be mentioned.

A third important change, first described by Strich (1956), is *axonal injury* **(Fig. 2 B,C)**. Probably, stretching and tearing with damage to the nodes of Ranvier is one of the causes of this.(Graham and Genarelli 1997). We can differentiate between tracts which are frequently involved and those which are not, depending on their direction as is observable in the lemniscus medialis. This means that a neighbouring tract with different direction may be unaffected. A second form axonal change is seen in foci of different sizes **(Fig. 2A)** Frequently but not always, the center of the lesion will be a small artery. This vessel will be surrounded in the early stage by plasma and erythrocytes. In older lesions, hemosiderin and macrophages are observable around the vessel and in the neighbouring tissue. The whole lesion is dominated by axon swelling and balls suggesting a demyelinisation when seen at lower magnification. But demyelinisation will be seen in later stages after the axonal damage. Foci surrounding the raphe are an example of a frequently overlooked pathomorphology when evaluation of the brainstem is performed only at the macroscopic level. To avoid misunderstanding of nomenclature we will call this type of lesion focal, even if many such foci may exist in the brainstem and are sometimes called "diffuse" for this reason.

The appearance of swelling and axon balls is demonstrated in **Fig. 2B** by Sudanblack B and in **Fig. 2C** by immunhistological reaction with neurofilament. Both figures are cut in a horizontal plane with regard to the fibers, so that the course of the fibers is not demonstrated.

Both types of axonal damage have to be considered as primary lesions which, until recently, frequently might not have been recognized in autopsy cases. Symptoms depend on the severity of axonal damage and the density of the fiber structures which are involved. Even some months after the traumatic event the axon changes may persist. Recently, it has been shown in an animal model that reinnervation may occur.

As to the group of *vascular* lesions listed under the primary traumatic effects, we may state that secondary lesions tend more to involve venous vessels, although hemorrhages can be found in both groups. The pattern of the whole brain including all affected structures, may be necessary to decide if a haemorrhage is a primary or a secondary lesion in the brainstem.

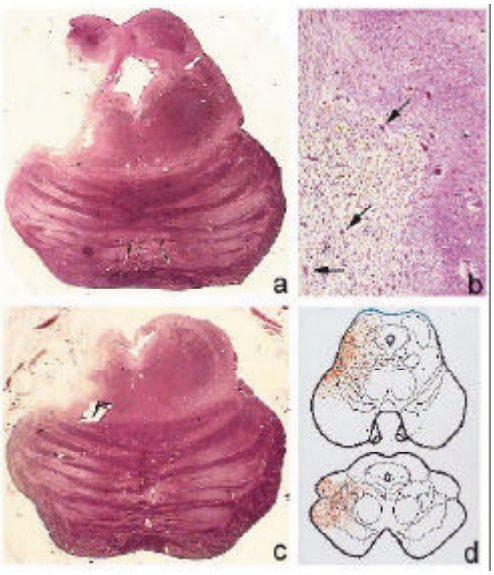

Fig. 4. A and B: Two sections from the serially cut brainstem (mesencephalon and pons). Large tissue defect dorsolateral. Sudanblack B, 3x. C: Border region between the cystic old softening and the still intact tissue. Meshwork of scavenger cells with iron and lipid as well as a number of neuromelanin containing neurons (←) of the locus coeruleus. Most of the neurons exhibiting central chromatolysis. Sudanblack B, 300x. D: Diagram of the lesion in mesencephalon and pons. The area involved is supplied by the dorsal half of the Aa. longitudinales laterales. All figures represent the findings in a 40 -year -old man who survived his accident for 5 ½ months.

We would like here to present a case of injury which may certainly be called a primary lesion. It concerns direct traumatic involvement of the large arteries of the brainstem. These run laterally and medially. Recently, we described the case of rupture and tearing of two branches of the medial artery in the mesencephalon, in a ten year old girl who survived 5 ½ months (Gerhard and Baumann in press). The other case **(Fig. 3)** is a shearing of the lateral artery in its dorsal half, including histologically the scars of a rupture of the arterial wall in two lateral large arteries and a large connecting artery in the arachnoidal space. The brainstem was fixed in toto and cut in serial sections. The lesion extended from the upper mesencephalon to the dorsal third of the pons.

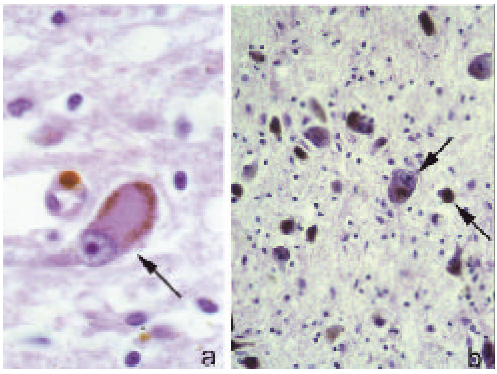

Fig. 5. A: Central chromatolysis in a neuromelanin containing neuron of the substantia nigra. Fe-Kernechtrot, 1000x. B: Transneuronal degeneration. Neurons of the substantia nigra of different sizes from normal to shrunken examples. The normal sized neuron (←) is accompanied by an extremely shrunken one (←). The latter is filled with pigment and a nucleus protruding from the surface. Male, 28 yrs., 5 month survival, Luxolblue-Cresylviolett 500x

It caused a hemorrhagic softening, involving the upper third of the Nucleus locus coeruleus. The mechanism of the injury was somewhat peculiar. The patient was sleeping and drunk, stretched out in bed with his head resting on the wooden board of the bed. Another person held his head and moved it a couple of times up and down, banging the head on the wooden board. Besides the brainstem lesions there were only a few smaller contusions.

Both described cases demonstrate that primary lesion may occur, if large brainstem vessels are injured, causing hemorrhage and softening in the area supplied by the corresponding vessels. Finally, we would like to contribute some findings to the group of *delayed events*. The *central chromatolysis* of neurons **(Fig. 5)** depends on axonal damage. If this happens very close to the nerve cell body, neuronal death will occur. If it is more distant, the neuron will swell and the Nissl substance will diminish or disappear. The nucleus will be shifted to the surface. These changes are caused by increased metabolism supplying the increased axonal transport. If the neuron survive, the typical picture of central chromatolysis will

be observable even for years. A good example of this are anterior horn cells after amputation of the leg.
In primary brainstem lesions we may find central chromatolysis at many locations.
In brain injury survived for some months or years, serial brainstem sections will show this frequently in the motor nuclei of the eye (Nucleus abducens, Nucleus trochlearis) and among the motor nuclei of the brainstem (Nucleus hypoglossus, N. facialis and trigeminus). Particularly in those patients who survived for a longer period of time, these findings with respect to all types of axonal injury can be observed.
Another example of delayed reaction may be *transneuronal degeneration* or atrophy. The well known example is loss of one eye and the reaction of the neurons of the ganglion geniculatum mediale which are extremely shrunken in those layers connected with the N. opticus of the lost eye.
All neuronal systems which show only one main neuronal input develop such transneuronal degeneration. We have demonstrated this atrophy for neurons of the Substantia nigra in a couple of cases (Gerhard 1996). The difference in size from normal or possibly hypertrophic neurons to shrunken nerve cells may be extreme **(Fig. 5B)**. This may explain why some observers could have misinterpreted the extremely shrunken cells for phagocytes filled with neuromelanin. Our observation is in accordance with Hassler, who has described this pathology of nigral neurons in a couple of diseases but not in brainstem trauma (Hassler et al 1979). Since there are other functional systems in the cerebellum and the brainstem (N. dentatus) which show a similar condition as given in the strio-nigral connection, transneuronal degeneration could also happen in other parts of the brainstem. Clinically, the extrapyramidal disturbances frequently observed in posttraumatic patients may be explained by transneuronal atrophy of nigral neurons.

Our contribution has been made by collecting autopsy cases of patients with times of survival of over 1 year. Mostly, serial sections of in toto paraffin-embedded brainstem were performed in close cooperation with clinical colleages.
We suggest that posttraumatic brainstem research is an interdisciplinary research and that it is only in its infancy.

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