Immediate, Irreversible, Posttraumatic Coma: A Review Indicating That Bilateral Brainstem Injury Rather Than Widespread Hemispheric Damage Is Essential for Its Production

William I. Rosenblum, MD

Abstract

Traumatic brain injury may result in immediate long-lasting coma. Much attention has been given to predicting this outcome from the initial examination because these predictions can guide future treatment and interactions with the patient’s family. Reports of diffuse axonal injury in these cases have ascribed the coma to widespread damage in the deep white matter that disconnects the hemispheres from the ascending arousal system (AAS). However, brainstem lesions are also present in such cases, and the AAS may be interrupted at the brainstem level. This review examines autopsy and imaging literature that assesses the presence, extent, and predictive value of lesions in both sites. The evidence suggests that diffuse injury to the deep white matter is not the usual cause of immediate long-lasting posttraumatic coma. Instead, brainstem lesions in the rostral pons or midbrain are almost always the cause but only if the lesions are bilateral. Moreover, recovery is possible if critical brainstem inputs to the AAS are spared. The precise localization of the latter is subject to ongoing investigation with advanced imaging techniques using magnets of very high magnetic gradients. Limited availability of this equipment plus the need to verify the findings continue to require meticulous autopsy examination.

Key Words: Ascending arousal system, Brainstem, Coma, Diffuse axonal injury, Trauma, White matter.

INTRODUCTION

The prognosis of patients with traumatic brain injury (TBI) has long been and continues to be a subject of great practical significance (1–4). Predictions have been based on the location and degree of brain injuries determined by various types of structural analysis. A subset of patients with TBI starts out in a coma and a further subset remains in a coma or without signs of awareness that persists until death (5). Structural examination of the brain in these patients and in those who demonstrate greater recovery may not only result in identifying the prognostic markers of greatest value but also may result in identifying the injuries responsible for immediate posttraumatic coma and subsequent failure to attain significant recovery. The following review of such studies, which used either postmortem examination or imaging techniques, indicates that, in almost all such cases, brainstem injuries are responsible for the coma and permanently impaired consciousness provided that such injuries are bilateral. This conclusion may not seem surprising because the ascending arousal system (AAS), which is responsible for maintaining consciousness, begins in the brainstem (6–8). However, TBI is accompanied by diffuse axonal injury (DAI), and the forces sufficient to produce coma not only produce axonal damage and focal lesions in the brainstem but also produce widespread axonal damage at higher levels (9–13). In fact, widespread axonal damage in deep white matter, which may disconnect higher centers from the AAS, has often been considered to be either a possible cause (page 29 in [6]) or an actual cause of disturbances of consciousness (9, 10). This review examines publications that may enable one to distinguish between these 2 alternative explanations for posttraumatic coma; the same publications also permit a conclusion concerning the sites of damage that might best lead one to predict that the patient will remain in coma.

Relevant articles were identified in PubMed and in a further search of the references in the culled articles. When an author was associated with multiple articles using the same techniques and coming to similar conclusions, only 1 article was selected for inclusion in this review. Several additional factors reduced the number of cited articles. First, many articles investigate the structural correlates of outcome after head trauma but are not primarily concerned with the category of patients to which this review directs attention: cases with immediate permanent posttraumatic coma. Some of these articles have concluded that brainstem damage is the best prognostic marker (14–16), whereas others have found that the total burden of lesions at other sites may provide the best prognostic indicator (3,4). Second, a Glasgow Coma Scale (GCS) score of 8 or less was generally used to define coma at entry into a study. However, it is now recognized that scores greater than 6 may include patients who lack awareness (vegetative state) or who may be aware in what has been called a minimal conscious state (5) but are not considered to be in true coma. In addition, many articles group various outcomes in a way that makes it difficult or impossible to separate coma cases from other cases of severely impaired consciousness. Nevertheless, in a few instances, articles with these limitations have been cited because some conclusion concerning the cause of posttraumatic coma and its duration...
can be made or because the data shed light on the relative importance of hemispheric versus brainstem damage. Taken as a whole, the cited articles clearly indicate that bilateral brainstem lesions rather than widespread lesions of cerebral white matter are the usual cause of posttraumatic coma in animals and humans, and that patients with such injuries will remain severely impaired until death. However, prognostication on this basis is not perfect because the brainstem lesions must be located exactly in sites that interrupt the AAS or destroy it at its origin on both sides of the brainstem. The reviewed articles begin at approximately the time when DAI was first described because those descriptions identify both the deep hemispheric white matter and the brainstem as simultaneous sites of damage in severe TBI while also concluding that it was the former rather than the brainstem lesions that was responsible for the coma (9, 10).

In 1981, 26 autopsied cases with immediate coma in which death was caused by closed head injury were described (17). Eighty-eight percent of these cases had midbrain lesions. Lesions were also found in the rostral pons. The brainstem lesions were distributed like those in DAI, a distribution that differs significantly from that produced during herniation (18). All cases had lesions in the hemispheres; however, the latter was often more limited in comparison with original descriptions of high-grade DAI (10–13). The authors concluded that brainstem lesions and especially midbrain lesions predicted ultimate death of comatose patients. Because the brainstem lesions were constant and the cerebral lesions, although always present, were highly variable in degree, it seems reasonable to conclude that the unremitting coma was caused by the former. Although bilaterality of the brainstem lesions was not stressed, it can be noted in the figures in the article.

In a study of 94 patients published in 1988, magnetic resonance imaging (MRI) also suggested that prolonged coma after closed head injury was not simply caused by widespread damage to deep white matter (19). Lesions of central gray matter and brainstem were treated as a single category. Coma was defined by a score of 8 or less on the GCS. Coma occurred in 10 (91%) of 11 of patients with deep central gray matter/brainstem lesions and only in 17 (38%) of 45 whose lesions were restricted to the subcortical white matter. Those with only white matter lesions had significantly shorter periods of ‘‘impaired consciousness.’’ When reporting duration of impairment, the authors combined coma cases and cases with lesser degrees of impaired consciousness. Those with lesions in the subcortical white matter had durations of 9 ± 19 (mean ± SD) days compared with 29 ± 33 days in the group with lesions in the deep central gray matter/brainstem.

In 1993, computerized tomography was used to study 239 cases in coma present from the onset of injury (20). Twenty-one were found to have brainstem damage at the initial examination. Ten scored 3 or 4 on the GCS, whereas the rest scored 5 to 8. Seventeen remained in coma until death, a result supporting the suggestion that brainstem lesions were a good predictor of unremitting coma. The times from injury to death were not given. Bilaterality of brainstem lesions was not analyzed. Detailed information was not provided about the distribution of lesions in the much larger number of patients who presented with coma in the absence of a brainstem lesion. In this regard, it should be noted that MRI, a more sensitive mode of examination than computerized tomography used here, might have uncovered brainstem lesions in these comatose patients (14).

When MRI was used in an investigation by Firsching et al (21), the importance of brainstem lesions as opposed to hemispheric injuries was clearly delineated. One hundred two patients with a GCS score of 7 or lower were studied. Seventy-two percent of those with only supratentorial lesions had good outcomes. These data provide strong evidence that supratentorial lesions by themselves do not generally produce irreversible coma or severe irreversible impairments of consciousness. A much higher death rate followed brainstem involvement. An essential element was the bilaterality of the lesions. Patients with bilateral pontine lesions had 100% mortality and apparently were comatose until death. The duration of coma was not stated. Only 23% of patients died in coma if brainstem lesions were unilateral. Only 24% of patients with bilateral mesencephalic lesions died in deepest coma, but 32% remained in persistent vegetative state and an additional 24% had a severe outcome—a 3 on the Glasgow Outcome Scale (GOS). The remaining 20% of patients with bilateral mesencephalic lesions had a better outcome, suggesting that their mesencephalic lesions produced less damage to the ascending fibers of the AAS.

The greater importance of brainstem lesions compared with supratentorial lesions in producing irreversible coma is illustrated by data from studies of miniature pigs whose heads were subjected to rotational force. Initial studies failed to produce long-lasting coma but also failed to produce brainstem lesions (22). Subsequently, by modifying their technique, the same authors not only elicited brainstem lesions but also clearly demonstrated a direct relationship between the degree of axonal damage in the brainstem and the severity of coma (23). Both were related to the degree of rotational stress. No statistical relationship was found between the severity of coma and the extent of axonal damage in other brain areas or in all hemispheric regions combined. The authors did not relate bilaterality of lesions to the presence or duration of coma, but the figures in the article illustrate only bilateral lesions.

In 2002, Wedekind et al (24) found that injuries to the pontomesencephalic brainstem identified by MRI and evoked potentials were associated with a greater severity of coma (GCS score ≤7). As noted at the beginning of this review, true coma may require a GCS score of 6 or less. However, it seems highly unlikely that a large proportion of the patients had a GCS score of 7. In any case, as expected with high-grade DAI’s, their injuries were also accompanied by supratentorial lesions and the authors did not opine as to the importance of the latter in producing coma.

Although they studied stroke patients rather than trauma patients, a study published in 2003 by Parvizi and Damasio (25) provided important confirmation of the importance of brainstem lesions and their bilaterality in the production of permanent disturbance of consciousness. Their attempt to more precisely localize critical brainstem lesions in humans as opposed to animals makes their study particularly significant.
Using 4.7-T MRI, they found that bilateral lesions in the rostral pontine tegmentum alone (n = 4) or in the upper pons and midbrain (n = 5) were present in comatose but not in control patients. One comatose patient with only unilateral lesions recovered after 3 days. With respect to the midbrain lesions, the authors pointed out that these may not be in critical nuclear areas but rather in areas interrupting signals from the pontine nuclei essential for the maintenance of consciousness.

Using MRI, Weiss et al (26) found that bilateral brainstem damage was significantly associated with poor outcome and was a significantly better predictor than unilateral damage. Seventy-six patients were studied. They were divided into 2 groups based on their GOS score 1 year after the trauma. Forty-one with poor outcome (GOS scores 1–3) had GCS scores of only 5 ± 3 (mean ± SD) on admission, whereas 32 with better outcomes (GOS scores 4–5) had GCS scores of 7 ± 3 on admission. The large SDs indicate that, on admission, some of the patients had GCS scores above 6 and thus were not in true coma when admitted. Indeed, although the authors state that all patients were comatose on admission (p. 219), on a previous page (p. 218), they use the phrase “... without clinical signs of awareness” to describe the patients. Some of the latter may have been in a vegetative state. Nevertheless, the 41 patients with worst outcome (GOS scores 1–3) and initial GCS scores of 5 ± 3 clearly had a very large proportion of patients with GCS score of 6 or less, indicating true coma. These patients had a significantly greater number of lesions in the right upper pons, left upper midbrain, and bilaterally in the lower midbrain than the group of 32 with better outcomes (GOS scores 4–5). These results support the conclusion that bilateral brainstem damage is a prognostic indicator of poor outcomes. However, the data also show a significantly greater number of bilateral frontal lesions in the patients with worse prognosis. Thus, the study does not eliminate the possibility that widespread axonal injury in the hemispheres plays a role in producing posttraumatic coma with bad outcomes. Moreover, poor outcome included patients who had progressed to a vegetative state, and some of the brainstem injuries may have been related to herniation rather than being the direct result of traumatic forces that cause high-grade DAI.

Using MRI to study 48 patients, Skandsen et al (27) also reported that brainstem injury was strongly predictive of outcome after severe head injury and that bilateral rather than unilateral injury was the better prognostic parameter. Only 25% of patients with a unilateral brainstem damage had a poor GOS score of 4 or less. In contrast, 86% of patients with a bilateral damage had such scores. The importance of bilaterality is emphasized by the odds ratios for death or severe disability. The odds ratio was 8 for patients with a unilateral brainstem damage versus 182 for those with a bilateral brainstem damage. Moreover, none of the 34 patients with lesions restricted to the cerebral hemispheres had a GOS score less than 5, indicating that hemispheric lesions without brainstem lesions were not sufficient to produce long-lasting coma or severe impairment of consciousness.

Another investigation using MRI (15) also showed that the presence of unilateral brainstem lesions is better than the presence of unilateral brainstem lesions in predicting outcome after head trauma (15). All 13 patients with a bilateral brainstem injury had a poor outcome, whereas 34% of patients with a unilateral brainstem injury escaped this fate. However, some of the patients may not have been comatose immediately after trauma because their GCS scores had decreased to 8 or lower within the first 24 hours after trauma. Moreover, the criterion of a GCS score of 8 or lower may include at its upper end patients in a vegetative state or a minimally conscious state. In addition, several different outcome categories were combined in each of the good and poor outcome groups so one cannot draw more precise conclusions about the relationship between their injuries and a final outcome of coma per se. Nevertheless, it is important to note that, when lesions were confined to the supratentorial area, only 30% of the patients had a poor outcome. Comparing this with the 100% incidence of poor outcome in the group with bilateral brainstem injury, one may conclude that traumatic injury to the hemispheres alone does not usually cause severe and long-lasting impairment of consciousness.

A study using a new and exciting technique supports the hypothesis that brainstem lesions must be bilateral if the coma is immediate and persistent after closed head injury (28). High angular resolution diffusion imaging tractography mapped postmortem the connectivity of axonal pathways mediating arousal or awareness in a single case of persistent coma. There was complete disruption of the pathway from the brainstem arousal nuclei, bilaterally, to the basal forebrain and the thalamic intralaminar and reticular nuclei. In contrast, the hemispheric arousal pathways connecting the thalamus and basal forebrain to cortex were only partly disrupted. Neuro-pathologic examination provided evidence of bilateral axonal damage extending as far as the deep white matter. And, indeed, in the introduction to this article, the authors repeated the opinion in the initial descriptions of DAI that “the primary cause of traumatic coma is axonal injury in the white matter.” Nevertheless, after presenting their findings, which showed disruption of an arousal pathway beginning at the brainstem level, the authors proposed that traumatic coma may be a subcortical disconnection syndrome related to the disconnection of specific brainstem arousal nuclei projecting to higher centers. In the case they described, the disruption occurred at the brainstem level and would occur if either the brainstem arousal nuclei or their ascending axons were severely damaged. Examination of the figures in the article suggests that both nuclei and axons were damaged.

The article just cited indicated the importance of brainstem damage in producing immediate irreversible posttraumatic coma. Nevertheless, a first reading of additional articles by the same group seems to challenge that conclusion. The data in the first of these articles are, in fact, consistent with the suggestion that coma is dependent on bilaterality of the brainstem injury (29). Thus, in the patient in question, initial MRI showed extensive diffusion restriction in the corpus callosum and in both cerebral hemispheres but only on the right side of the brainstem. At 1 year after trauma, the patient was able to communicate and perform activities of daily living. Subsequent review of the history and the data suggested to the authors that the
widespread hemispheric lesions may have been caused not only by trauma but also by an initial hypoxic episode. Because the brainstem lesions were unilateral, the authors suggested that recovery from coma may have been possible because either other ipsilateral arousal-related nuclei or contralateral arousal pathways were preserved.

Although the latter suggestion emphasizes the importance of bilaterality, their study of one more patient indicates that simply demonstrating the presence of bilateral brainstem lesions does not necessarily predict unremitting coma (30). Rather, this case demonstrates the importance of identifying the precise bilateral location of the damaged nuclei and/or their ascending pathways. In the patient in that study, conventional MRI revealed multiple microhemorrhages in cerebral hemispheres, corpus callosum, and brainstem bilaterally at 7 days after injury. Fourteen months after injury, the patient had a GOS score of 7 (maximal possible is 8) and returned to work. Then his brain and that of 4 normal controls were imaged for the purpose of performing diffusion tractography using an MRI scanner with magnetic gradients that are stronger than those used in clinical MRI scanners. The pedunculopontine nucleus (PPN), an important component of the AAS in the rostral pons (7, 31, 32), was the main focus of the tractography investigation. The PPN was chosen because it is an important component of the AAS (6, 7, 29–32). The PPN was also chosen because it was found at the initial MRI study to be a unilateral left-sided focus of hemorrhagic axonal injury. On each side of the brainstem, connections were traced between the PPN and several higher nuclei. In the patient, the connectivity between the PPN and reticular nucleus on the left was markedly less than the connectivity on the right, and this left-right difference was significantly greater than the left-right differences in this pathway in the 4 healthy controls. Left-right differences in the connectivity of the PPN to other critical nuclei were not different in the patient than in the controls. In other words, damage to the pathway from the PPN to the reticular nucleus on the left was correlated with the production of coma in this patient, but the preservation of this pathway on the right side of the brainstem or the preservation of other critical structures in the brainstem apparently accounted for the patient’s ultimate recovery.

It should be noted that limited resolution in many of the studies reviewed above may have resulted in their failure to identify small lesions in the brainstem that are essential for the production of irreversible severely impaired consciousness or coma. Magnetic resonance imaging tractography may resolve this problem, but advanced imaging instruments required to obtain high-resolution MRI tractography data are not readily available. Therefore, detailed autopsy studies are advisable to confirm the conclusion that bilateral brainstem damage is essential for production of irreversible posttraumatic coma and to identify the brainstem loci whose injury results in that outcome. It is possible that very small central lesions at the bottom of the third ventricle or in the paramedian midbrain tegmentum may interrupt the AAS in such a way as to produce permanent coma without significant bilateral disruption of tissue adjacent to these midline sites. Future detailed studies as just alluded to will be necessary to rule this out. But even in such cases, calling the damaged tissue in such lesions “midline” or “central” rather than bilateral may be more of a semantic than a structural issue because such lesions must, to some degree, straddle the actual anatomic midline. In any case, all of the cited imaging studies together with the autopsy evidence and the data from animal investigations in miniature pigs strongly suggest that neither widespread axonal damage to deep white matter in DAI nor unilateral brainstem damage is sufficient to produce posttraumatic coma without recovery of awareness. Instead, bilateral brainstem damage destroying the origins of or interrupting the pathways from the AAS is the essential requirement for such a coma.

REFERENCES


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