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MRI-based brain volumetry in chronic whiplash patients: no evidence for traumatic brain injury

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Introduction – Cognitive complaints, such as poor concentration and memory deficits, are frequent after whiplash injury and play an important role in disability. The origin of these complaints is discussed controversially. Some authors postulate brain lesions as a consequence of whiplash injuries. Potential diffuse axonal injury (DAI) with subsequent atrophy of the brain and ventricular expansion is of particular interest as focal brain lesions have not been documented so far in whiplash injury. *Objective* – To investigate whether traumatic brain injury can be identified using a magnetic resonance (MR)-based quantitative analysis of normalized ventricle–brain ratios (VBR) in chronic whiplash patients with subjective cognitive impairment that cannot be objectively confirmed by neuropsychological testing. *Materials and methods* – MR examination was performed in 21 patients with whiplash injury and symptom persistence for 9 months on average and in 18 matched healthy controls. Conventional MR imaging (MRI) was used to assess the volumes of grey and white matter and of ventricles. The normalized VBR was calculated. *Results* – The values of normalized VBR did not differ in whiplash patients when compared with that in healthy controls ($F = 0.216$, $P = 0.645$). *Conclusions* – This study does not support loss of brain tissue following whiplash injury as measured by VBR. On this basis, traumatic brain injury with subsequent DAI does not seem to be the underlying mechanism for persistent concentration and memory deficits that are subjectively reported but not objectively verifiable as neuropsychological deficits.

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Introduction

Common whiplash injury is a controversial disorder in most aspects. It usually results from an acceleration/deceleration injury to the neck in car accidents. Common whiplash injury excludes head contact injury and loss of consciousness including post-traumatic amnesia (1, 2). Although around 80% of patients suffering a whiplash injury recover within 6 months, some patients develop chronic somatic, psychological and cognitive complaints, resulting in disability (1, 2). The most frequently reported persistent symptoms are neck pain, headache, attention and memory deficits (2). In most cases, the origin of these complaints is unknown, and detailed neurological examination does not reveal any somatic dysfunctions. The lack of objective signs has led to various hypotheses regarding the origin of cognitive complaints. Some authors mainly assumed underlying psychological factors (3). Others have argued that whiplash injury is a disorder mainly caused by litigation and outcome expectancies (4, 5). Furthermore, brain damage resulting from whiplash injury has been discussed (6), but conventional MRI or positron emission tomography (PET) and single photon emission computed tomography (SPECT) have not revealed any consistent findings indicating brain damage after whiplash injury (7).

The cognitive symptoms of chronic whiplash patients are similar to those of patients with mild traumatic brain injury (MTBI). Even in the absence of a head trauma, altered consciousness, amnesia and structural lesions in cerebral MRI, brain injury that is either diffuse or selectively focal, e.g. in the cingulum, cannot be fully excluded in whiplash patients (6). In acceleration–deceleration injury, the mechanism of diffuse axonal injury (DAI) is of particular interest. Animal experiments have shown that pure acceleration forces on the skull can cause DAI (8). DAI has also been shown in humans after MTBI (9). DAI leads to brain atrophy, particularly of cerebral white matter, with subsequent expansion of the brain ventricles. Ventricular expansion after MTBI has been shown in several studies (10–13). The quantitative MR-based measurement of brain and ventricle volumes, resulting in the so-called ventricule–brain ratio (VBR), has been shown to be a valid method to detect changes in brain degenerative dementias or due to DAI following MTBI (14, 15). In addition, VBR correlated well with cognitive deficits (14), and both VBR and cognitive performance correlated significantly with the severity of brain injury (15). In this study, we used the method of MR-based measures of VBR to test the hypothesis of cerebral damage resulting in tissue loss after whiplash injury in patients with persistent symptoms.

Materials and methods

Subjects

Twenty-one patients with persistent symptoms after having suffered a whiplash injury and 18 healthy controls were scanned according to the same protocol at the same hospital-based MRI unit.

Patients

None of the patients with whiplash injury reported a direct head trauma, altered consciousness, or any amnesia during or after the accident. All patients had suffered rear-end car collisions and were classified as grade I or II according to the Quebec Task Force (16). Patients were recruited from primary care physicians by announcing the study in a Swiss medical journal. All patients underwent a detailed neurological examination and neuropsychological testing. None of them had a major medical illness. The average delay between accident and recruitment for the study was 9.05 months (SD 3.26, range 5–16 months). All patients suffered from persistent head and neck pain and all reported cognitive complaints (memory deficits and difficulties in concentration) sufficient to request medical treatment.

Controls

The healthy controls were recruited by announcing the study in a newspaper. Controls were included if they reported to be healthy, have no pain, had never suffered a whiplash injury or a traumatic brain injury or any other major neurological disease and had the requested age, sex and educational level. Patients and healthy controls did not differ significantly in age, gender or education (see Table 1).

Methods

Magnetic resonance imaging – A localization series in three planes was performed on a Magnetom Symphony SMI-5 Turbo Sparc/1.5 T MRI; Siemens, Erlangen, Germany. Sagittal T1-weighted, inversion recovery series (5 mm slice thickness, 0.5 mm slice gap, TR (repetition time): 6000 ms, TE (echo time): 60 ms, TI (inversion time): 350 ms, FOV (field of view): 260 mm, matrix: 256 × 198, one transmission, acquisition time: 1 min and 54 s) and transversal T1-weighted, three-dimensional MPRAGE (magnetization prepared rapid gradient echo imaging; three-dimensional turbo gradient echo sequence; TR: 11.08 ms, TE: 4.3 ms, flip angle: 15°, FOV: 200 mm, matrix: 256 × 190, one transmission, acquisition time: 10 min and 34 s) were obtained. The scans were saved under a randomly assigned number. Images were saved on optical discs and then transferred to a Windows-based microcomputer.

Image analysis – Images were transferred to a microcomputer on which they were analysed quantitatively. Two trained observers, who were blind to clinical data, performed the quantitative MRI analysis. The measurement of brain tissue

Table 1 Demographic data of the whiplash patients and the healthy controls

	Age in years mean (SD)	Education in years mean (SD)	Gender, % female/% male
Whiplash patients (n = 21)	35.7 (10.6)	12.1 (1.4)	71/29
Healthy controls (n = 18)	38.2 (10.2)	11.9 (0.8)	72/28
Statistics	F = 0.56, P = 0.46	F = 0.18, P = 0.68	Pearson χ^2 = 0.003, P = 0.96

and ventricle volumes was performed using the software OSIRIS version 4.11 (Digital Imaging Unit, Radiology Department, University Hospital of Geneva, Switzerland, online at: http://www.expasy.org/www/UIN/html1/projects/osiris/osiris.html). In all subjects, transverse slices were used for analysis. Brain tissue volume was measured by a standardized semi-automated segmentation procedure called 'region growing'. With this procedure, a polygon including the areas with similar grey scales is created by the computer. For this purpose, we defined a seed value of 80 and a tolerance of 30 in every scan. If the computer included parts of the head other than brain tissue (e.g. eye tissue), these parts were cut away manually. The measurement started in the most superior slice showing one or both lateral ventricles. Measurements ended in the first inferior slice showing the optic chiasm. To obtain the brain volume, we first subtracted the area of ventricles from the area of brain tissue. We then added the brain tissue area of all slices and multiplied the result by 5.5 mm (corresponding to the sum of the gap between the slices and the slice thickness).

Figure 1 shows a measurement of brain tissue. Ventricles were also measured by a standardized semi-automated procedure. In Osiris, this procedure is called 'intensity isocontours'. In this procedure, the contours of a defined area are highlighted by the computer. In this way, the ventricles are given a clearly defined contour. By following the contour manually, we obtained a polygon including the entire area of the ventricles. Ventricle volume measurement started in the most superior slice showing one or both lateral ventricles and ended in the most inferior slice on which the temporal horn was still visible in one or both hemispheres. To obtain the ventricle volume, the added ventricle areas of all slices were multiplied by 5.5 mm (corresponding to the sum of the gap between the slices and the slice thickness).

Figure 2 shows the contours of the ventricles as highlighted by the semi-automated procedure. The randomly selected MRI scans of five subjects were used to establish inter-rater reliability. For measurement of cerebral tissue, inter-rater reliability was $r = 0.9997$ ($P < 0.05$), and, for ventricular measurements, inter-rater reliability was $r = 0.9980$ ($P < 0.05$). Brain tissue volume and ventricular volume of the left and right hemispheres were added separately resulting in a total brain volume and a total ventricular volume for each patient. VBR was calculated by dividing the ventricular volume by the brain volume. To correct for different brain sizes, the VBR was normalized. The normalization procedure was performed by measuring the horizontal distance between the frontal and the occipital poles on the horizontal

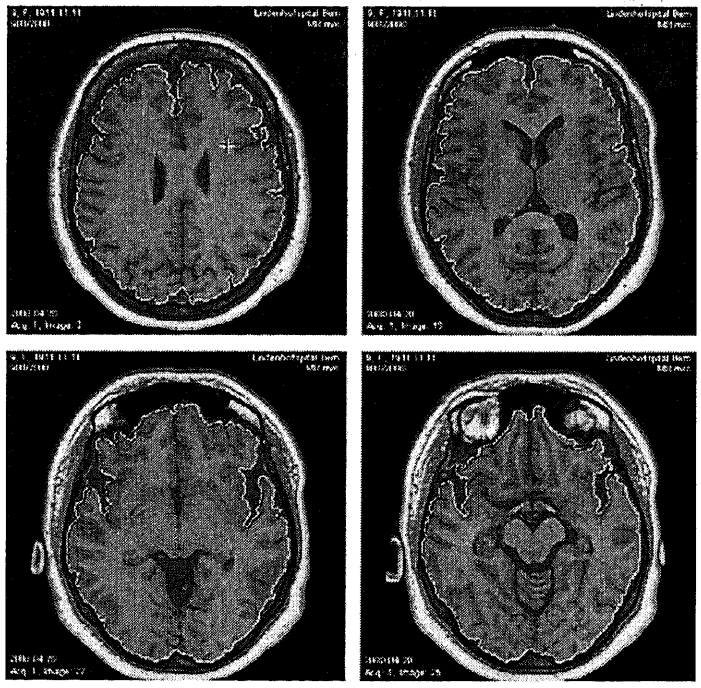

Figure 1. Measurement of brain tissue: the outlined areas in these representative slices show the highlighted contours of brain tissue as performed by the semi-automated procedure.

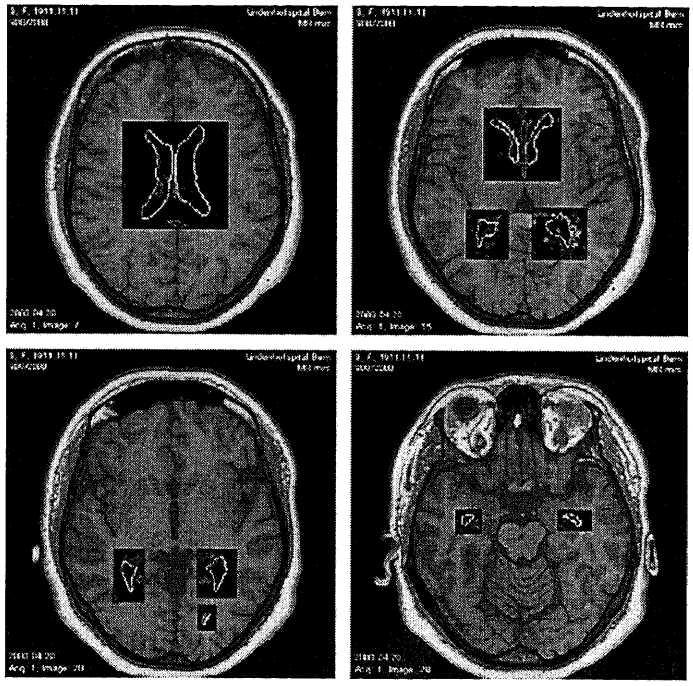

Figure 2. Measurement of ventricles: the outlined areas in these representative slices show the highlighted contours of the ventricles as performed by the semi-automated procedure.

slice showing the largest distance. VBRs were then normalized by using the average extension of the entire study group between the frontal and the occipital poles.

Neuropsychological tests – Various aspects of attention and concentration were tested in the whiplash group. By using the computer-based 'Test battery for Attention Assessment' (17), we assessed tonic and phasic alertness, divided attention and working memory. The Stroop test was used to assess the aspect of executive functioning (18).

Statistical analysis

Group differences of brain volumetry were assessed by independent *t*-test. The Pearson *r* statistic was used for correlations between continuous variables. The threshold for statistical significance was set at 0.05. To compare nominal variables, we used Pearson chi-squared test.

Results

The results of the VBR measurement in whiplash patients and in healthy controls are summarized in Table 2. The comparison of the two groups by *t*-test showed no statistically significant group difference ($t = 0.218$, $P = 0.83$).

Table 2 Results of ventricle–brain ratios (VBR) measurement

	Normalized VBR, mean (SD)	Correlation of VBR and age, Pearson r (P)	Correlation of VBR and education, Pearson r (P)	Gender differences in VBR, F (P)
Whiplash patients ($n = 21$)	0.030 (0.014)	0.360 (0.10)	0.545 (0.01)	8.730 (0.01)
Healthy controls ($n = 18$)	0.031 (0.019)	0.764 (0.000)	−0.096 (0.70)	5.879 (0.03)
Entire group ($n = 39$)	0.030 (0.016)	0.564 (0.000)	0.265 (0.10)	12.766 (0.001)

The correlations of VBR with age and education are shown in Table 2. The VBR correlated significantly with age in the entire sample and in the healthy controls ($P < 0.05$). In whiplash patients, the correlation between VBR and age was not significant ($P = 0.10$). VBR correlated significantly with education in whiplash patients ($P < 0.05$), but no such correlation was found in the healthy controls or in the entire sample ($P = 0.10$). For both groups and for the entire sample, significant differences were found between VBRs of males and females ($P < 0.05$).

Ventricle–brain ratios did not correlate significantly with any neuropsychological test result in the whiplash group (Table 3). We could, however,

Table 3 Neuropsychological test results in whiplash patients and correlation with VBR

	Tonic alertness (reaction time T-score)	Phasic alertness (reaction time T-score)	Divided attention (errors T-score)	Working memory (errors T-score)	Stroop test (errors in trial C)
Whiplash patients (n = 21)	47.33 (6.99)	50.86 (9.63)	47.95 (7.79)	47.67 (9.23)	0.9 (1.38)
Correlation with VBR Pearson r (P)	0.334 (0.14)	−0.185 (0.42)	0.023 (0.92)	0.12 (0.61)	−0.28 (0.21)

Values are given as mean (SD).

not correlate with individual cognitive deterioration, as no pretraumatic tests were available. As the average test scores of whiplash patients were within the range of the test norms (Table 3), we did not perform neuropsychological testing with the healthy controls.

Discussion

This quantitative MR-based study does not show any statistically significant difference between the VBRs of patients suffering from persistent symptoms following a whiplash injury and healthy matched controls. Furthermore, the test results of attention and executive functioning did not correlate with VBR in the whiplash group. Interestingly, all average neuropsychological test results of whiplash patients were within the normal range according to the test norms despite subjective symptoms. However, VBRs in both groups were related to demographic variables, such as age, gender and education, a well-documented finding from previous studies in healthy people (19). The method used has been shown to be sensitive in the detection of brain atrophy in several conditions such as early primary degenerative dementias (14) or mild-to-moderate traumatic brain injury (15). Our findings do not support the hypothesis of cerebral damage, cerebral trauma or DAI resulting from whiplash injury and suggest that cognitive complaints in whiplash injury, even if persistent, do not have the same underlying mechanisms as in traumatic brain injury (TBI).

This study, however, has several limitations preventing final conclusions: (i) the MR methodology used to evaluate brain tissue loss may not be sensitive enough to detect very mild diffuse atrophy or selective focal atrophy, e.g. in the prefrontal cingulum; (ii) the method certainly will not detect functional (not structural) defects such as defective activation of certain brain areas; (iii) the neuropsychological test battery used may not be adequate for the complaints, yet these tests are well established and validated in this setting; (iv) the patients analysed may not be representative of the whole group of whiplash patients as they represent only the very mildly injured; however, we selected patients with long-term symptoms; v) the sample size was rather small.

The results of this study are in line with previous structural and functional imaging investigations where no evidence for a traumatic brain injury after whiplash injury was found (7, 20). The results of these studies suggest again that the origin of cognitive complaints in whiplash patients cannot be attributed to traumatic cerebral damage caused by the accident. In previous research, the role of various other factors causing cognitive disturbances was discussed. Some authors argued that the intensity of pain (1) or the use of centrally acting medication such as analgesics (1, 21) is primarily responsible for cognitive impairment of whiplash patients. Regarding pain symptoms previous research showed that the intensity of headache was significantly related to focused attention in whiplash patients (22). Other authors argued that psychological factors, such as anxiety and depression, the patient's expectations and also litigation may contribute significantly to the subjective perception of cognitive deficits (23). The recently published study by Robinson et al. confirms the importance of these factors and demonstrates equal performance on neuropsychological testing in patients with or without cognitive symptoms after whiplash. Based on these results cognitive complaints were attributed to heightened somatic vigilance (24).

Although this study included whiplash patients who complained of subjective loss of concentration and memory deficits, all patients scored within the normal range on neuropsychological testing. This may indicate the mainly subjective nature of cognitive complaints of whiplash patients the basis of which, as discussed previously, may be that they are suffering pain (1, 22) or psychological problems (23) and, consequently, organic brain failure in whiplash cannot be assumed. Therefore, taken strictly, our conclusion cannot be applied to whiplash patients who demonstrate deficits on neuropsychological testing.

In conclusion, our quantitative analysis of VBR provides evidence that whiplash injury without direct trauma to the head, without loss of consciousness and without post-traumatic amnesia,

even when symptoms are persistent over months, does not cause brain damage in the form of a diffuse axonal loss, for example. However, these results certainly must be confirmed with a larger patient sample, with patients demonstrating cognitive deficits and also using more sensitive imaging methodology to detect diffuse or focal brain damage.

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References

1. Radanov BP, Di Stefano G, Schnidrig A, Sturzenegger M. Cognitive functioning after common whiplash: a controlled follow-up study. Arch Neurol 1993;**50**:87–91.
2. Radanov BP, Sturzenegger M, Di Stefano G. Long-term outcome after whiplash injury – a two years follow-up considering features of accident mechanism, somatic, radiological and psychosocial findings. Medicine 1995; **74**:281–97.
3. Hodge JR. The whiplash neurosis. Psychosomatics 1971;**12**: 245–9.
4. Schrader H, Obelieniene D, Bovim G et al. Natural evolution of late whiplash syndrome outside the medicolegal context. Lancet 1996;**347**:1207–11.
5. Obelieniene D, Schrader H, Bovim G, Miseviciene I, Sand T. Pain after whiplash: a prospective controlled inception cohort study. J Neurol Neurosurg Psychiatry 1999;**66**:279–83.
6. Alexander MP. In the pursuit of proof of brain damage after whiplash injury. Neurology 1998;**51**:336–40.
7. Radanov BP, Bicik I, Dvorak J, Antinnes J, von Schulthess GK, Buck A. Relationship between neuropsychological and neuroimaging findings in patients suffering from late whiplash syndrome. J Neurol Neurosurg Psychiatry 1999;**66**:485–9.
8. Gennarelli TA, Thibault LE, Adams JH, Thompson CJ, Marcincin RP. Diffuse axonal injury and traumatic coma in the primate. Ann Neurol 1982;**12**:564–74.
9. Blumbergs PC, Scott G, Manavis J, Wainwright H, Simpson DA, McLean AJ. Topography of axonal injury as defined by amyloid precursor protein and the sector scoring method in mild and severe closed head injury. J Neurotrauma 1995;**12**:565–72.
10. Bigler ED, Kurth SM, Blatter D, Abildskov TJ. Degenerative changes in traumatic brain injury: post-injury magnetic resonance identified ventricular expansion compared to pre-injury levels. Brain Res Bull 1992;**28**:651–3.
11. Bigler ED, Burr R, Gale S et al. Day of injury CT scan as an index to pre-injury brain morphology. Brain Inj 1994;**8**:231–8.
12. Levi L, Guilburd JN, Lemberger A, Soustiel JF, Feinsod M. Diffuse axonal injury: analysis of 100 patients with radiological signs. Neurosurgery 1990;**27**:429–32.
13. Blatter DD, Bigler ED, Gale SDS et al. MR-based brain and cerebrospinal fluid after traumatic brain injury: correlation with neuropsychological outcome. Am J Neuroradiol 1997;**18**:1–10.
14. Bigler ED, Neely ES, Miller MJ et al. Cerebral volume loss, cognitive deficit and neuropsychological performance: comparative measures of brain atrophy. I. Dementia. J Int Neuropsychol Soc 2004;**10**:442–52.
15. Gale SD, Baxter L, Roundy N, Johnson SC. Traumatic brain injury and gray matter concentration: a preliminary voxel based morphometry study. J Neurol Neurosurg Psychiatry 2005;**76**:984–8.
16. Spitzer WO, Skovron ML, Salmi LR, Cassidy JD, Duranceau J, Suissa S. Scientific monograph of the Quebec Task Force on whiplash associated disorders: Redefining 'whiplash' and its management. Spine 1995;**20**(Suppl.): 1S–73S.
17. Zimmermann P, North P, Fimm B. Diagnosis of attentional deficits: theoretical considerations and presentation of a test battery. In: Stachowiak FJ, ed. Developments in the assessment and rehabilitation of brain-damaged patients. Perspectives from a European concerted action. Tübingen: Günter Narr Verlag, 1993;3–15.
18. Regard M. Cognitive rigidity and flexibility: a neuropsychological study. PhD Thesis. BC, Canada: University of Victoria, 1981.
19. Blatter D, Bigler E, Gale SD et al. Quantitative volumetric analysis of brain MR: normative database spanning 5 decades of life. Am J Neuroradiol 1995;**16**:241–51.
20. Borchgrevink G, Smevik O, Haave I, Haraldseth O, Nordby A, Lereim I. MRI of cerebrum and cervical columna within two days after whiplash neck sprain injury. Injury 1997;**28**:331–5.
21. Di Stefano G, Radanov BP. Course of attention and memory after common whiplash: a two-years prospective study with age, education and gender pair-matched patients. Acta Neurol Scand 1995;**91**:346–52.
22. Blokhorst M, Swinkels M, Lof O, Lousberg R, Zilvold G. The influence of 'State' related factors on focused attention following whiplash associated disorder. J Clin Exp Neuropsychol. 2002;**24**:471–8.
23. Sullivan MJ, Hall E, Bartolacci R, Sullivan ME, Adams H. Perceived cognitive deficits, emotional distress and disability following whiplash injury. Pain Res Manag 2002;**7**:120–6.
24. Robinson JP, Burwinklw T, Turk DC. Perceived and actual memory, concentration, and attention problems after whiplash-associated disorders (Grades I and II): prevalence and predictors. Arch Phys Med Rehabil 2007;**88**:774–9.