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Diffusion-weighted MRI in diffuse axonal injury of the brain

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Abstract The goal of this study was to identify and describe the different types and patterns of tissue injury which are encountered by diffusion-weighted imaging (DWI) in diffuse axonal injury (DAI) of the brain. The DWI data sets of 98 patients who suffered from a closed-head injury were retrospectively evaluated. Medical records were reviewed to rule out pre-existing neurological diseases. Lesions were studied for their DWI signal characteristics and lesion size or extension. Traumatic lesions were classified into three categories depending on their signal characteristica on DWI and apparent diffusion coefficient (ADC) maps: type 1, DWI- and ADC-hyperintense most likely representing lesions with vasogenic edema; type 2, DWI-hyperintense, ADC-hypointense indicating cytotoxic edema; type 3, central hemorrhagic lesion surrounded by an area of increased diffusion. According to the size and extent of lesions, injury was classified into three groups: group A, focal injury; group B, regional/confluent injury; and group C, extensive/diffuse injury. Our study showed that diffusion-weighted imaging differentiates between lesions with decreased and increased diffusion in patients with DAI. Different degrees of tissue injury extent were noticed. Future prospective studies should study if this additional information can be used as a predictor of injury reversibility, final outcome and prognosis.

Keywords Diffusion-weighted imaging · Diffuse axonal injury · Brain injury

Introduction

Trauma is the leading cause of death and disability in the United States for individuals less than 45 years of age. More than 50% of these deaths are related to head injury [1, 2]. Traumatic brain injury can be focal or diffuse. Focal brain injury usually occurs due to direct impact of forces to the head which may result in cerebral contusions and intra- or extracerebral hematomas [3]. Diffuse brain injury, also referred to as diffuse axonal injury (DAI) refers to damage to the white matter caused by unequal rotation and/or deceleration/acceleration forces acting at the interface of tissues that differ in density or rigidity [4, 5]. Lesions are typically located at the gray–white matter interface or along/within fiber tracts, e.g., the centrum semiovale, internal capsula, corpus callosum, fornix, superior and middle cerebellar peduncles, and the brain stem [6]. These lesions are also known as shearing injuries. The resulting neurological deficits (decreased consciousness and cognitive defects) can be profound and cannot be managed surgically. There is increasing evidence that DAI is a significant factor in determining patient prognosis [2]. An exact and complete radiological work-up of patients with traumatic brain injury is mandatory in guiding correct acute treatment to prevent or limit secondary injury [2]. The identification and characterization of trauma-induced tissue injury has been the focus of multiple imaging studies [7, 8, 9, 10, 11]. Computed tomography and MRI, however, tend to underestimate the exact extent of DAI. This is supported

by studies in which patients showed progressive, global cerebral atrophy on follow-up after initial imaging did not show pathology or only discrete findings [12, 13]. In addition, Kelly et al. reported that although extensive white matter injury is consistently associated with a poor prognosis, the presence of a few foci of shearing injury was seen in patients with both poor (severe intellectual limitations and/or diminished level of consciousness) and good clinical outcome [14]. New imaging methods could possibly detect the extent of injury more accurately and preferably earlier.

Diffusion-weighted imaging (DWI) has been proven to be very sensitive in diagnosing early/acute cerebral ischemia. The combined information yielded by isotropic DWI maps and their corresponding apparent diffusion coefficient (ADC) maps allow discrimination between lesions with increased and/or decreased diffusion [15, 16]. Diffusion-weighted imaging is also reported to be sensitive in disease processes other than cerebral stroke [7, 8, 9, 10, 11, 15]. Since we have routinely used DWI in the MRI evaluation of patients with traumatic brain injury for the past 4 years, we reviewed all DWI studies for the signal characteristics and patterns of injury as displayed by DWI.

Materials and methods

Patients were selected by an electronically assisted search of all radiological reports between November 1996 and January 2000 for various keywords related to diffuse axonal injury (e.g., shearing injury, diffuse axonal injury, petechial hemorrhages). Those that contained such keywords in the final radiological diagnosis were reviewed. In total, 98 patients were identified. Discharge summaries were studied to determine if the mechanism of trauma was consistent with DAI of the brain, deceleration/acceleration forces, or unequal rotational forces. Clinical data were studied to rule out lesion etiology other than trauma related. All DWI examinations were performed within 14 days of acute trauma. The MR imaging was performed on a 1.5-T clinical MRI unit (Signa, GE Medical Systems, Milwaukee, Wis). All patients underwent full tensor DWI averaged over three data sets for a total acquisition time of 128 s as previously described [15]. The entire diffusion tensor was sampled by using a T2-weighted spin-echo (SE) single-shot echo-planar imaging technique repeated in six noncolinear directions. A repitition time of 5000–6000 ms and an echo time of 112–118 ms was used obtaining up to 20 axial slices with a 5- to 6-mm slice thickness and a 1-mm interslice gap. A field of view of 40×20 cm was used with an acquisition matrix of 256×128 pixels. Diffusion gradients were applied in turn at a finite low b-value (3 s/mm^2) and a high b-value (1221 s/mm^2). Isotropic DWIs were calculated by taking the geometric mean of the six images obtained with a b-value of 1221 s/mm^2. ADC maps were computed. In addition, according to the departmental protocols, standard conventional MRI sequences were available (sagittal or axial T1-weighted SE; TR=400–500 ms/TE=14 ms/no. of excitations=2), axial T2-weighted fast spin-echo (FSE; TR=5000–6000 ms/TE=108 ms/no. of excitations=2), axial T2*-weighted gradient-echo (GRE; TR=750 ms/TE=25 ms/ no. of excitations=2) and axial fluid-attenuated inversion recovery (FLAIR; TR=8000 ms/TE=110 ms/no. of excitations=2).

All DWI examinations were reviewed in consensus by three experienced neuroradiologists (T.H., K.H., P.S.). Because the goal of our study was focused on the characterization of DAI lesions on DWI, no systematic correlation was performed with conventional MRI sequences. T2*-weighted GRE images were reviewed to rule out DWI signal changes due to magnetic susceptibility effects induced by blood products. Lesions on DWI were investigated for their signal characteristics on the isotropic DWI maps as well as on the ADC maps. Signal intensity of the lesions was compared with normal-appearing adjacent brain tissue or with the corre-

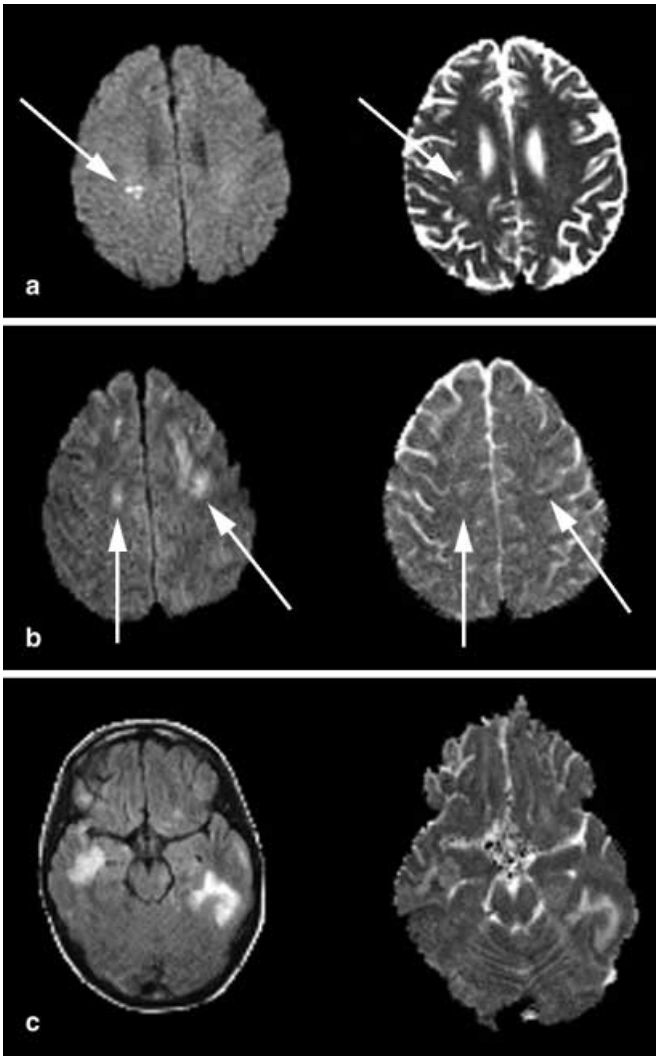

Fig. 1 **a** An 83-year-old man with a focal type-1 DAI. Three small focal shearing injuries (*arrows*) less than 10 mm in diameter are encountered within the right centrum semiovale. Lesions are diffusion-weighted imaging (DWI)- and apparent diffusion coefficient (ADC)-hyperintense indicating increased diffusion (e.g., vasogenic edema). The DWI hyperintensity is most likely due to T2 shine-through effects. **b** A 17-year-old girl with focal type-1 diffuse axonal injury (DAI). Multiple small shearing injuries (*arrows*) are identified at the frontal cortico-medullary junction. Most lesions are DWI- and ADC hyperintense. Lesion conspicuity on DWI maps is better than on the corresponding ADC maps. **c** A 22-year-old man with regional/confluent type-1 DAI. Fluid-attenuated inversion recovery images show extensive shearing injury within the white matter of both temporal lobes. These lesions are ADC hyperintense related to an increased water diffusion indicating vasogenic edema

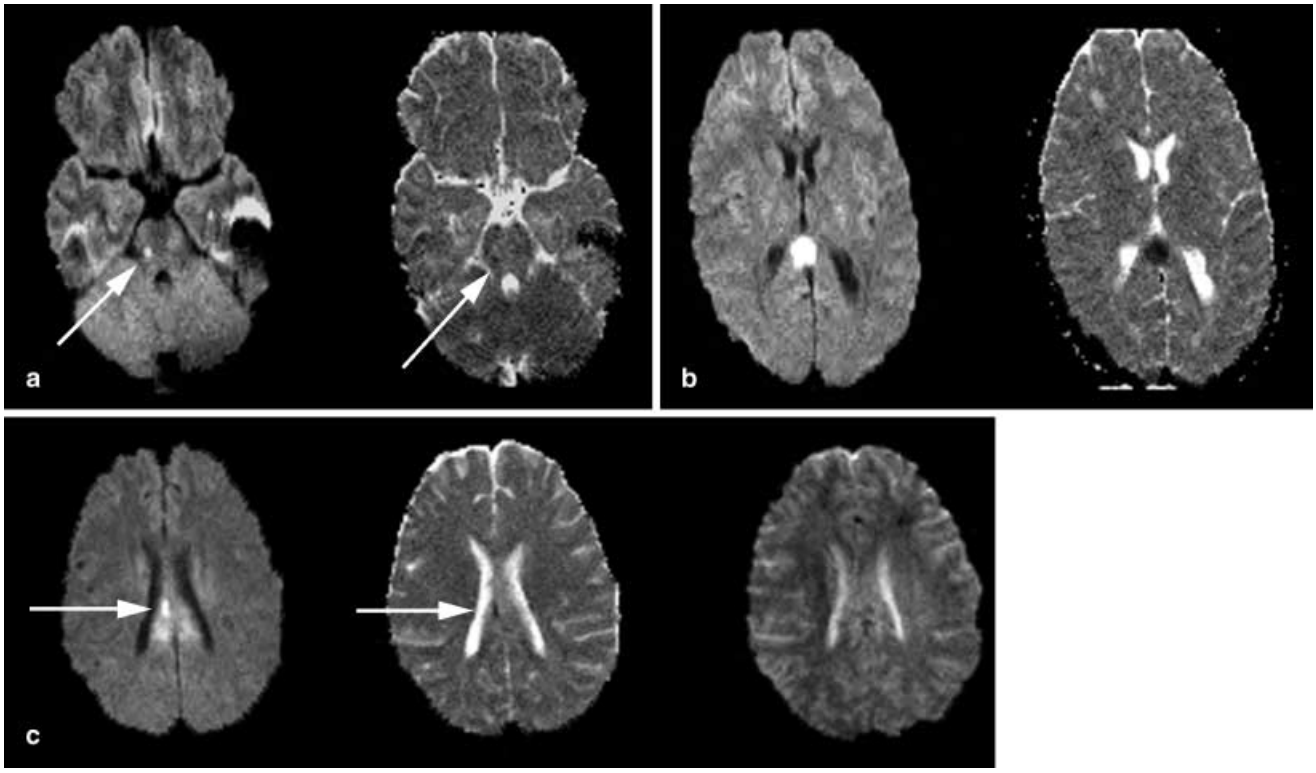

Fig. 2 a A 32-year-old man with focal type-2 DAI. The DWI-hyperintense, ADC-hypointense lesion (*arrows*) is located within the dorsal portion of the right brain stem. The signal characteristics indicate decreased diffusion, possibly due to cytotoxic edema. **b** A 14-year-old boy with regional type-2 DAI. A DWI-hyperintense, ADC-hypointense regional shearing injury is seen at a predilection site of DAI within the splenium of the corpus callosum. Additional focal type-1 shearing injuries are encountered at the cortico-medullary junction of the right frontal lobe. **c** A 17-year-old girl with mixed type-1 and type-2, regional DAI. Extensive regional type-1 injury of the corpus callosum. In addition, a focal type-2 shearing injury with restricted diffusion (ADC-hypointense) is seen within the center of the corpus callosum (*arrows*). Correlation with T2*-weighted images excluded a focal hemorrhage

sponding contralateral brain area. In addition, the size and extent of the lesions was categorized into three groups: group A, focal injury; group B, regional/confluent injury; and group C, extensive/diffuse injury. Focal injury was defined as lesions up to 10 mm in diameter; regional/confluent DAI was defined as a conglomerate of lesions up to 10 mm in diameter or a single lesion larger than 10 mm in diameter; and extensive/diffuse DAI was defined as lesions which follow neuroanatomical structures such as white matter tracts over multiple sections (e.g., cortico-spinal tracts, corpus callosum) or involve large areas of brain tissue where multiple fiber tracts cross such as with the centrum semiovale. Since most cases were well known to the reviewers, there was no attempt to perform the study in a blinded manner. Because currently no data are available of the time evolution of the ADC values in head trauma, our retrospective study design prevents a reliable quantitative assessment of the ADC values. In our study the DWI examinations were performed in a wide time frame, ranging between 1 and 14 days after acute trauma. Consequently, our study focused on the qualitative description and characterization of DAI lesions, rather than on a quantitative analysis of the ADC values.

Results

The DWI/ADC signal characteristics allowed a classification into three different types of DAI lesions: Type-1 lesions are DWI- and ADC hyperintense indicating increased diffusion (Fig. 1); type-2 lesions are DWI hyperintense and ADC hypointense indicating reduced or restricted diffusion (Fig. 2); and type-3 lesions are hemorrhagic lesions characterized by a central area of hypointensity on DWI and ADC maps surrounded by an area of DWI and ADC hyperintensity (similar to type-1 lesions) indicating a surrounding area of increased diffusion (Fig. 3).

In addition, DWI showed three different patterns of injury based on the anatomical extension of signal alterations seen on DWI/ADC maps. Focal, type A, lesions were well delineated, round to oval-shaped lesions. These lesions were located at the predilection site of DAI along white matter tracts and at the interface of gray and white matter (Figs. 1, 2). Most of the lesions were identified subcortically. No focal lesions were seen in the cortical gray matter. Regional/confluent, type-B lesions were ill-defined and it appeared difficult to discriminate a conglomerate of neighboring small focal lesions from single large regional lesions (Fig. 3). All lesions were again located at known predilection sites of DAI. Extensive/diffuse, type-C lesions were characterized by DWI signal abnormalities that respect the anatomical borders of well-known functional systems such as the cortico-

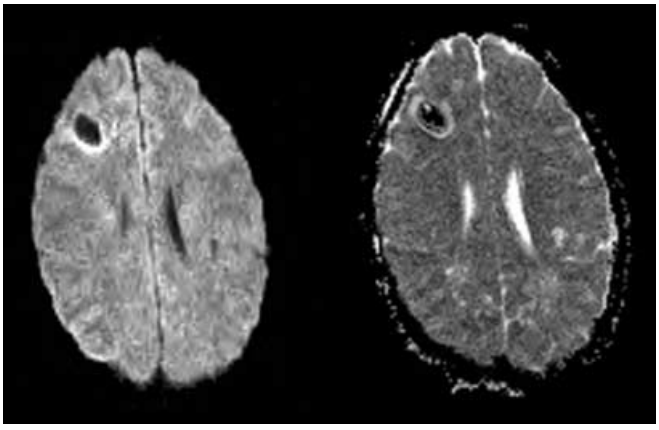

Fig. 3 A 13-year-old boy with regional type-3 DAI. The lesion is DWI- and ADC hypointense due to hemorrhage which was confirmed on T2*-weighted imaging. The lesion is surrounded by a DWI- and ADC-hyperintense rim of increased diffusion, probably due to vasogenic edema

spinal tracts and the corpus callosum. The splenium of the corpus callosum was most frequently involved, followed by the truncus of the corpus callosum. No involvement of the genu of the corpus callosum was seen. Involvement of the cortico-spinal tract could extend from the corona radiata along the internal capsule into the brain stem. In addition, these lesions involved large areas where multiple fiber tracts in different orientations cross like in the centrum semiovale (Fig. 4).

Discussion

Type-1 lesions represent lesions with increased diffusion. Most likely these lesions are related to areas with vasogenic edema. Vasogenic edema is characterized by a relative increase in water in the extracellular compartment where water is relatively more mobile. Consequently, vasogenic edema results in increased ADC values. These

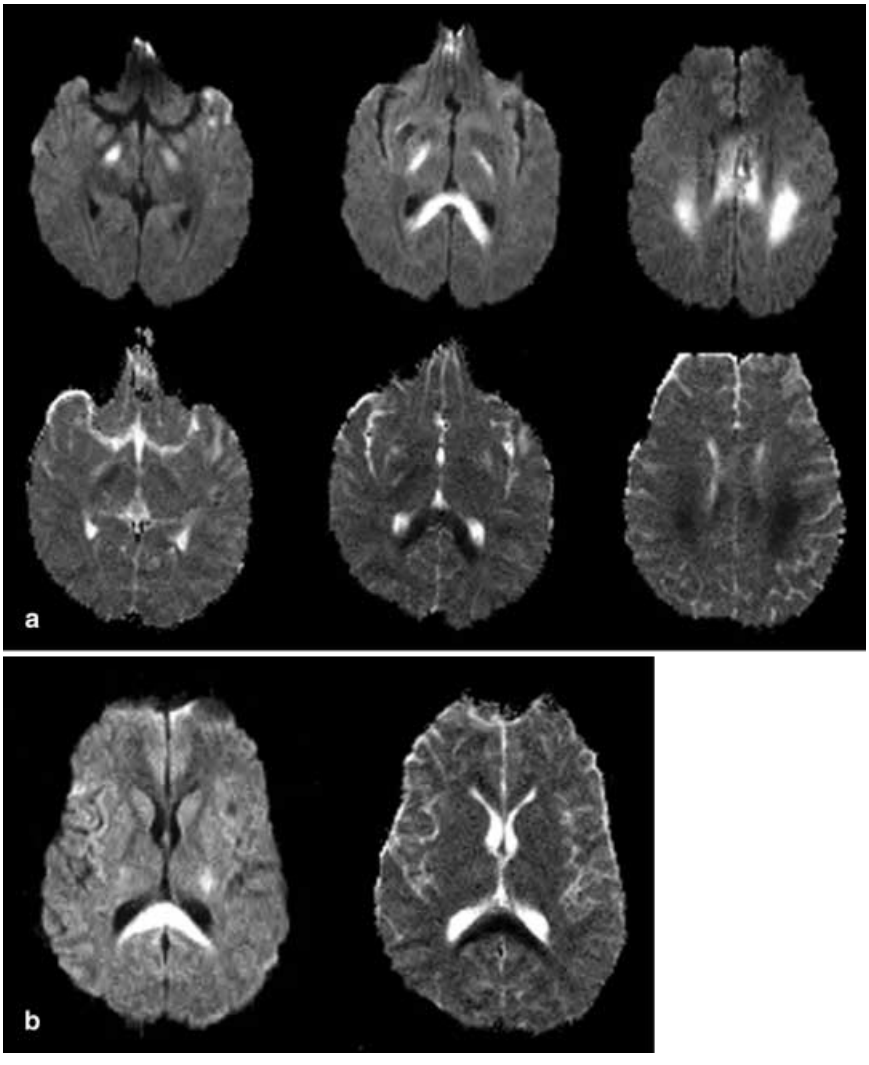

Fig. 4 **a** A 19-year-old man with extensive type 2 DAI. Extensive DWI-hyperintense and ADC-hypointense shearing injuries are encountered following both cortico-spinal tracts, extending into the corona radiata. In addition a partially hemorrhagic shearing injury is seen within the corpus callosum. **b** A 24-year-old man with extensive type-2 DAI. A DWI-hyperintense and ADC-hypointense injury of the entire splenium of the corpus callosum is visualized. The signal alterations are limited to the anatomical borders of the splenium reflecting the selective susceptibility of the corpus callosum for shearing forces

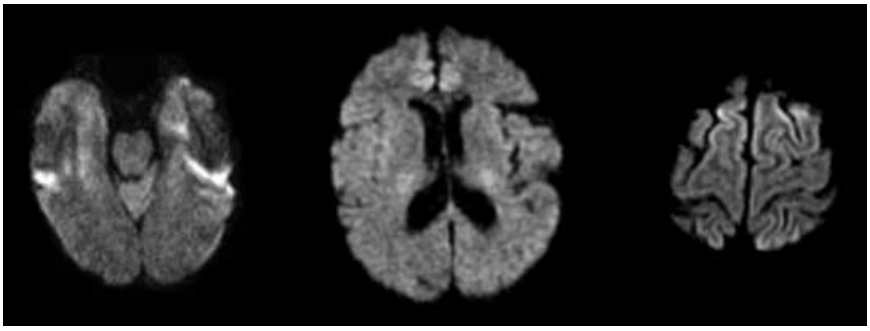

Fig. 5 Possible pitfalls of DWI signal changes mimicking pathology. Air–bone interfaces result in local field inhomogeneities with increased DWI signal within the adjacent temporal lobes. Similar signal increases are encountered within the parasagittal frontal cortex superior to the sphenoid sinus or frontal skull base. In addition, DWI signal increase is seen within the frontal and parietal cortex near the vertex

lesions appear DWI hyperintense due to the T2 shine-through effect. It is important to understand that DWI maps are diffusion weighted and incorporate a remaining amount of T2-weighted signal intensity. Lesions with long T2-relaxation times, e.g., accumulations of free mobile water within the extracellular space, consequently contribute to the effective signal intensity on DWI images. This T2-component is referred to as T2 shine through. The T2-weighted signal contribution is removed on the ADC map, which is essentially an image whose signal intensity is equal to the magnitude of the ADC. The exact etiology of vasogenic edema in DAI is currently not yet fully understood. Animal and human studies have confirmed that vasogenic edema occurs in DAI [17, 18] and has been reported to be potentially partially reversible. Type-2 lesions represent lesions with restricted or decreased diffusion. The reduced mobility of the water molecules results on the DWI images in an increased signal intensity against the suppressed signal intensity of the normal-appearing adjacent brain tissue. The reduced diffusion is characterized by lowered ADC values; consequently, these lesions are ADC hypointense. Again, the exact etiology of restricted diffusion in DAI is still under investigation. One likely, important contributor is cytotoxic edema. Cytotoxic edema has been observed in multiple studies involving traumatic brain injury [17, 18, 19]. An animal study using a controlled cortical impact injury in rats showed that vasogenic and cytotoxic edema can occur simultaneously. Cytotoxic edema is known to occur in acute cerebral stroke [15]. Ito et al. [20] demonstrated that trauma in combination with hypoxia and hypotension, mimicking secondary trauma related ischemia, induces neuronal injury with decreased ADC values. They concluded that brain ischemia associated with severe head trauma leads to cytotoxic edema [20]. The predominant theory for the restriction of water diffusion in stroke is a disruption of energy metabolism, leading to failure of the membrane pumps. This leads to a net translocation of water from the extracellular space to the intracellular compartment, where water mobility is relatively more restricted. In addition, cellular swelling results in a reduction of the volume of the extracellular space. An increased tortuosity of the extracellular space is believed to contribute to restricted diffusion. Cytotoxic edema or lesions with restricted diffusion are less likely reversible and indicate nonviable tissue [15]. Type-3 lesions are identified as separate lesions because of their signal characteristics. The ADC and DWI maps are, however, less reliable in the presence of blood products. The appearance of blood products on DWI is complex and can be unpredictable. Hemorrhage which contain deoxyhemoglobin, intracellular methemoglobin, or hemosiderin are hypointense on DWI because of magnetic susceptibility effects [15]. These susceptibility effects prevent a reliable calculation of ADC values [15]. Oxyhemoglobin, as present in fresh hemorrhagic shearing injuries, is hyperintense on DWI and has a lower ADC value than normal brain tissue [15]. The surrounding halo of increased diffusion most likely represents vasogenic edema in reaction to the hemorrhage.

The anatomical extent of signal abnormalities encountered by DWI follow the biomechanical and biophysical nature of shearing forces acting on an anatomical substrate consisting of areas with different rigidity and structure. The encountered presentation of lesion extension and location most likely represent a continuous spectrum of tissue damage which relates to the degree of force, kind of trauma (rotational vs linear acceleration/deceleration), duration of injury and anatomy of the brain. Small focal lesions have a better prognosis than regional/confluent focal lesions which again have a better outcome than extensive/diffuse shearing injuries. Diffusion-weighted imaging has been proven to have an increased lesion conspicuity in cerebral stroke compared with conventional MRI [16]. An up to 20-fold higher percentage of contrast-to-noise ratio on DWIs of acute ischemic stroke compared with proton-density and/or T2-weighted MR images explains the greatly improved sensitivity for lesion detection with diffusion-weighted MR imaging [16]. Similarly, in our experience the high signal intensity of shearing injuries on DWI allowed identification of extent of injury easily, especially at subcortical white matter locations. Studies comparing lesion detection by DWI with conventional MRI are currently performed in our institution.

Possible pitfalls of DWI in DAI include regions with signal alterations due to local field inhomogeneities or susceptibility artifacts (near the skull base, superior to the temporal pyramid, along the frontal or sphenoid sinus, along the vertex or due to metallic implants) (Fig. 5). In addition, as mentioned previously, intracerebral hemorrhages are known to influence ADC values. Finally, T2 shine-through phenomena can mimic lesions.

Limitations of our study include the retrospective study design and the fact that DWI was performed during a wide range after acute trauma. Time-dependent DWI and ADC signal changes were not considered in this study. The objective of our study was, however, primarily focused on the identification of the different types and characteristics of lesions encountered by DWI. In addition, no gold standard was available. The review of the clinical data, however, confirmed that the mechanism of injury was consistent with DAI in all patients, and that no other medical diseases were known that could explain the encountered signal abnormalities. Quantitative ADC analysis and correlation with clinical scores, such as the Glasgow coma scale and Glasgow outcome scale, are mandatory to determine the value of ADC measurements in guiding treatment and predicting outcome.

Conclusion

In conclusion, DWI represents a new non-invasive imaging tool which allows identification of shearing injuries in the brain, distinguishes between lesions with increased diffusion (e.g., vasogenic edema) and restricted diffusion (e.g., cytotoxic edema), and could serve as a valuable adjunct to conventional MRI. The short acquisition times make DWI less susceptible to motion artifacts. The differentiation between lesions with increased and decreased diffusion could possibly serve as an indicator for reversibility of tissue injury and final outcome. The high lesion conspicuity/contrast could improve detection of small shearing injuries missed by conventional MRI.

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