Diffusion tensor magnetic resonance imaging: A promising technique to characterize and track delayed encephalopathy after acute carbon monoxide poisoning.

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BACKGROUND
A delayed neurological syndrome (DNS) consisting of various forms of cognitive and motor impairment may develop within 8 weeks following 10 to 30% of cases of acute carbon monoxide (CO) poisoning (1-2). There is a paucity of generally accepted effective treatment and markers to predict clinical evolution of DNS (3). The regions most commonly involved in imaging abnormalities of DNS include the deep white matter and globus pallidus (4).

Diffusion weighted magnetic resonance imaging (DWI) is a technique that reflects patterns of molecular motion of water in the brain. In different brain disease states, loss of normal diffusion anisotropy is reported as abnormal values of diffusion coefficient represented by fractional anisotropy maps (5). DWI is thought to provide unique information for early identification of white matter changes and viability of brain tissue and therefore containing potential prognostic value. Diffusion of water in the brain can be defined along a single axis (defined by a single matrix) or along multiple encoding directions (multiple matrix amenable to be integrated mathematically). In the latter case, the image is designed as Diffusion Tensor Imaging (DTI) (6). DTI has been proposed as an effective tool for representing, quantifying and evaluating structural integrity of fiber tracks in the brain white matter (7). To our knowledge, there are no published reports of DTI evaluation of DNS.

We present a case of DNS with reversible neurological deficit in which sequential DTI demonstrated a closer correlation with initial clinical presentation and subsequent clinical evolution than conventional T2W, FLAIR or DWI sequences in magnetic resonance imaging (MRI).

CASE REPORT
A 51-year-old male was admitted in coma following acute CO poisoning. The patient recovered consciousness six hours after mechanical ventilation with 100% normobaric oxygen. After progressive improvement,
the patient was discharged from the hospital four days after admission, asymptomatic and apparently fully recovered. An MRI performed 7 days after discharge showed bilateral globus pallidus changes and moderate diffuse high intensity of white matter (Fig 1A).

Three weeks after the poisoning, the patient developed progressive neurological deterioration. Cognitive dysfunction included impaired executive attention and memory of recent events, dyscalculia, apathy, alexia, motor aphasia in the form of slow speech, agraphia and mutism. Motor dysfunction included bradykinesia, generalized hypertonia, axial and limb paratonia, loss of facial expression, decreased blinking with preserved although slow ocular movements, abasia, forced dorsal decubitus, hyperreflexia without Babinsky sign, bilateral grasp reflex more marked on the right side, right Marinesco sign and right palmomentale reflex. Patient was unable to swallow and a nasogastric tube was necessary for feeding. Within 10 days, the patient progressed to a state of akinetic mutism with urinary and fecal incontinence without sensory deficit and with normal visual fields. This constellation of symptoms and signs suggested a lesion localized in the frontal lobes, predominantly in the right. During this initial phase of DNS, conventional MRI images revealed diffuse increase in signal intensity in brain white matter (Fig 1B). Similar generalized high signal intensity was seen in DWI (Fig 1 C, D), which also demonstrated uniform diminution of values of Apparent Diffusion Coefficient (ADC) in the white matter of both frontal lobes (Fig 1E). These images suggested bilateral symmetric widespread brain involvement. In contrast with DWI, DTI fractional anisotropy maps (FAM) (Fig 2 A, B) and color maps (Fig

![Fig. 1](https://example.com/image1.png)

**Fig. 1.** A: Increased intensity of white matter on MRI one week after apparent full clinical recovery from acute CO poisoning. B: Further increase in intensity of white matter on MRI obtained 3 weeks later, during DNS. C, D: increased white matter signal as represented by DWI. E: DWI demonstrating low frontal ADC value (red arrows) during DNS. Four months after the start of DNS and nearly complete clinical recovery DWI shows reduced white matter hyperintensity (F & G); and normal ADC (H).
3 A) showed changes limited to the frontal lobes, with incomplete loss of visualization of neural tracts and with asymmetrical frontal periventricular WM changes. In DTI, mean FAM was 0.15 on right frontal and 0.24 on left frontal white matter respectively. The DTI results, therefore, correlated with the above-described neurological exam and suggested a localized lesion in the frontal areas (with right predominance) rather than a global brain injury.

After the development of DNS, the patient was treated with hyperbaric oxygen therapy (35 consecutive daily sessions of 45 min each at 2.5 ATA). After completion of the HBO series, the patient was placed on oral amitriptilin and bromocriptin, 25 mg and 2.5 mg per/day, respectively.

Commencing during the HBO treatment period, the patient experienced progressive improvement in symptomatology and three months after the development of DNS, neurological examination revealed strictly frontal signs: Marinesco sign and right grasp reflex, axial paratonia, and cognitive frontal-subcortical impairment assessed with conventional scales including Frontal Assessment Battery (FAB), Barthel Index, Folstein Mini Mental State Examination, and Rankin scale (8), (9).

Five months after onset, the patient was asymptomatic. At this time, his neurological examination was normal, except for minimal frontal dysfunction with some difficulty in task planning and minimal loss of memory. Conventional scores of tests of cognitive function normalized. At that time, FAM and color maps became nearly normal. In DTI, the diffusion pattern of frontal areas improved significantly, with almost complete recovery of normal anisotropy and normal visualization of neural tracts (Fig 2C and Fig 3B). In contrast with these results, the generalized hyperintensity signal by DWI was less, but persistent, and ADC improved with respect to the first study but did not normalize (Fig.1 F, G, H). While these images demonstrated improvement, they suggested a more significant residual generalized brain abnormality than what was reflected by clinical status.

**MR Imaging**

MRI was performed with a CVi/NVi 1.5 T imager (General Electric Medical System,
Milwaukee, WI) with a standard head coil. The following sequences were performed in the patient: axial T₁-weighted imaging (500/8 -TR-TE-), section thickness, 5 mm with 2 mm gap; field of view (FOV), 24 cm; acquisition matrix 288 x 160, Fast Liquid Attenuated Inversion Recovery (FLAIR) weighted imaging (11000/110/2200 -TR/TE/TI-); axial T₂-weighted imaging (4000/100 -TR/TE-), section thickness, 5 mm with 2 mm gap; FOV, 24 cm, acquisition matrix 320 x 224.

Diffusion-tensor imaging was performed by single-shot spin echo-planar imaging (7600/minimum -TR/TE-), FOV, 24 cm, acquisition matrix, 128 x 128. By use of a 5-mm section thickness without gap, images were acquired throughout the entire brain. Diffusion-sensitizing gradient encoding was applied in 31 directions by use of a diffusion-weighted factor (b value = 1000 s/mm²), and one image was acquired without use of a diffusion gradient (i.e.: b value = 0 s/mm²). Sixteen images were obtained at each section, yielding an approximate total of 496 images. DTI time was roughly 5 minutes. The DW-MR image time was transferred to an Advantage Workstation (GE medical system) for data processing by using a commercial software program (Functool, GE Medical System) to generate qualitative maps. MR Data Analysis: Conventional MR images were evaluated for the severity of WM bundle fibers. Quantitative values of fractional anisotropy were measured by manually placing normal on round shaped regions of interest (ROIs) onto FA maps (performed by the same radiologist). ROIs were placed on sites identical on both cerebral hemispheres on frontal periventricular and subcortical WM. Regions were first defined on conventional FLAIR images, and ROIs were transferred onto FA maps at the identical level. ROIs were placed such that they encompassed as much WM as possible, and care was taken to avoid gray matter and CSF.

DISCUSSION

We present a case of severe DNS after CO poisoning that improved after five months to near normalcy. The contribution of HBO to the favorable clinical outcome remains uncertain, since a significant number of patients with
DNS improve spontaneously (13). We hereby show DTI images during the acute phase and eventual evolution of DNS that in contrast with conventional MRI and DWI, correlated well with the clinical evolution. Considering the current lack of markers for prognosis and objective tracking of the evolution of DNS, this observation suggests that DTI may become an important additional tool in the management of the disease and in the objective evaluation of therapeutic intervention.

Conventional MRI findings in patients with DNS following CO poisoning has been well described in the literature. Several authors showed diverse degrees of subcortical and periventricular white matter lesions (usually ascribed to demyelination) and bilateral globus pallidus involvement (10-11). Teksan et al. (12) first showed DWI findings of acute CO poisoning, including additional lesions in right frontal lobe cortex not seen on FLAIR images. Recently, Kim et al. reported five patients with delayed encephalopathy after CO poisoning who presented diffuse high signal intensity, as well as confluent areas in periventricular white matter and centrum semiovale in conventional MRI and DWI. The authors speculated that late development of cytotoxic edema or some other mechanism related to accumulation of unknown toxic biochemical products resulted in restricted diffusion of water in brain tissue (11).

In agreement with the above observations, we found on MRI in our patient after the development of DNS diffuse bilateral white matter hyperintensities and globus pallidus lesions. At the same time, we observed a mismatch between DWI and DTI: in DWI we found changes suggesting generalized bilateral restriction of diffusion, while DTI demonstrated changes restricted to the frontal lobes, in the form of asymmetrical involvement of frontal white matter. This representation of localized frontal white matter changes correlated well with the syndrome clinically associated to frontal areas and the asymmetrical neurological defect found on neurological examination described above. In contrast with DTI, DWI and ADC presented a picture consistent with generalized brain damage, which is associated with a much worse prognosis than a localized damage to the frontal lobes as demonstrated by DTI.

After recovery, DWI demonstrated reduction but not disappearance of the hyperintensity signal and improvement but not normalization in ADC compared with the previous study. In DTI, the pattern of frontal areas improved significantly, with almost complete recovery of normal anisotropy and with normalization of imaging of neural tracts. Once again, the latter images paralleled findings on clinical exam at that stage of the evolution.

In summary, the initial presentation and eventual improvement in white matter changes detected by DWI followed the general direction of clinical evolution of the DNS, but did not accurately reflect topographical representation of neurological deficits as they were represented by DTI. Moreover, DWI during the initial phase of this case of DNS suggested more generalized and advanced brain damage, and consequently according to standard interpretation, a worse prognosis than suggested by DTI. In addition, unlike DWI, sequential DTI accurately reflected quantitative clinical improvement.

In conclusion, DTI appears to improve the diagnostic capacity to localize and assess the nature and extension of brain damage in DNS. As data accumulates, this information may be of prognostic value. addition, sequential analysis of white matter water diffusion properties may add in tracking structural brain repair and consequently in the evaluation of therapeutic intervention for DNS.
REFERENCES

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