Chapter 6

# Diffuse Axonal Injury: A Devastating Pathology

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Additional information is available at the end of the chapter

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**Abstract**

Traumatic brain injury (TBI) also known as intracranial injury is the result of a lesion within the brain due to an external force. Common forms of TBI result from falls, violence, and/or vehicle crashes; the classification of this pathology is dependent on the severity of the lesion as well as the mechanism of trauma to the head. One of the most common onsets of traumatic brain injuries result from mild to severe lesions to the white matter tracts of the brain called diffuse axonal injury (DAI); however, additional forms of TBI's can present in non-penetrating forms. Penetrating forms of TBI's such as trauma to the head via a foreign object do also contribute to the many millions of TBI cases per year, but we will not discuss these traumatic injuries as in depth within this chapter. The onset of diffuse axonal injury will vary on a per-patient basis from mild to severe, based on a standardized neurological examination rated on the Glasgow Coma Scale (GCS), which indicates the severity of brain damage present. While there is a spectrum of severity for DAI patients, a concussion is typically observed within a larger majority of patients in addition to other overwhelming trauma.

**Keywords:** trauma, diffuse, axonal, injury, intracranial

## 1. Introduction

In this chapter, we will discuss in depth the pathology of diffuse axonal injury (DAI) touching upon clinical presentation/keynote characteristics, medical diagnosis, radiological imaging, treatment, prognosis, historical outcomes, and quality of life aftercare [1]. While diffuse axonal injury is included within the broader category of intracranial injury, it is essential to note the physiological severity it plays on the life of the patient. Trauma to any region of the head should prompt immediate concern and medical attention. While DAI is one of the worst

forms of lesions to the brain, we would like to approach this topic with a sense of urgency as it is frequently seen in medical centers worldwide [2].

## 2. Diffuse axonal injury: a devastating pathology

### 2.1. Keynote characteristics

Alongside the many forms of intracranial injuries, the differential key characteristics of DAI are the lesions which occur within the white matter. White matter is composed of several bundles of myelinated axons which connects gray matter together. Gray matter houses the neuronal cell bodies within the brain and is highly regulated in regard to transmission of neuronal impulses [3–5]. Lesions of white matter can vary in size greatly, as they typically present as 1–18 mm wide in trauma and affect the frontal and temporal lobes mostly. However, it is not limited to that region entirely as regions of the brainstem and corpus callosum have also been affected quite frequently according to literature [6, 7]. Axonal injury to the brain is at times an irreversible trauma, which results in loss of consciousness and even death. Forces of greater magnitude striking the head almost immediately disconnect axons within the site of impact. Secondary axon disconnections also develop resulting in severe brain injury [8, 9]. Human physiological symptoms as a result of trauma also set in, such as swelling and degeneration of nerves. The bodily response places the brain under the extreme amount of pressure and is often exposed to irreversible damage [10, 11]. While it was once assumed that sheer force is the responsible factor for the disconnection of axons, it is indeed false to assume that. It is the biochemical response to the impact stimuli which causes that largest impact on axons. However, impact does in fact cause some lesions but not comparable to the damage done by biochemical cascades which follow the impact [12, 13]. Biochemical pathways within our bodies are greatly responsible for the axonal disconnect which occurs secondary to the traumatic impact. The biochemical response is due to the physical stress and stretching caused by the force of impact. The impact disrupts the proteolytic metabolism and degradation of cytoskeleton; sodium channels open within the axolemma causing a strong wave of neuronal depolarization. To balance the influx of cationic sodium, calcium channels also open allowing the stronger cation metal to leave the neuron and into the cell to depolarize the neuron. The excess of calcium ions within the extracellular cavity activates a cascade of enzymes, leading to the activation of phospholipases and other enzymes that act on the cytoskeleton and cause severe damage. This biochemical pathway ends with axonal separation and cell death [14]. Axonal stretching and disconnect occur 1–6 hours after initial trauma. While irreversible brain damage has already occurred, severe damage is yet to come. While the axonal network is compromised, the axonal transport still continues and is halted at any point where the neuronal network is cleaved or compromised. At the site of axon disconnect, transport products and cell debris begin to build up, causing local swelling and severe compression [15–17].

In **Figure 1**, take note of the leading causes of diffuse axonal injury, their severity, and chance of recovery.

### 2.2. Clinical presentation

Many patients that have sustained a traumatic brain injury (TBI) to a certain degree suffer from diffuse axonal injury (DAI). Many patients presenting to emergency and trauma centers with DAI are unconscious and have strikingly poor neurological examination results. The Glasgow Coma Scale (GCS) (**Figures 2** and **3**) is a neurological scale which establishes an objective way to rate the state of consciousness of patients. The sum of the three categories will allow for the determination of the GCS score and patient consciousness [18]. Patients presenting with DAI are often reflecting vivid signs of functional impairment of the brainstem and impairment of the reticular activating system as many of the physiological vital signs are maintained through external sources (e.g., life support) [19]. While alertness and responsiveness may develop slowly over a longer course of time with intensive rehabilitation, the rate of mortality with patients presenting with DAI is extremely high, as high as 50% in severe cases. In patients whom consciousness can be restored, cognitive and memory impairments persist through the remainder of the patient's life [20, 21].

| Cause | Severity | Chance of Recovery |
|---|---|---|
| 1. Automobile Accidents | Extreme | Mild |
| 2. Sport Related Accidents | Extreme | Mild |
| 3. Violence | Extreme | Low to Mild |
| 4. Accidental Falls in Elderly | Extreme | Low |
| 5. Child Abuse (Shaken Baby) | Extreme | Minimal to None |
| 6. Intoxicated Related Falls | Extreme | Mild |

**Figure 1.** Most common causes of diffuse axonal injury. Listed from the highest to the lowest occurrence.

| | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| Visual | Eyes closed | Eyes open to sharp stimuli | Eyes open to sounds | Eyes open without induced stimuli | | |
| Motor | No movement | Movement to sharp stimuli | Muscle flexion to sharp stimuli | Muscle flexion and bodily movement | Able to localize touch | Appears to have normal movement |
| Verbal | No sounds | Slow intensity sounds | Incoherent words | Understandable words spoken | Normal conversation | |

**Figure 2.** The Glasgow Coma Scale.


**Figure 3.** The Glasgow Coma Scale range.

The GCS ranges from 3 to 15, three being coma/death and 15 being a fully functioning and awake person. These scores can be the summation of the visual, motor, and verbal scores.

### 2.3. Medical diagnosis

Due to the fact that there are no distinctive clinical symptoms that patients present with that allow medical professionals to immediately diagnose DAI, physicians must rely on neurological examinations and radiographic imaging to diagnose patients and predict their prognosis. Magnetic resonance imaging (MRI) is the preferred examination for DAI, accompanied with computed topography (CT) scans [22]. A key indicator for the onset of DAI is the minimal yet visible bleeding within the region of the corpus callosum and/or the cerebral cortex. It is essential to note that while trauma may cause axonal disconnect, the vast majority of axonal damage occurs through secondary biochemical degradation. Thus, patients may first appear to be in a functional state, but over 1–6 hours, a patient's condition may drastically change [23, 24].

### 2.4. Use of DTI to diagnose DAI

Newer radiographic studies such as diffusion tensor imaging (DTI) is an MRI technique, which enables radiologists to measure the diffusion of water in the tissue to then create neural tract images. This method provides pertinent structural information and can even do so for cardiac muscles and prostate muscles [25]. In cases where MRI may demonstrate a negative result to DAI, DTI has been able to show a degree of injury to the white matter fiber tract [26].

### 2.5. Use of evoked potential to diagnose DAI

Sensory-evoked potential examination studies the electrical activity within the brain and its responsiveness to stimulations such as light, sound, and touch. Neuronal impulses travel via chemical and electrical pathways; these studies detect electrical potentials within the cerebral neuronal network. When patients present to medical centers already in a state of a coma, medical teams must perform a series of neurological examinations which may be challenging when patients are unconscious. A neurological examination conducted typically by neurosurgeons is to test all the 12 cranial nerves and observe appropriate reflexes; a positive result indicates the level of intactness of the central nervous system [27]. Visual-evoked response (VER) test can be used to test and diagnose nerves that affect sight; these are called optic nerves. Electrodes placed along the patient's scalp can detect and record electrical signals as the patient's eyes are exposed to light stimuli [28]. Brainstem auditory-evoked response (BAER) test examines one's hearing ability and the neuronal network involved in the detection of sound. Results that signify a compromised neuronal network can be indicative of brainstem damage or the presence of a tumor within the brainstem; for the sake of this chapter, we will assume that head trauma was the result of brainstem damage. Once again, through electrodes placed on the patients scalp and earlobes, auditory stimuli are presented to the patient, and the patient's reactions are recorded. Auditory stimuli must vary in frequency and tone to establish a complete understanding of the patient's responses [29]. Lastly, somatosensory-evoked response (SSER) examinations can be utilized to detect issues within the spinal cord

often seen clinically with patients presenting with numbness of the arms and legs. In patients presenting with TBI, verbal communication is limited or unsustainable; thus SSER can be utilized to detect any neurological issues present within the spine [30]. Mild electrical stimuli will be presented to the patients scalp via electrodes; nerves will then transfer the electrical signal to the brain through which reading can be visualized on a medical recorder device. The duration of time which it takes for electrical signals to travel can indicate the presence of spinal trauma or compromise [31]. These examinations are utilized quite commonly throughout medical practice especially when neurological compromise is suspected; through the detection of electrical impulses through the scalp, medical personnel can gain an understanding of the patient's neurological state, especially in suspected DAI patients where an unconscious state is commonly presented with.

### 2.6. Use of electroencephalogram to diagnose DAI

Traumatic brain trauma is indicative of patients with suspected DAI; electroencephalograms provide medical teams a sufficient amount of information regarding a patient's state of consciousness and cognitive processing. DAI patients have experienced a traumatic injury, which is accompanied with impaired consciousness and cognitive function as well as impaired motor functions with severe cases posing with damage to vital neuronal structures such as the brainstem [32, 33]. Essentially, the severity of the traumatic impact on the brain may alter or completely change the prognosis and outcome of rehabilitation efforts [34]. Within the chronic stage of diffuse axonal injury, it has been observed that the mean frequency of the brain alpha wave activity was dramatically low and remained low over the mean of all the wave peaks. Brain waves are monitored via electroencephalogram, and low alpha waves do indicate an abnormal brain function. In addition, brain spindle activation in normal patients appears to have similar activity and strengths; in patients presenting with DAI, activation spindle activity varies across the brain and greatly varies among slow to fast spindle fibers. Despite the low alpha waves observed in patients presenting with a coma, delta and theta waves are also diminished; thus, sleep cycles are dysregulated and abnormal adding to the uphill climb during the rehabilitation process [35–37]. While electroencephalograms carry a stigma that they present no meaningful results which a diagnosis can be based off of, we would like to emphasize the impactful contribution electroencephalograms have on medical diagnosis as well as their daily use in medical centers worldwide.

### 2.7. Radiological findings: computed topography (CT)

As we have discussed previously, diffuse axonal injury (DAI) is characterized through lesions within the white matter of one's brain; severe case lesions are present within the corpus callosum and brainstem. Thus far, we have discussed many of the electro-neuromonitoring techniques utilized within medical centers, but to obtain a clear diagnosis, radiographic imaging techniques are coupled with electro-neuromonitoring practices and physician neurological exams to yield a confirmed DAI diagnosis. Within this section we discuss in depth the radiological examinations conducted to confirm DAI diagnosis. Computed topography (CT) scans is typically utilized first, while CT scans are not entirely as sensitive to visualize subtle DAI; a slight abnormality observed in a CT scan can spark the interest for further investigation

by MRI. A non-contrast CT scan of the brain with head injury is a routine and can allow visualization of lesions which are overtly hemorrhagic. A hemorrhagic lesion within the brain will appear hyperdense and present as a few millimeters in diameter [38].

While lesions may be apparent on CT imaging following trauma, the highest visibility will be observed a few days after the trauma, followed by a significant amount of cerebral swelling, compression, and intracranial pressure [39, 40]. While computed topography is not recommended for the sole diagnosis of TBI, coupling with additional diagnostic data allows CT scans to add to the holistic diagnosis. CT scans have been shown to identify TBI in only 19% of nonhemorrhagic lesions; however, when utilizing T2-weighted imaging (T2WI), identification rate rises to 92% accurate diagnosis [41]. T2-weighted imaging (T2WI) is the basic pulse sequence within an MRI; weighting highlights the variability between T2 relaxation times. When lesions are of hemorrhagic entity, CT scans are sensitive enough to visualize lesions quite well; only for nonhemorrhagic lesions do CT scans have difficulty visualizing with appropriate detail. A general rule of thumb is that if small lesions are visible in CT scans, then the overall damage is greater than expected and often classified as severe trauma.

As we mentioned above, a significant amount of damage results after the initial traumatic impact; **Figure 4** illustrates the CT scan of a patient's head for whom was diagnosed with DAI.

### 2.8. Radiological findings: magnetic resonance imaging (MRI)

While computed topography (CT) scans provide valuable information to the medical care team, the use of magnetic resonance imaging (MRI) is by far the modality of choice when a DAI is suspected [43]. If a CT scan shows a normal pathology, an MRI will be performed to validate those results. There are specific series of MRI's that can be completed to assess for the presence of a DAI. In this section, we will discuss two forms of MRI. The first form is gradient-recalled echo (GRE) sequence imaging, and the second is susceptibility-weighted

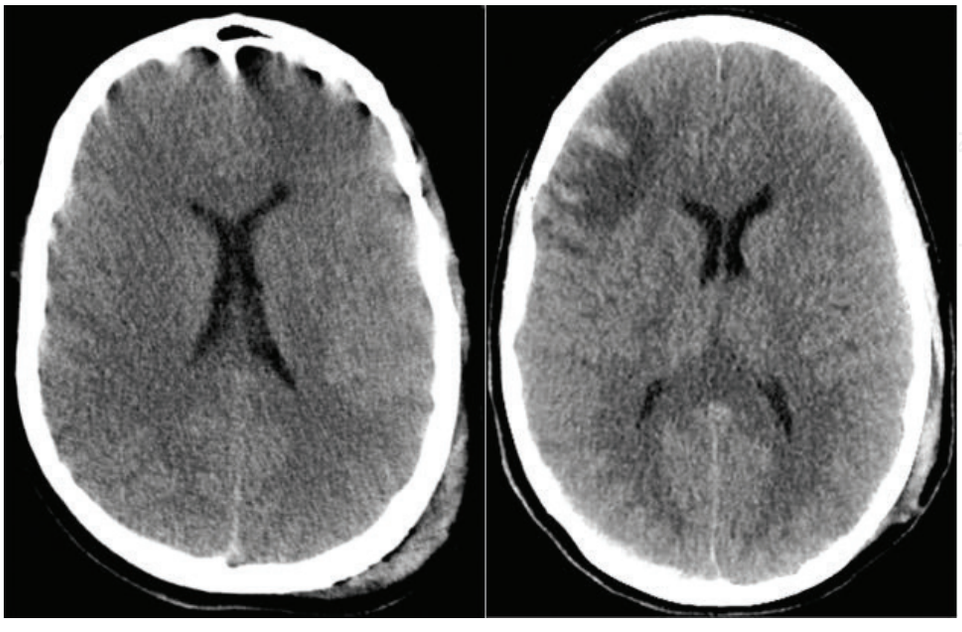

**Figure 4.** Computed topography scan of patient diagnosed with DAI [42]. From left to right, CT scan of day 1 vs. 11.

imaging (SWI) [44]. GRE imaging methods utilize gradient fields to produce transverse magnetism and flip angles that are less than 90°. SWI is an MRI sequence, which is particularly sensitive to substances which disturb the magnetic field; this method of MRI is extremely useful in detecting blood [45–47]. The use of SWI and GRE is paramount in analyzing the severity of lesions that occur in TBI and suspected DAI. As the junction point of white-gray brain matter is most susceptible to lesions, the use of MRI, specifically GRE and SWI, is crucial in obtaining a diagnosis and severity of DAI [48]. As lesions can be both hemorrhagic and nonhemorrhagic, the use of MRI with increasing fluid-attenuated inversion recovery (FLAIR) signal can be utilized to study lesions that are completely nonhemorrhagic [49]. A FLAIR is fluid attenuation inversion recovery, which utilizes a long inversion time (TI) of the pulse sequence such that at equilibrium there is no net-transverse magnetism of the fluid and thus is visualized. The use of FLAIR is quite common in evaluation of the central nervous system (CNS), especially for head injuries [50, 51]. While MRI technologies are among the most accurate in the field of medicine and modern technology has opened the door to even more precise medical diagnosis, just because the MRI does not show a problematic pathology for the diagnosis of DAI, it does not mean the patient is clear of that diagnosis.

In **Figure 5** through **Figures 6–8**, we can see the MRI scans of patients who were diagnosed with DAI using the GRE and SWI technologies we discussed earlier, as well as the T2 W1 and FLAIR methodologies.

### 2.9. Treatment options for DAI

While there are many events that may bring on DAI, the treatment is very much similar to that of any head trauma. DAI-suspected patients present to medical centers worldwide with

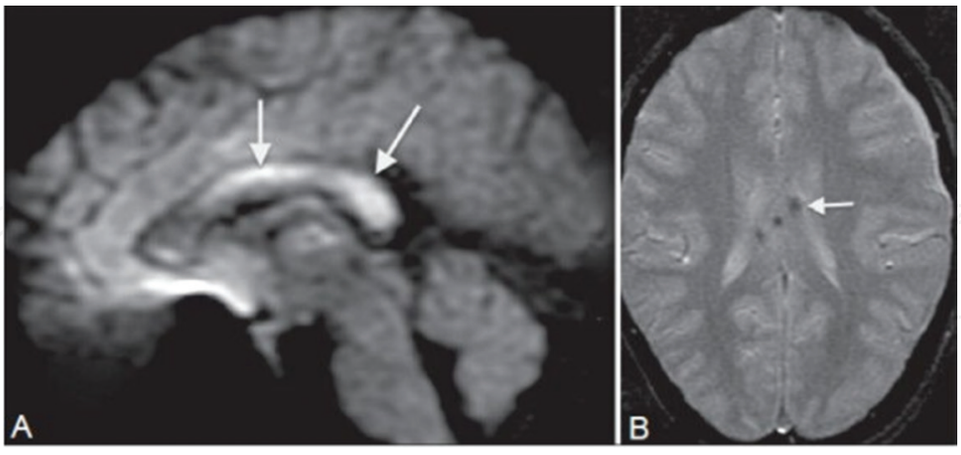


**Figure 5.** (A) MRI-GRE image of a 30-year-old male patient presenting with head trauma. (B) Image depicting hemorrhagic DAI [52]. Magnetic resonance imaging (MRI) of a 30-year-old patient which presented to medical professionals in an unconscious state of mind with a severe brain injury. (A) Arrows pointing to high-signal foci within the corpus callosum, a structure responsible for cerebral cortex communication between paralleled structures on the two hemispheres. Arrows indicate a restricted diffusion, technically known as abnormally low ADC (apparent diffusion coefficient) values. (B) Appearance of "blooming," indicated by the arrow, apparent in a gradient-recalled echo (GRE) sequence, much similar to a spin-echo MRI. Blooming is an artifact of radiological images which exaggerates the presence of lesions which is extremely useful in the detection of small lesions. Blooming may be seen when certain elements/compounds are present during imaging such as hemosiderin or metals (calcium).

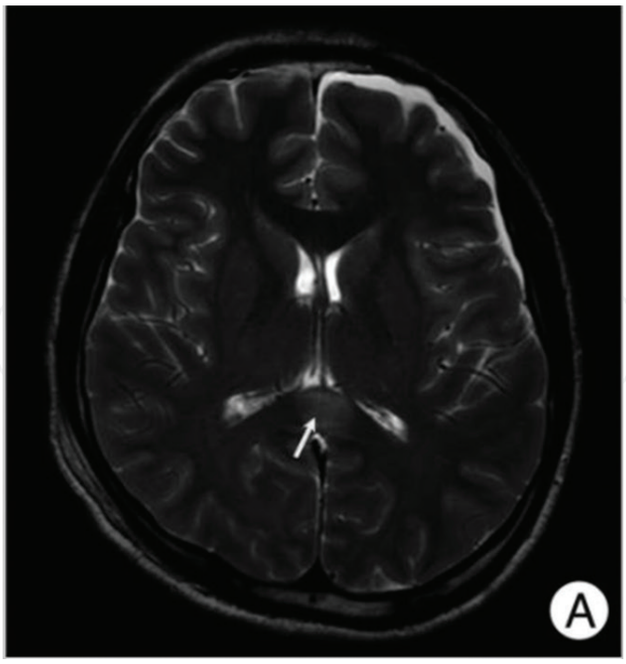


**Figure 6.** A 21-year-old patient presenting to ER following traumatic bicycle accident. Glasgow coma scale score of 6 (see **Figures 2–3**). Patient presents with nonhemorrhagic lesions visualized through high signal intensity at T2 W1, discussed above. This image is shown under high signal intensity at T2W1 indicating lesions within the corpus callosum of a 21-year-old patient following a traumatic brain injury resultant of a bicycle injury. The arrow is indicative of a nonhemorrhagic lesion at the splenium (posterior end) of the corpus callosum [53].

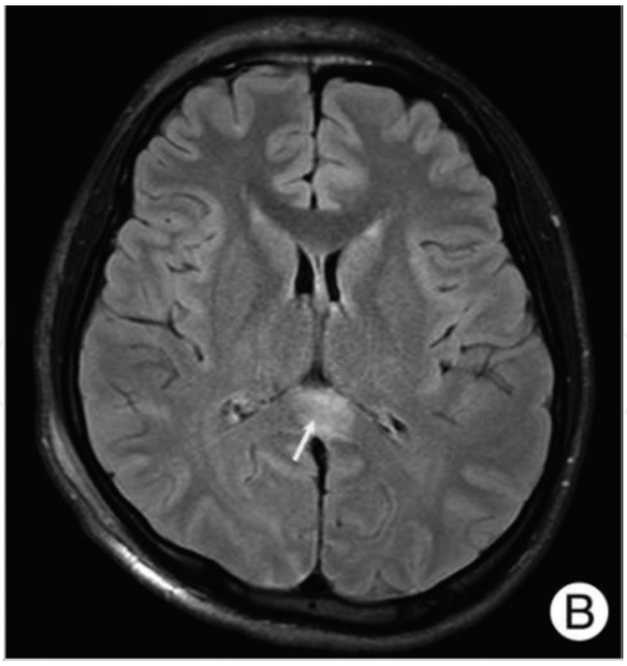


**Figure 7.** Additional imaging of the 21-year-old bicycle accident patient described above. Image captured using the FLAIR methodology also discussed above. Same patient as above (21-year-old bicycle accident patient) presenting with traumatic brain injury and nonhemorrhagic lesions of the splenium of the corpus callosum. This image is obtained using the fluid-attenuated inversion recovery MRI sequence, often called FLAIR sequence. This form of imaging is useful in suppressing the cerebrospinal fluid (CSF) effects on radiological imaging allowing the higher-intensity appearance of lesions. In this image, the FLAIR imaging also confirms the initial diagnosis [53].

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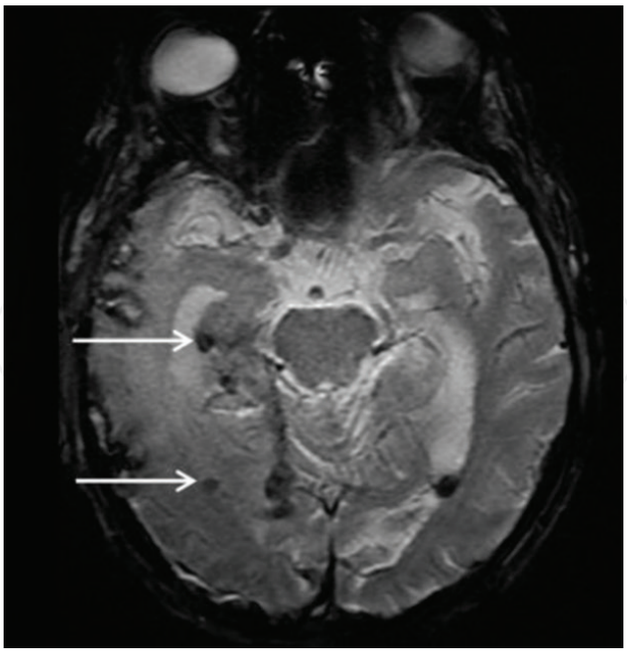

**Figure 8.** Hemorrhagic DAI [54]. An 83-year-old female patient presenting to the clinic post-fall. The image above is an axial gradient-recalled echo (GRE) image, which indicates and draws focus to the right temporal lobe which, indicated by the white arrows, shows the resulting injury of a hemorrhagic diffuse axonal injury.

symptoms of being unconsciousness and/or in a severe coma to which the patient has sustain mild to severe brain damage often of the irreversible form. In the event that a patient regains consciousness and makes a near-full recovery through the management of brain swelling, hemorrhage, and neurological network status, there are a multitude of therapeutic modalities that can be pursued to maximize the chance of a near-full recovery. This plan entails a variety of medical professional care for the patient each in a specific regard [55]. Upon discharge from trauma and emergency centers, patients enter a long and intensive program for multiple forms of therapeutic care consisting of the following modalities: speech therapy, physical therapy, occupational therapy, recreational therapy, adaptive equipment training, and counseling [56]. Deficits resulting from TBI include impairments in movement, balance, and coordination, accompanied by sensory deficits, behavioral changes, cognitive defects, and communicative defects. In our efforts to restore quality of life back to the patient's life, we will discuss the several modalities of therapy and their application to patients recovering from DAI.

Speech therapy, conducted by a licensed speech and language therapist, first completes a formal evaluation of patients cognitive and communication skills as well as their swallowing skills. An oral examination is also conducted to ensure the strength and coordination of the muscles involved in producing speech. Following the assessment, therapists will engage in a series of short conversations to gage the patient's ability to form understandable and coherent speech; patients are often presented with a series of questions relating to their life and daily tasks prior to the traumatic accident. In the event that a patient presents difficulty utilizing muscles involved in speech or forming speech in itself, therapists will then evaluate the patient's ability to swallow or gag in the presence of a gag stimulus. Concluding the series of examination, the therapist conduct is a developed plan that highlights the focus areas for a patient, often separated into primary, secondary, and tertiary goals. Primary goals are to get

the patients general responses to sensory stimuli to appropriate levels, followed by education of the patient's family and friends on proper interactions with a person going through speech therapy. Secondary goals are to build cognitive skills such as attention and reduce any confusion a patient may have. Gaining a sense of balance while sitting and standing is also a secondary goal of therapists, allowing the patient to reestablish the necessary muscle memory and neuronal demands balance has on a human body. Later on, through the process of recovery, tertiary goals include the patient reestablishing cognitive maps and problem-solving skills. Often hard to accomplish even for the first time, therapists work on these skills as well as social skills for life outside of the medical center. While the title of speech therapy seems limited to the physical act of producing speech, it is actually a major component of not only speech-forming techniques but also techniques that must be remastered in areas such as cognition and basic physical skills such as balance [57–60]. The process of relearning task one learned earlier in life, involves the reconstruction of neuronal networks, is an example of the many neuronal networks and pathways within a human mind [61].

In addition to speech therapy, patients also go through extensive physical therapy to restore the patient's life as close to their pre-trauma life as possible. Physical therapists work closely with both the patient and their family to develop goals and an individualized treatment plan pertaining to the symptoms displayed by the patient. Depending on the severity of damage the brain has sustained and the patient's level of consciousness, a series of daily task-specific trainings will be conducted. A patient who is said to be in a "vegetative state" has retained basic brain function but is unaware of their surroundings and requires assistance with body positioning. Additionally, patients who are said to be in "minimally conscious state" show beginning signs of inconsistent awareness; however, they require assistance with almost all physical movement. A vast majority of patients presenting to physical therapists are in a form of a vegetative state following a mild to severe head trauma, specifically when a DAI is diagnosed [62]. The primary goals for physical therapy are to aid the patient in regaining a sense of alertness, the understanding of physical movement, and the ability to follow commands. Secondary goals include movement, muscle strength, and flexibility. Additionally, movement around common daily objects such as beds is also a secondary concern for physical therapists. The activities conducted within physical therapy sessions include a tremendous amount of both mental and physical learning, balance and coordination, as well as strength and energy [63–65].

While physical therapy focuses on movement, strength, and balance as a whole, occupational therapy takes a more targeted approach in dealing with day-to-day activities such as walking down stairs, brushing one's teeth, and opening a door, to name a few. Occupational therapists, just like any other therapist, begin therapy by assessing the severity of the patient's physical disability. Often, the Canadian Occupational Performance Measure (COPM) is used to assess the patient's performance and life satisfaction [66]. Additionally, patient questionnaires are utilized to gain a psychological baseline as the school of thought behind occupational therapy strongly believes in the patient's psychological motivation. The Community Integration Questionnaire (CIQ) and the Satisfaction with Life Scale (SWLS) both assess a patient's social interaction, productivity, and cognitive judgments. With these metrics, occupational therapists are able to design personal goals for the patient to first improve self-awareness, then improve physical activity which related to daily life, and lastly to restore as much as memory recall as possible [67, 68]. Occupational therapy is not as structured as speech or physical therapy; this form of therapy truly evaluates a patient's quality of life and psychological state prior to beginning any

form of therapy which involves movement. **Figure 9** illustrates the many factors of occupational therapy in a primary care setting, highly correlative to what is seen in post-trauma care [69].

While patients receive a tremendous amount of in-hospital care, they also receive a unique and more social form of treatment called recreational therapy. This form of therapy involves the therapist designing activities to improve and enhance the patient's self-esteem and social skills while also practicing balance, coordination, strength, and additional motor skills. These therapists aim to design social outings for the patient and their friends/families to allow the patient to not only feel loved and supported but to also reintroduce key life skills such as team building and social interaction. Within this form of therapy, highly trained canines may be utilized as well as more hobby-like activities such as gardening, recreational sports, and even holiday functions, such as decorating or baking [70, 71]. While this form of therapy is less aggressive and directed, data has continuously shown the remarkable outcomes that recreational therapy has not only on the patient's physical abilities but also on the overall happiness of the patient and their quality of life, a truly life-changing treatment in the posttraumatic realm [72].

For many patients that have suffered from a severe form of DAI, adaptive assistive technologies will be essential to restoring the quality of life back for the patient. Adaptive assistive technologies are medical devices that are used to aid the patient in completing daily living activities such as bathing, walking, and eating [73]. These forms of medical devices are crucial for the treatment of DAI in that they provide patients who otherwise would be confined to a bed the ability to be mobile again. Common forms of these devices include wheelchairs, crutches, prosthetics, and orthotics. Despite the mobility, these devices can also assist with sensory such as hearing and touch, as well as safety with devices that alert the patient when an alarm may sound or a door bell may ring. For many of us, we take these devices for granted and do not understand their true lifesaving powers, especially for DAI patients who have experienced a great deal of trauma and require these devices in order to live a quality of life [74, 75]. Engineers today are working on the development of novel assistive technologies, such as the intelligent power wheelchair seen in **Figure 10**, which will allow


**Figure 9.** Factors involved in occupation therapy [69].

**Figure 10.** Assistive technology: Intelligent power wheelchair prototype for clinical applications.

many DAI patients who may never have the ability to walk again to be able to venture the world and be more independent. Many posttraumatic DAI patients buffer from immobility and are confined to the limits of a wheelchair; with technological advances such as these, we expect to see a tremendous gain in patient's quality of life [76].

We have currently discussed the many forms of treatment available to patients who have sustained a TBI, specifically DAI; however, despite all form of treatment to restore mental and physical quality of life, counseling is also just as an important characteristic. Any injury to the brain is catastrophic and especially for the patient and their family. One of the most highly utilized forms of treatment is counseling, often for patients that present with a sense of worthlessness, loneliness, and frustration over their predicament [77, 78]. Counseling sets out to answer a series of questions regarding the patient's life; these questions tend to deal with first, identifying the problem and then understanding the severity of the problem. Through every second of counseling, it is important that the patient feels that counseling will be the solution to many of their problems as well as that patient's privacy will be upheld to the maximum extent [79].

Through the many different modalities of therapy, the treatment for DAI is one that can span over the year with no real guarantee that progress will be made. The diagnosis of DAI is life-changing at best and is often the result of severe brain trauma. In the event that a patient is successful in the battle to regain consciousness and expelled out of their coma, the uphill battle to restore a quality of life begins [80]. Through the many forms of DAI treatment available to patients today, slight improvements are possible, and faith in the various treatment methods is at an all-time high [81, 82]. The primary form of counseling patients receives frankly a conversation regularly with therapists focusing on reducing frustration and anxiety and resorting the sense of self-worth. At the end of the day, the patient must come to term with their new situation and establish a new life; while this is easier to be said than done, counseling has successfully completed this task multiple times. To patients climbing the uphill battle of DAI treatment, we wish you the best of luck and a speedy recovery.

### 2.10. The history behind DAI

In 1956, Sabina Strich, the scientist known to have first identified and described the diffuse degeneration of white matter and white-gray matter lesions, published the first ever study

focused on the matter seen within the cerebral region of five patients that had sustained closed-head injuries of severe form [83]. A case study of five patients set the landmark for pathological investigations into brain damage and traumatic head injuries, specifically diffuse axonal injury [84]. While in 1956, the human brain was not entirely understood as well as technology was not at the level it is today to have been able to radiographically or investigatingly screen for the presence of head trauma, thus the rate of mortality was strikingly high. Of the five subjects Strich was investigating, all patients succumbed to their brain injuries weeks to months after the initial trauma. While there was no striking evidence for the presence of DAI, Strich came to the realization that extended degeneration of axons over a time period after the trauma was responsible for the high rate of mortality. The pathologic term DAI was established after Strich published her findings; later, it was agreed that DAI was a multipart pathology in that not only does the initial trauma cause severe damage, but also secondary factors such as biochemical cascades, edema, and hypoxia also contribute to the pathology as a whole [85, 86]. It was in the early 1980s where the official term, DAI, was introduced and accepted worldwide as a pathology which played a key integral role in the posttraumatic development of the patient [87].

### 2.11. Neuroinflammation: a novel understanding

Inflammatory response within the brain resulting after a traumatic brain injury, specifically a DAI, is mediated by microglia. Oehmichen et al. conducted an experiment in which microglia were immunohistochemically labeled to enable their ability to track areas of axonal injury by observing infiltration [88–90]. Microglia will localize to the region of trauma and become activated such that they are able to isolate compromised structures and locate injured axons. Infiltration mentioned briefly above will become evident after 24 hours in young patients or 48 hours in elder patients and can last for as long as 2 weeks or even a month for particular cases [91]. Cytokines are the key factor involved in inflammation; interleukin (IL) families 1, 6, and 10 also play a role as mediators of inflammation, accompanied by TNF, a tumor necrosis factor which is a cell signaling protein utilized by the body during inflammation. Within a rat model, traumatic brain injury is correlated with a rapid increase in cortical IL-1 alpha and beta sub-factors of the IL-1 family. These interleukins were demonstrated to rapidly increase the rate of inflammation within the rat model [92]. Additionally, interleukin-6 (IL-6) family has also been shown to increase in expression 1–6 hours after the traumatic brain injury. The highest levels of IL-6 mRNA transcription and IL-6 cytokine expression occurred in regions where diffuse axonal damage was the greatest [93]. Within the body, interleukin (IL)-6 plays a key role in the homeostatic control of inflammation-activating cofactors such as granulocytes, lymphocytes, and NK, which rapidly diffuse within the blood in the event of a traumatic injury [94, 95]. The inflammatory response while deadly if not controlled actually increases the likely hood of neuronal damage recovery; however, due to the constant volume of the given region and risk of cerebral compression, inflammation must be controlled to minimize any risks of mortality or compression-induced damage.

### 2.12. Conclusion

In this chapter, we have discussed in detail the pathology of diffuse axonal injury (DAI) as a result of traumatic brain injury (TBI). Although this pathology represents a mild to severe disease which complicates or often deprives patients from a normal life, implementation of effective therapy and rehabilitation treatment, along with the adaptation of novel therapy

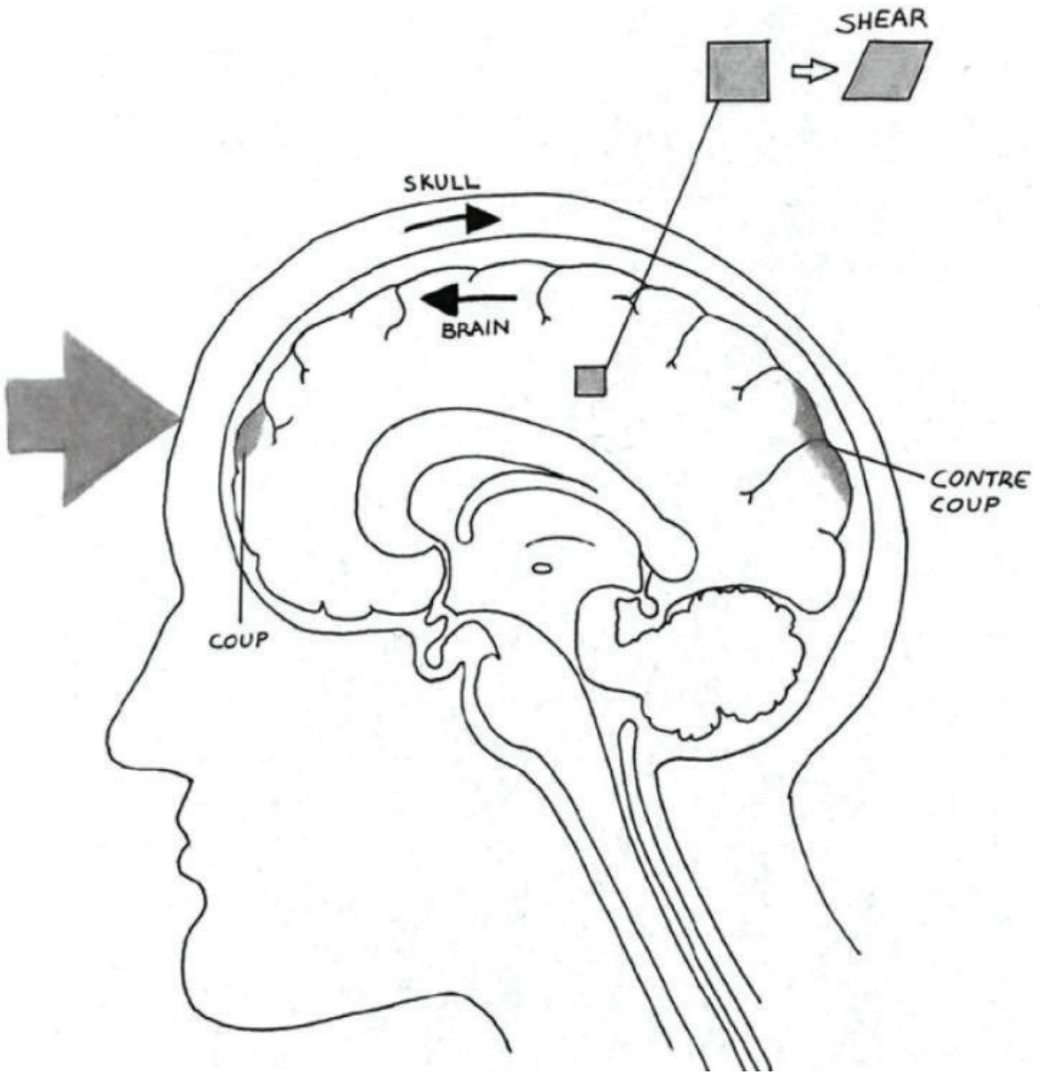


**Figure 11.** Demonstration of the most common form of DAI impact injury [96].

methodologies, patient course and prognosis may be substantially improved, mitigating traumatic sequelae and long-term posttraumatic outcomes. We hope that you have learned a great deal in regard to DAI, its pathology, and biochemical characteristics. In **Figure 11**, we hope to visualize the most common physical action that results in DAI. Axonal injury is typically resulting from an external force that is acted upon the brain causing a rotational force to be acted upon the axon along with a severe impact of the brain along the skull. Stay safe!

## Disclosure

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