PFO and ASD case reports

Delayed blood-brain barrier disruption after shallow-water diving demonstrated by magnetic resonance imaging

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Abstract

(Hadanny A, Tal S, Fishlev G, Bechor Y, Efrati S. Delayed blood-brain barrier disruption after shallow water diving demonstrated by magnetic resonance imaging. *Diving and Hyperbaric Medicine*. 2015 June;45:116-120.)
A 22-year-old diver presented to our emergency room complaining of headaches and left side numbness three days after diving to a depth of 6 metres for 25 minutes. On examination, he had left-sided hypaesthesia, and a post-contrast FLAIR brain MRI sequence revealed significant diffuse meningeal enhancement, indicating blood-brain-barrier (BBB) disruption. The patient was treated with hyperbaric oxygen; the initial four sessions resulted in only partial symptom improvement correlating with partial improvement in the MRI findings. Ten additional hyperbaric treatments resulted in complete resolution of the symptoms and normalization of MRI findings. The main aim of this case report is to present a probable, atypical, delayed-onset case of shallow-water decompression sickness culminating in significant BBB damage, which was demonstrated by special MRI techniques.

Key words
Decompression sickness; persistent foramen ovale; radiological imaging; brain; hyperbaric oxygen therapy; case report

Introduction

Decompression sickness (DCS) occurs rarely after a single dive to depths less than 10 metres' sea water (msw).[1] We present a patient who developed neurological symptoms after a single dive to 6 msw and in whom there was radiological evidence of endothelial injury to the blood-brain barrier (BBB).

Case report

A healthy, experienced, 22-year-old, male diving instructor developed headaches and left-sided numbness three days after diving to 6 metres' sea water (msw) for 25 minutes with no decompression violations. There were no preceding, provocative dives, his last dive being a no-decompression dive to 30 msw a week earlier, or unusual ascents during the dive. The dive profile was confirmed from his computer. His headaches were described as non-localized, fluctuating, pressure-like pain partially relieved with paracetamol and associated with nausea. His symptoms started gradually 24 hours after surfacing and he presented to the nearest emergency medicine department (ER) from where he was discharged after neurological examination and brain contrast induced CT scan were all normal. He presented to our ER three days later as the symptoms had worsened. On arrival, he was apyrexial and had normal vital signs, blood count and basic metabolic panel. However, neurological evaluation revealed left leg hypaesthesia. A brain MRI with FLAIR post-gadolinium injection sequence revealed marked diffuse meningeal enhancement indicating significant blood-brain barrier (BBB) disruption (Figure 1). Normobaric oxygen had not been given and lumbar puncture was not performed prior to the MRI.

Despite the unusual presentation and long delay, a diagnosis of DCS was considered the most likely. The patient was treated with four daily hyperbaric oxygen treatments (HBOT) at 203 kPa for 90 minutes, resulting in significant clinical improvement though a mild headache persisted. Follow-up MRI revealed partial improvement in meningeal enhancement. The patient continued with 10 additional daily HBOTs with complete symptom relief. A second follow-up MRI demonstrated complete resolution of the BBB disruption with normal FLAIR sequence (Figure 1). A transoesophageal echocardiogram evaluation revealed a 2–3mm persistent foramen ovale (PFO), and a contrast echocardiogram revealed a right-to-left shunt of gas bubbles during coughing.

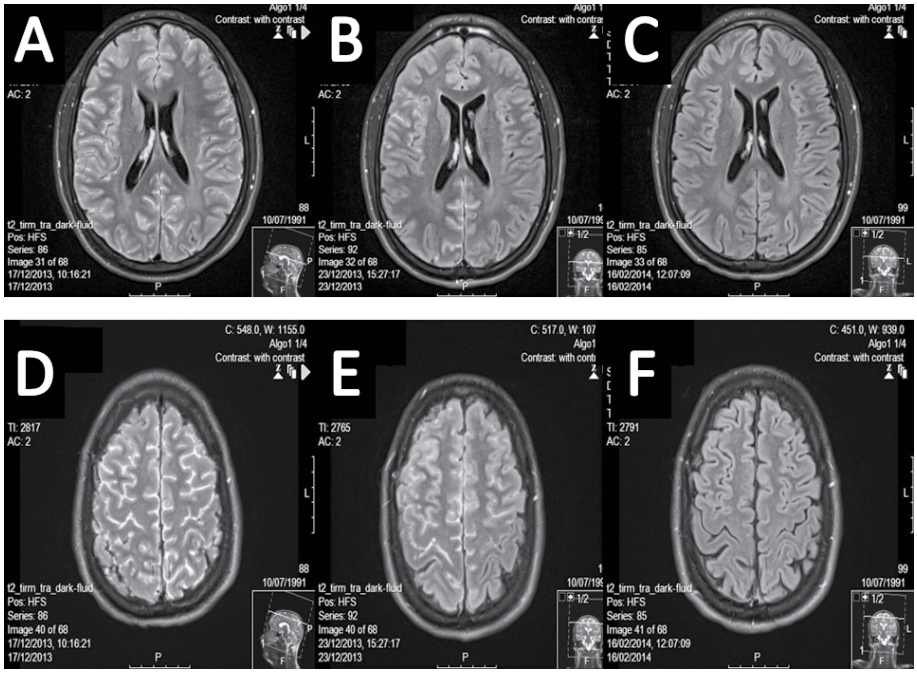
Discussion

DCS AND BBB DAMAGE

Brain MRI scans are considered to have a low sensitivity for the diagnosis of cerebral DCS, often being normal or infrequently revealing T2-weighted high signal intensity lesions in the subcortical white matter, which represent ischaemic changes.[2,3] The hyperintensity changes usually do not correlate with the clinical presentation. Recently a case report of cerebral DCS demonstrated hyperintense areas in the bilateral occipito-parietal lobes mimicking posterior reversible encephalopathy.[4] In our patient, there was a unique pattern of diffuse meningeal enhancement in the FLAIR post-contrast sequence, indicating BBB disruption. Bubble-related injury may be the result of direct mechanical distortion of tissues by extravascular bubbles, tissue hypoxia due to vascular obstruction and secondary effects related to intravascular bubble-induced endothelial

Figure 1

FLAIR post-gadolinium images on presentation (A, D) show massive diffuse hyperintensity signal in CSF spaces representing meningeal enhancement; no focal lesions, gray matter or white matter changes were observed. One week later after four hyperbaric oxygen treatments (HBOT) (B, E) images show decreased meningeal enhancement, and one month later the images (C, F) show normal brain MRI



damage.[5–7] Several animal models have shown induced BBB endothelial damage;[8,9] however, in humans, we are aware of only a single, recent case report of impaired endothelial dysfunction of a scuba diver with inner-ear DCS.[10]

The BBB is a neurovascular unit consisting of endothelial cells and the foot processes of astrocytes, and has the ability to control the exchange of humoral factors and cells between the circulation and the brain, thus playing a crucial role in maintaining cerebral homeostasis. The mechanisms of BBB disruption involve endothelial cell activation and endothelial basement membrane degradation by matrix metalloproteinases.[11]

RADIOLOGICAL IMAGING IN DCS

Imaging studies generally are not considered to be part of the standard assessment of DCS. However, in the current unusual presentation, brain imaging was important for establishing a diagnosis and for follow up. The findings correlated with the clinical presentation. A post-contrast FLAIR sequence MRI, which is not commonly performed, was used in the current evaluation. Under normal conditions, the gadolinium contrast particles do not cross the BBB. When the BBB is disrupted, it allows diffusion of particles into the cerebrospinal fluid (CSF).[15] The gadolinium shortens the T1 signal and, therefore, disrupts the CSF signal suppression of FLAIR sequence; hence the CSF spaces appear hyperintense.[16,17] The sensitivity of FLAIR for lower concentrations of contrast is ten-fold higher than T1WI.[17] This enhancement of CSF serves as an excellent imaging biomarker for BBB disruption called 'hyperintensity reperfusion marker' (HARM).[18] Recently BBB dysfunction was demonstrated in reversible encephalopathy, using the same MRI sequence.[19]

The unique pattern of the imaging in the current case enables analysis of dynamic contrast enhanced MRI (DCE MRI) and diffusion tensor imaging (DTI). DCE MRI is used to interrogate BBB permeability as part of microvascular permeability studies of human brain tumors.[20,21] Under normal cerebral blood flow, the kinetic parameter K^{trans} reflects BBB leakage into the CSF. Thus, high values of K^{trans} indicate high permeability. As seen in Figure 2, on presentation, the DCE MRI revealed diffuse high K^{trans} values, which had normalized at one month. This advanced imaging supports the BBB disruption induced by DCS as discussed above.

By using DTI in MRI scanning, gray and white matter microstructural integrity can be evaluated based on the directionality of diffusion in the brain. Mean diffusivity (MD) provides a measure of the average of total diffusion within a voxel. Damage to brain matter increases the MD through loss of barriers to free diffusion.[22,23] Recently, an animal model demonstrated decreased MD values even in spinal gray matter.[24] In the current case, the cortical (gray matter) MD values at presentation and after completion of HBOT sessions were compared. MD measurement was in exactly the same areas of interests. At the end of the treatment MD values had decreased significantly. Moreover, the most significant decrease/improvement was

Figure 2

K^{trans} values in a region of interest within the right post central gyrus; K^{trans} imaging reflects diffusion of gadolinium across the capillary endothelium; red colours mean high permeability, whereas blue represents normal permeability; at presentation, K^{trans} values are diffusely high (A; mean 0.027 min^{-1}); lower one week later (B; mean 0.023 min^{-1}) and normal at one month post presentation (D; mean 0.014 min^{-1})

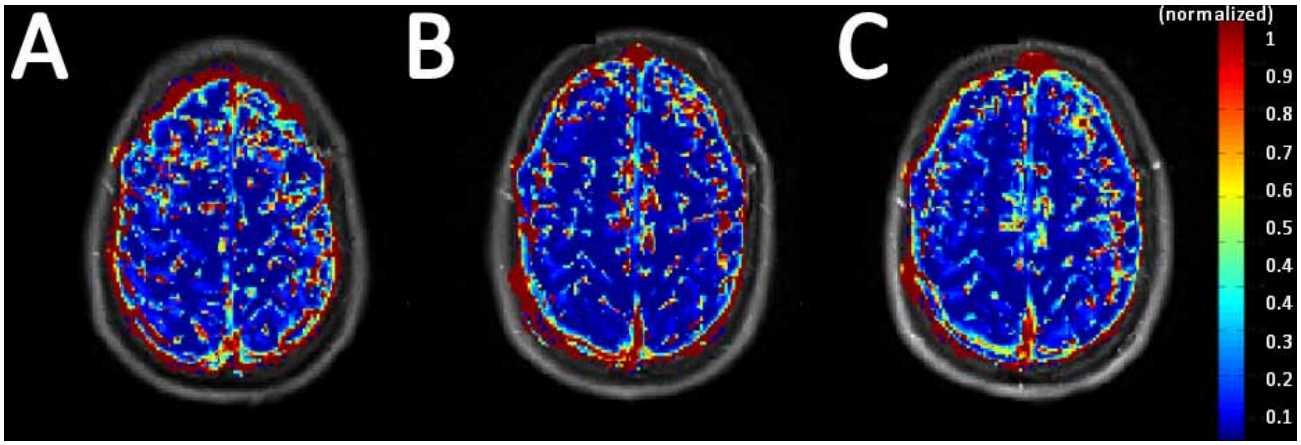


Figure 3

Mean diffusivity (MD) of grey matter/cortex using DTI imaging; red colours mean high diffusion and blue low diffusion; Post HBOT (B) compared to presentation imaging (A) shows lower values of MD (darker blue), in particular, the right post-central gyrus (responsible for left-sided sensation, shows the most improvement (shown in black rectangle), correlating with the diver's left-sided hypaesthesia

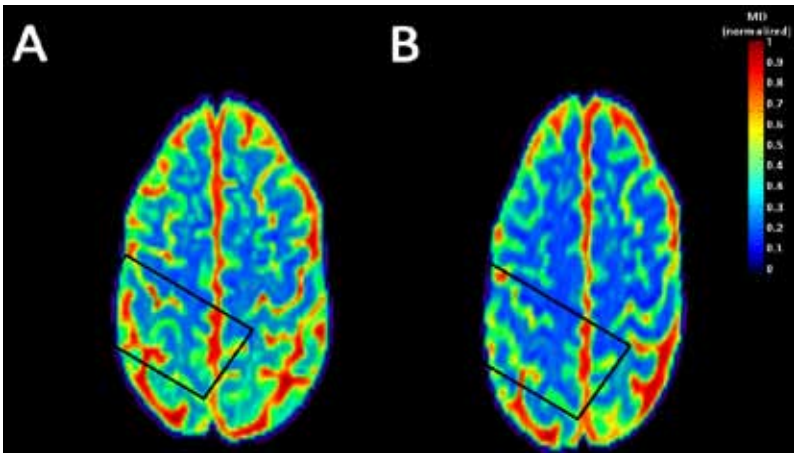
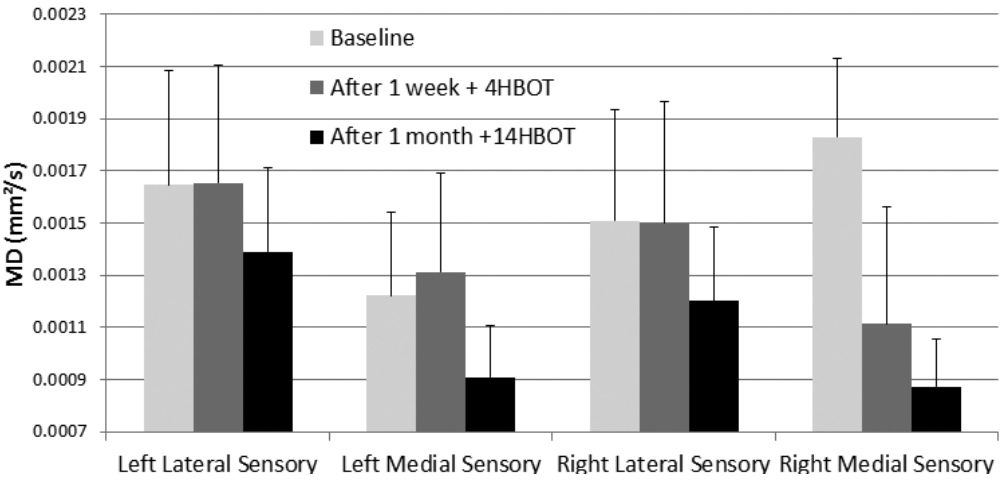


Figure 4

Mean diffusivity (MD) of grey matter/cortex using DTI imaging values; the right medial post-central gyrus, which is responsible for left leg sensation, showed the greatest change in MD, correlating with the diver's left-sided hypaesthesia



seen in the right medial post central area, which correlates anatomically with the patient's left-sided numbness (Figures 3 and 4).This is the first case in which DTI provides analysis of microstructural damage in DCS. With the increasing availability of this technology, DTI may add important information on the pathophysiology of DCS.

UNUSUAL FEATURES IN THIS CASE

Despite its unusual features, we believe this case represents atypical, shallow-water DCS, with delayed onset of neurological symptoms and signs, and associated with significant BBB damage on MRI.

Shallow water DCS

DCS is rare at depths of less than 10 msw, but neurological involvement is more likely in the presence of a PFO, as was demonstrated post injury in this diver.[12]

Delayed presentation

Most cases of DCS occur soon after surfacing, especially when the central nervous system (CNS) is involved. In a cohort of 1,070 CNS decompression patients, 56% of divers developed symptoms within 10 minutes and 90% within 4 hours after surfacing.[13] In the present case, the symptoms started 24 hours after surfacing, which is rare. Recently, the lymphatic system has been suggested as a slow carrier of micro-bubbles resulting in delayed presentation;[14] however, this delay could be related also to the time needed for endothelial dysfunction to develop.

DIFFERENTIAL DIAGNOSIS

Due to the unusual presentation, other neurological diagnoses should be considered. Subarachnoid haemorrhage commonly presents with acute, severe headaches and may be associated with nausea, vomiting and loss of consciousness. However, localizing signs, such as the hypaesthesia seen in our patient, are usually absent. Non-contrast CT performed within 6 hours of symptom onset, approaches 100% sensitivity.[25] Our patient had a negative CT scan in the first few hours from symptoms. A T2* MR sequence is more sensitive than CT in the subacute phase for detecting haemorrhage, which is seen as a low-intensity signal.[26,27] In our patient, the T2* sequence after three days did not demonstrate low signal intensities. Considering the extensive enhancement in our case, small and undetected subarachnoid haemorrhage is unlikely. Lumbar puncture should be considered with negative CT scan and high suspicion for haemorrhage, but was not considered to be indicated in this case.

Infectious meningitis commonly presents with fever and meningeal signs associated with signs of increased intracranial pressure such as headaches, nausea, vomiting, papilloedema, loss of consciousness and focal deficits. CT is usually normal in the early disease process. Of patients with meningitis, 90% may show post-contrast FLAIR hyperintensities in different locations; 70% of these also show post-contrast T1W hyperintensities.[28] Bacterial and viral meningitis exhibit enhancement that is typically thin and linear.[29] In our case, there were no post-contrast T1W changes, and post-contrast FLAIR showed diffuse and thick hyperintensities. Also, our patient did not have fever or meningeal signs, as well as normal blood tests. Again, owing to a low suspicion for an infectious cause, lumbar puncture was not performed. Moreover, the patient had clinical improvement after the first HBOT, which would not be expected in an infectious aetiology without concomitant antibacterial or antiviral agent administration.

Primary headaches syndromes (e.g., migraine, thunderclap headache) present with characteristic patterns of headache and have normal neurologic examination. In most cases, brain imaging is normal, yet in 12–46% of migraine patients, MR studies show white matter abnormalities,[30] which were not seen in our patient. Other iatrogenic causes for meningeal enhancement, such as oxygen administration or lumbar puncture were not done before the MR imaging.

HBOT FOR BRAIN RELATED INJURIES

Due to the delayed atypical symptoms, the shallow water diving profile and the fact that all bubbles would be dissolved by day three after surfacing, it was decided to use a 203 kPa, 90 minutes HBOT protocol rather than a US Navy Treatment Table 6 (USN TT6). In an animal model, HBOT has been shown to stabilize the BBB following a global cerebral injury.[31] However, in a recent study, we reported that divers with delayed decompression had better clinical outcomes when treated with USN TT6 compared to 203 kPa HBOT.[32]

In conclusion, we report a case of probable DCS-induced BBB disruption (demonstrated with special MRI techniques) in a diver with a PFO following a shallow scuba dive, treated with HBOT and resulting in full recovery, symptomatically and radiologically.

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