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Editorial

Diffuse axonal injury in non-missile head injury

Brain damage brought about by a non-missile head injury takes two forms—focal and diffuse.[1] The principal types of focal brain damage are contusions on the surface of the brain, intracranial haematoma and the various types of brain damage secondary to intracranial expanding lesions and a high intracranial pressure. In this era of sophisticated scanning, the clinician usually knows that lesions of this type are present during life, and their nature. Diffuse brain damage is more subtle and consists of axonal injury, hypoxic brain damage, brain swelling and vascular injury. The clinician usually suspects that diffuse brain damage is present when faced with an unconscious patient who does not have an intracranial haematoma. Although in the last decade computed tomography has played a very important role in the diagnostic evaluation of head injured patients, the advent of magnetic resonance imaging has been found to be particularly useful in the detection and classification of traumatic lesions in closed head injury[2] but it may be very difficult to define the type of damage during life. It may also be difficult to define diffuse brain damage post mortem unless the brain is properly fixed before dissection and the appropriate histological studies are carried out.

As a result of a comprehensive clinical study on head injuries carried out in the University of Pennsylvania, it became apparent that two lesions—acute subdural haematoma and diffuse axonal injury—were responsible for two thirds of the deaths, that is, more than all other lesions combined.[3] It could, however, be argued that diffuse axonal injury (DAI) is of particular importance in governing the outcome in anyone who sustains a non-missile head injury. Certainly patients who sustain severe DAI are unconscious from the moment of injury, do not experience a lucid interval and remain unconscious, vegetative or at least severely disabled until they die.

The first publication to focus attention on this type of brain damage was by Strich in 1956[4] when she described four cases of "diffuse degeneration of the cerebral white matter in severe dementia following head injury". The term "vegetative state"[5] would amost certainly now be the term used to describe what Strich referred to as severe dementia. Other authors in the 1960s, particularly Nevin,[6] and Peerless and Rewcastle,[7] stressed the importance of damage to white matter in head injury. During this period the term "shearing" injury was introduced. Later this type of brain damage was referred to as diffuse damage to white matter of immediate impact type[8] or diffuse white matter shearing injury.[9] Currently the term DAI is used internationally to describe this type of brain damage.

The structural features of DAI and their time course were reviewed and redefined by Adams and his associates in Glasgow in 1982[10] when they described a series of 45 fatal cases. In its most severe form, DAI has three distinctive structural features: a focal lesion in the corpus callosum; a focal lesion or lesions in the rostral brain stem; and diffuse damage to axons. The first two of these can often be identified macroscopically post mortem and increasingly by modern neuro-imaging techniques during life.[11 12]

In patients of short survival the focal lesions are usually haemorrhagic but with the passage of weeks or months they come to be represented by shrunken scars that may be difficult to identify at necropsy but they are often brown in colour because of the persistence of haemosiderin. The lesion in the corpus callosum typically occurs in its inferior part and to one side of the midline. It may, however, extend to the midline and, if this occurs, there is often disruption of the interventricular septum resulting frequently in some blood within the lateral ventricles. On occasion the splenium is particularly affected. In the rostral brain stem the lesions characteristically occur in the dorsolateral quadrant or quadrants adjacent to a superior cerebellar peduncle. The clinical state is not attributable to these focal lesions but to the diffuse damage to axons that accompanies them. This damage can be seen only on microscopical examination and takes three forms depending on the duration of survival. In patients of short (days) survival there are large numbers of axonal swellings in the white matter: they are not restricted to the corpus callosum and the dorsolateral quadrant of the rostral brain stem but occur throughout the cerebral hemispheres, the cerebellum and the brain stem. In patients of intermediate (weeks) survival, there are many small clusters of microglia throughout the white matter: these are thought to occur in relation to small tissue tears and degenerating axons. And in patients who survive for many months severely disabled or in the vegetative state the typical feature—as originally described by Strich[4]—is the occurrence of Wallerian-type degeneration in the white matter throughout the cerebral hemispheres, the brain stem and the spinal cord. If a patient with DAI survives for several months, there is progressive enlargement of the ventricular system as a result of loss of bulk of the white matter. By this stage the focal lesions may be very difficult to identify and unless the pathologist is acquainted with the entity of DAI he might think that he is simply faced with a case of post-traumatic hydrocephalus.

The 45 cases described by Adams *et al* [10] were compared with a group of 112 fatal non-missile head injuries encountered over a similar period in the same centre but who did not have DAI. In the patients with DAI there was a statistically significant lower incidence of lucid interval (indeed not one of the patients with DAI in this series had experienced a lucid interval), fracture of the skull, cerebral contusions, intracranial haematoma and evidence of a high intracranial pressure. There was also a higher frequency of head injury due to road traffic accidents in comparison to falls. Brain swelling and hypoxic brain damage were not

statistically different in the two groups, the importance of this being that it had in the past been suggested that DAI was secondary to brain swelling or hypoxic brain damage.[13] Subsequent clinico-pathological studies from the same centre have established that in patients with DAI there is an increased incidence of gliding contusions[14] and small deeply seated basal ganglia haematomas[15] than in patients without DAI. It was also established that DAI seems never to be produced by a fall[16] unless it is from more than one's own height although it can be produced by an assault.[10] It should also be emphasised that in some patients there may be a combination of DAI and an intracranial haematoma.[17]

One of the problems in the early understanding of the pathogenesis of DAI was that it had not been produced experimentally. Despite the seminal work of Denny-Brown and Russell in the 1940s[18] which established that a change in the velocity of the head was a vital factor in the production of concussion, no experimental group had been able to produce persistent traumatic coma in a laboratory situation. The experience in many centres was that the experimental animal either made an excellent recovery from head injury—there were often a few small surface contusions—or died rapidly as a result of an acute intracranial complication usually in the form of subdural haematoma. In 1982,[19] however, Gennarelli and his group in the University of Pennsylvania published an account of diffuse axonal injury and traumatic coma in the non-human primate using a head-acceleration machine known as the Penn II device. This provided a non-impact distributed acceleration load to move the head in a controlled pathway; thus the effects of angular acceleration could be studied without there being any impact to the head. Diffuse axonal injury identical to that known to occur in humans, namely, focal lesions in the corpus callosum and in the rostral brain stem and microscopical diffuse damage to axons had been produced. In these animals gliding contusions and small deeply seated haematomas in the cerebral hemisphere were also frequently encountered. Further subsequent studies established that sagittal or horizontal accelerations did not produce such severe damage as coronal acceleration.[20] In this experimental situation it was possible to define various grades of severity of DAI.[19] Three grades were identified: in grade 1 there is microscopical evidence of diffuse injury to axons without there being any focal lesions; in grade 2 there is also a focal lesion in the corpus callosum; and in grade 3 there is, in addition, a focal lesion in the dorsolateral quadrant of the rostral brain stem. There was a close correlation between the grade of DAI identified post mortem and the clinical state of the affected animals. All those with grade 1 DAI remained only moderately disabled; the two with grade 2 were severely disabled; and the 12 with grade 3 were either severely disabled or remained in persistent coma until death.

As a result of this experimental work, it became clear that in their earlier studies Adams *et al*[10] had concentrated on what was the severe end of a spectrum and that there was a need to undertake more extensive studies on DAI in humans. In a more recent analysis by Adams *et al*[21] of 434 fatal non-missile head injuries that had been subjected to comprehensive histological studies, 122 cases with DAI were identified—10 grade 1, 29 grade 2 and 83 grade 3. In 24 of these cases the diagnosis of DAI could not have been made without microscopical examination, hence emphasising that microscopic DAI is a not infrequent entity that can only be diagnosed post mortem if adequate histological studies are undertaken.[22] This has important implications for forensic pathologists. As described in the earlier study there was again an increased incidence of gliding contusions, basal ganglia haematomas and road traffic accidents in patients with DAI: this contrasted with a higher incidence of fracture of the skull, intracranial haematoma and evidence of a high intracranial pressure in patients without DAI. One major difference compared with the earlier series, however, was that 17 of the 122 cases with DAI had experienced a lucid interval: this was total in two, that is, the patient had been able to talk rationally after the injury, whilst 15 were partial, that is, the verbal response had been confused. In all of these cases, however, there was only microscopic evidence of DAI and none had sustained the most severe form with macroscopic lesions in the corpus callosum and in the brain stem. It is now clear that patients with milder degrees of DAI may be rendered unconscious for as little as five minutes after injury.[23] All of the patients with DAI who had talked died as a result of complications of the original injury. An essentially similar type of grading of DAI in humans has been established by the group in Adelaide.[24]

The incidence of DAI, particularly the milder grades, is probably higher than published figures suggest since, in our experience, it takes some hours, perhaps at least 18 to 24, for classic axonal swellings to appear in the human brain. Thus it is difficult to establish the diagnosis beyond doubt in patients who die within a few hours of their injury. Because we believe that axonal swellings are essential for the diagnosis of DAI we cannot agree with Vanezis *et al*,[25] who contended that variation in axonal diameter but without bulb formation associated with an astrocytosis soon after a head injury was diagnostic of DAI. The time taken for axonal swellings to appear has raised the question as to whether or not actual disruption of axons occurs at the moment of injury. There is no doubt from clinical observations in humans and experimental animals that some catastrophic event does occur at the moment of injury but this does not mean that the axons are necessarily disrupted at that stage. Certainly immediate or primary axotomy has not been identified electron microscopically in experimental models of head injury. This has given rise to the hypothesis that there may be a process of secondary axotomy, that is, axonal transport is interrupted at the moment of injury but actual axotomy is delayed.[26] If this were so there might in theory be some means by which this process could be arrested. This would seem at the present time to be the only potential treatment for this type of brain damage in humans.

Against this possibility is the recent observation, using perfusion fixation, freeze fracture and thin section techniques[27 28] in experimental preparations, that within 15 minutes of subjecting axons to tensile strains similar to those that bring about axonal injury in humans there are structural abnormalities at the nodes of Ranvier. This takes the form of membrane-bound blebs of extruded axoplasm within which there are membranous vesicles, smooth endoplasmic reticulum and groups of neurofilaments. In some axons these changes progress and by six to 12 hours aggregates of membranous organelles, lysosomes and neurofilaments within axons precede by some hours the formation of classic axonal swellings.

A number of studies have implied that calcium is an important mediator in the production of axonal damage resulting from trauma.[29 30] There is normally a steep gradient of the order of 10 000:1 in the concentration of calcium between extracellular fluid and axoplasm. Under experimental conditions exposure of the axoplasm to high levels of calcium can produce irreversible blockade of axonal transport, disassembly of microtubules and neurofilaments, swollen endoplasmic reticulum and vacuolated mitochondria. Although still speculative there is considerable evidence that a similar mechanism of calcium mediated axonal degeneration as characterised by the use of in vitro peripheral nerve preparation also occurs

as a consequence of axonal injury produced by tensile strain in human DAI. Membrane channels opened at the time of injury may therefore be a mechanism by which an influx of calcium occurs at the damaged node. Thus in the next few years, there should be concerted efforts to identify treatments which prevent calcium mediated secondary axonal degenerations. We suggest that study of voltage dependent calcium channels is likely to be the most rewarding since present evidence indicates that receptor mediated channels are limited to the cell soma and possibly dendrites. Other possibilities include the blockade of voltage dependent calcium channels, the inhibition of calcium activated proteases and the mitigation of the effects of the cascade of events that result from calcium mediated phospholipase activation, especially involving free radicle events.

Unless some progress can be made along these lines the outlook for patients who sustain severe diffuse axonal injury will remain bleak.

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Neurological stamp

Rhazes (850–923)

Named after the town where he was born (Rai, near modern Tehran), Rhazes was one of the great figures in Arabian medicine. His most noteworthy contributions were the distinction between smallpox and measles, and the use of animal gut in sutures. In a treatise on anatomy he described the recurrent laryngeal nerve.

Rhazes practiced in the town of his birth and later in Baghdad. It is said that when he was asked to choose a site for the hospital there, he hung pieces of meat at various points in the city, and selected the place at which putrefaction was longest delayed. He was honoured on a stamp issued by Syria in 1968 (Gibbons No 995, Scott No C414).

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