Rom J Leg Med [2] 115 – 120 [2010]
DOI: 10.4323/rjlm.2010.115
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Dilemmas surrounding the occurrence mechanism of cerebral diffuse vascular injury

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Abstract: The multiple petechial hemorrhages in the white brain matter, i.e. the diffuse vascular injury is a kind of diffuse brain injury which occurrence mechanism hasn't been explained so far. In a purpose to enlighten some dilemmas surrounding this, in this paper 11 cases with diffuse vascular injury, that make 18% from a material of 60 closed head injury cases where forensic neuropathological examination was conducted, were analyzed regarding these several issues: the type of traumatic event; the survival time; the presence and the extent of the skull fractures; and particularly, the mutual correlation between the diffuse axonal injury, which is known to occur as a result of acceleration-deceleration rotational forces, and the diffuse vascular injury, whose mechanism of occurrence has hitherto not been established.

Our results indicate that diffuse vascular injury is a fatal diffuse brain injury with a survival time of up to several hours (4 hours is longest time in our material) that occurs mainly in traffic accidents, but also in some cases of a fall from height. Most of them are accompanied by extensive damage to the bones of the skull, implying that this kind of injury occurs as a result of the direct impact of a high-intensity force on the head. There are differences between diffuse vascular injury and diffuse axonal injury regarding some of the analyzed issues which is why we believe that these are two distinct types of diffuse brain injury and not different degrees of manifestation of the same type of brain injury.

Key words: diffuse vascular injury; closed head injury; traumatic brain damage; diffuse brain damage

In a head injury obviously occurred as a result of the impact of the high intensity force, it is often medical doctor to perceive extensive injuries to the scalp and the bone tissue, but almost nothing in a brain tissue, except for minute spotty haemorrhages diffusely arranged throughout the white brain matter. This injury represents a diffuse vascular injury (DVI) and its importance was first stressed by Tomlinson in 1970 [1] who suggested that injuries with such an appearance and distribution are incompatible with life.

This description was supported by other authors [2,3], who reached the conclusion that it is more appropriate to treat DVI as diffuse brain damage, bearing in mind its wide distribution throughout the brain and the brain stem.

Macroscopically, the injury is manifested with multiple minute haemorrhages "petechial haemorrhages" throughout the white brain matter which are particularly pronounced in the front poles of the frontal and temporal lobes, and also in the white matter surrounding the thalamus and in the brain stem. Microscopically, they can be seen as periarterial, perivenous and pericapillary haemorrhages.

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The mechanism of occurrence of DVI has hitherto not been established, even there have been some attempts. It is clear that it occurs as a result of the impact of high-intensity dynamic force, but unlike the diffuse axonal injury (DAI) which, as was experimentally proved, occurs as a result of the impact of acceleration-deceleration rotational forces, DVI has not been experimentally reproduced so far.

9	F 22	TA-ped	1 h			Fr, SAH	Cont	DVI
10	M 39	TA-driver	4-5 h	HOSP	Coma, GCS=3	Fr, SAH, IVH	Cont	DVI, DAI 1
11	M 89	TA-ped	3 h	HOSP	Coma	SAH		DAI 1
12	M 23	TA-driver	2 d	HOSP+	Coma, GCS=3	SAH, SDH		DAI 3,
13	M 28	TA-pass	Imm			Fr, SAH		Swell
14	F 19	TA-ped	1/2 h			SAH		Swell
15	M~60	F-height	3,5 w	HOSP	Sopor	Fr, SDH, SAH	Cont	Swell
16	M 40	TA-ped	11 d	HOSP	Coma	Fr, SAH		DAI 1, Swell
17	M 33	TA-driver	3 d	HOSP	Coma, GCS=3	Fr, SAH		DAI3,Swell,ISH
18	M 26	F-height	12 d	HOSP+	Coma, GCS=3	Fr, EDH, SDH, SAH	Cont c-c	DAI3,Swell,ISH
19	M 45	TA-motor	Imm			Fr, SAH		DVI, signs of DAI
20	M~50	RA	10 d	HOSP+	Coma	Fr		Swell
21	F 38	TA-pass	Imm			SAH		DVI
22	M 30	TA-motor	10 d	HOSP	Coma, GCS=5	Fr, SAH, SDH	Cont c-c	AI-ish, Swell, ISH
23	M 70	F-height	Imm			Fr, SAH		Swell
24	M~35	F-height	2 d	HOSP+	Coma, GCS=4	Fr, EDH, SDH, SAH, IVH	Cont c-c	Swell
25	M 55	F-height	1,5 m	HOSP+	Coma, GCS=3	EDH, SAH	Cont	Swell, ISH, DAI1
26	M 69	TA-cyc	3 w	HOSP+	Coma	Fr, SDH, SAH	Cont c-c	AI-ish, Swell, ISH
27	F~70	TA-ped	3 d	HOSP+	Coma	Fr,SDH, SAH,IVH	ICH	DAI2/3,Swell, ISH
28	F~60	TA-ped	1-2 h	HOSP	Coma	SAH		
29	M 10	TA-ped	8 d	HOSP	Coma, GCS=4			Swell, ISH, DAI1
30	F 17	TA-ped	1/2h			SAH		Swell
31	M 43	F-height	Imm			Fr, SAH		DVI
32	F 75	F-height	Imm			Fr, SAH	Cont	DVI
33	M 81	TA-cyc	15 d	HOSP	Coma	Fr, SDH, SAH	Cont c-c	Swell, DAI 1
34	F 64	TA-ped	4 d	HOSP	Coma, GCS=3	Fr, SDH, SAH	Cont	Swell, DAI2/3, ISH
35	M 61	TA-cyc	5 d	HOSP	Coma	Fr, SAH, IVH	Cont, ICH	DAI 2, ISH, Swell
36	M 60	F-simple	7 d	HOSP+	Coma	SDH, SAH	Cont c-c	AI-ish, Swell, ISH
37	M~30	TA-pass	4 h	HOSP	Coma			DAI2, Swell, ISH
38	M~50	Blow	3-5h	HOSP+	Coma, GCS=3	Fr, SDH, SAH, IVH	Cont	Swell, ISH
39	M 60	TA-ped	1 m	HOSP+	Coma, GCS=8	SDH, SAH, IVH		DAI 2, Swell, ISH
40	M 37	F-simple	5 d		Sopor	Fr, EDH, SDH,	Cont	Swell
41	M 26	F-height	min			Fr, EDH, SDH, SAH		DVI
42	M 53	TA-driver	min			Fr, SAH		DVI
43	M 30	TA-driver	2-3h	HOSP	Coma	Fr, SAH		DAI3, Swell, ISH
44	M 29	TA-driver	Imm			Fr fac, SAH		DVI
45	M 60	TA-pass	Imm			Fr, SAH		DVI, DAI 2, Swell
46	F 74	TA-ped	3-4h	HOSP	Sopor	SAH		DAI 1
47	M 70	TA-ped	4 h	HOSP	Coma	Fr, SAH		
48	F 56	TA-ped	1-2h	HOSP		Fr, SAH		DVI, DAI 2, Swell
49	F 46	TA-ped	24 h	HOSP	Coma	SAH		DAI 1, Swell, ISH
50	M 25	TA-motor	4 d	HOSP	Sopor			DAI 1, ISH
51	M~50	TA-cyc	7 h	HOSP	Coma, GCS=4	Fr, SAH	Cont c-c	DAI 3, Swell, ISH
52	F 94	Blow	1-2h			Fr, SAH, IVH		
53	M 63	F-simple	10 d	HOSP	Coma, GCS=7	Fr, EDH, SAH	Cont c-c	ISH, Swell, AI-ish
54	M 67	TA-ped	2,5 d	HOSP	Sopor	Fr, SDH, SAH	Cont c-c	Swell
55	F 72	TA-ped	6d	HOSP	Coma, GCS=6	Fr, SDH, SAH	Cont	DAI2/3, Swell,ISH
56	M 55	B-F	5d	HOSP+	Coma	Fr, SDH, SAH	Cont	Swell
57	M 58	F-height	6 d	HOSP	Coma	Fr, SDH, SAH	Cont c-c	Swell, ISH
58	M 59	F-height	1-2h	HOSP+	Coma, GCS=4	Fr, SDH, SAH	Cont c-c	Swell, DAI 2/3, ISH
59	F 20	TA-ped	7 d	HOSP+	Coma	Fr, EDH, SDH, SAH	Cont	DAI 2, Swell, ISH
60	M 50	RA	2 d	HOSP	Coma	Fr, SAH		DAI1, Swell

Table 1. Case-material with clinical data and findings from forensic medical autopsy and forensic neuropathological examination

* A-G - age and gender; Trauma - type of traumatic event where closed head injury occurred: TA - traffic accident (ped - pedestrian, cyc - cyclist, mcyc - motorcyclist; pass - passenger; RA - railway accident), F - fall (F-simple - fall from one's own height, F-height - fall from a height of more than 2 metres), B-F - blow and fall; TS - time of survival (imm - immediate death; min -minutes; h -hour; d -day, w -week, m - month); Hospitalisation (HOSP - hospitalised, HOSP+ - hospitalised and receiving surgical intervention); Consciousness - state of consciousness immediately after the impact (GCS - Glasgow Coma Score); Fr - fractures of the skull, ICH - intracranial haemorrhage (SAH - subarachnoidal haemorrhage, EDH - epidural haematoma, SDH - subdural haematoma, IVH - intraventricular haemorrhage); FBI - focal brain injury (cont - contusion, cont c-c - contusion coup-contra-coup, ICH - intracerebral haemorrhage); DBI - diffuse brain injury (DAI 1, 2, 3 - diffuse axonal injury - Adams grading system (Adams 1989); AI - microscopically diagnosed axonal injury with ischemic pattern; DVI - diffuse vascular injury; ISH - ischemia; Swell - brain swelling.

Based on our own experiences, in this paper we made a try to enlighten some dilemmas surrounding the mechanism of occurrence of DVI. 11 cases with DVI were analyzed with a regard to these several issues: the type of traumatizing event that led to the brain injury and DVI: traffic accidents, blow or fall; DVI in correlation with the survival time; the presence and the extent of the skull fractures; and particularly the correlation between DAI, which is conclusively proved to occur as a result of the impact of acceleration-deceleration rotational forces and DVI, whose occurrence mechanism thus far hasn't been established.

Materials and methods

The forensic neuropathological examination [4] was conducted on 60 closed head injury cases, previously subjected to forensic medical autopsy and complete forensic investigation (Table 1). Cases with a post mortem interval of up to 24 h for which there was undeniable evidence regarding the source of the head trauma were included in the study, while cases with a post-mortem interval longer than 24 hours and open cranial-cerebral injuries (impressive and comminutive fractures of the skull bones breaching the dura mater, and firearm injuries) were not included. The material comprises 42 male and 18 female cases, with a minimum age of 10 and a maximum age of 94 years. Survival time ranged from instantaneous death to 1.5 months.

The injury mechanism was analyzed based on the findings from the injuries to the scalp and the skull bones, all types of intracranial haemorrhage: epidural and subdural haematoma, subarachnoid haemorrhage, as well as focal and diffuse injuries to the brain tissue.

Brains were fixed in 10% buffered formalin, in a timeframe ranging from 14 to 21 days, followed by a macroscopic examination which was documented in photographs. The brain tissue sample collection included: the frontal white matter; the thalamus with the posterior limb of the internal capsule; the body of the corpus callosum and the adjacent tissue of the cingular gyrus; the splenium of the corpus callosum, and the pons and superior cerebellar peduncles.

Aiming to analyse the correlation between the occurrence of DVI and DAI, in addition to the conventional staining methods, (haematoxylin and eosin), immunohistochemical staining was performed with the application of antibodies to β – Amyloid precursor protein (β–APP) by employing the method of Sheriff et al. [5]. After antigen retrieval by microwave treatment in citrate buffer (pH 5.0), each specimen was incubated with mouse monoclonal antibody against β–APP (Mouse anti-alzheimer precursor protein A4 monoclonal antibody, clone 22 C 11, diluted 1:200, Chemicon International, Temecula, CA) overnight at 4C. The enzyme complex used was ABC (Universal VECTASTAIN ABC-Peroxidase kit, Vector Labs, Burlingame, CA) with a secondary antibody - biotinylated anti-mouse IgG (Biotinylated Anti-mouse IgG, produced in horse, Vector Labs). Diaminobenzidine (Peroxidase Substrate Kit (DAB) Vector Labs) was used for visualisation.

RESULTS

DVI was diagnosed in 11 (18 %) of the total of 60 examined cases. They are presented on Table 2. (Figures 1, 2)

No	A-G	Trauma	TS	Hospital	Consiousness	Fr and ICH	FBI	DBI
No 9	f 22	TA-ped	1 h	/	/	Fr, SAH	cont	DVI
No 10	m 39	TA-driver	4-5 h	HOSP	GCS=3	Fr, SAH, IVH	cont	DVI, DAI 1
No 19	m 45	TA-motor	imm	/	/	Fr, SAH		DVI, signs of DAI
No 21	f 38	TA-pass	imm	/	/	SAH,		DVI
No 31	m 43	F-height	imm	/	/	Fr, SAH		DVI
No 32	f 75	F-height	imm	/	/	Fr, SAH	cont	DVI
No 41	m 26	F-height	minutes	/	/	Fr, EDH, SDH, SAH		DVI
No 42	m 53	TA-driver	minutes	/	/	Fr-fac, SAH		DVI
No 44	m 29	TA-driver	imm	/	/	Fr-fac, SAH		DVI
No 45	m 60	TA-pass	imm	/	/	Fr, SAH		DVI, DAI 2
No 48	f 56	TA-ped	1-2h	HOSP	/	Fr, SAH		DVI, DAI 2

Table 2. Cases with diagnosed DVI (Fr fac - fractures of the facial bones)

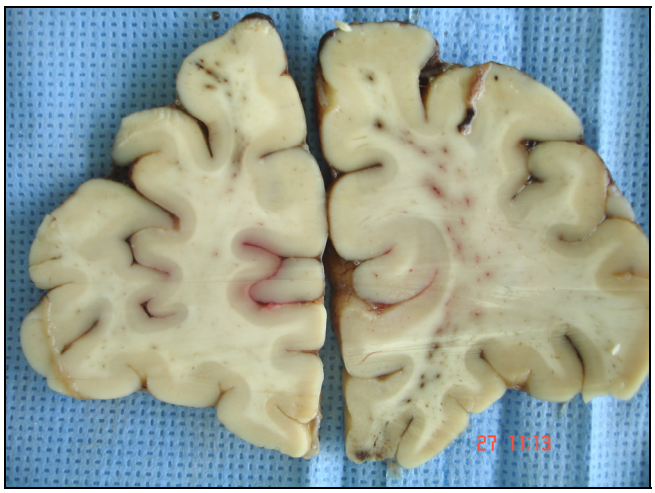

Fig. 1 Coronal slice of the frontal lobes in a case with DVI – case No 48.

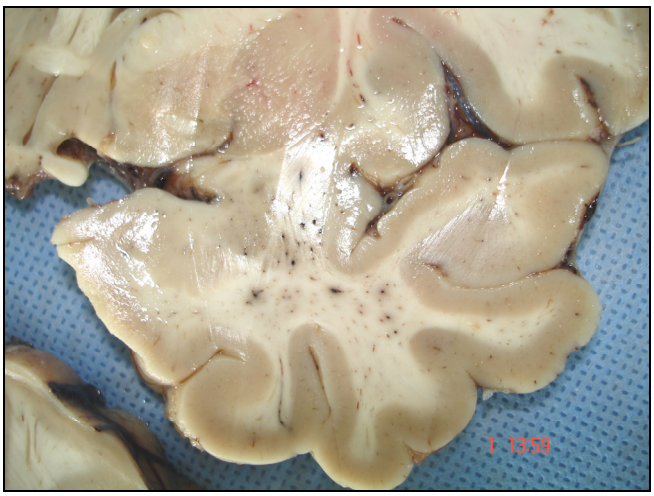

Fig. 2 Coronal slice of the temporal lobe in a case with DVI – case No 44.

Type of traumatic event	Total	DVI	%	DAI	%
Traffic accident	**44**	8	18	27	61
Pedestrian	**22**	2	9	14	64
Cyclist	**6**	0	0	4	67
Motorist	**4**	1	25	2	50
Driver	**6**	3	50	4	67
Passenger	**4**	2	50	2	50
Railroad accident	**2**	0	0	1	50
Fall	**13**	3	23	3	23
Simple fall (<2m)	**3**	0	0	0	0
Fall from a height (>2m)	**10**	3	30	3	30
Blow-assault	**3**	0	0	0	0
Total	**60**	**11**	**18**	**30**	**50**

Table 3 DVI and DAI in a relation with the type of traumatic event that caused head injury

	Total	Fractures of the skull	%
All cases examined	**60**	**42**	**70**
DAI cases	**30**	**18**	**60**
DVI cases	**11**	**10**	**90**

Table 4 The presence of the fractures of the skull in DVI cases, compared with the total cases and DAI cases

Regarding the type of the traumatic event that caused head injury, DVI occurs mostly in traffic accidents, but also in the cases of falling from a considerable height (>2m).

Table 3 shows that these two types of traumatic event are responsible for the occurrence of DAI also.

Fractures of the scull as a most appropriate prove of the direct impact of force to the head were evidenced in almost all cases of DVI, which was compared with the cases of DAI and with the total cases in the study (Table 4).

Discussions

Survival time was analyzed as a particularly important parameter of the severeness of the head injury. As shown on Table 2, eight of the DVI cases (73%) died immediately or in a couple of minutes, two cases died in a timeframe of one to two hours, and only one case, case No. 10, survived 4-5 hours, i.e. lived long enough to be hospitalised and to have his state of consciousness examined, which revealed a state of deep coma with GCS=3. This is in accordance with the description made by Adams and co-workers that these injuries are probably restricted to patients who die very soon after head injury [2].

Although with the accumulation of experiences, the indicated survival time in DVI cases seems to be prolonged – longest described is 11 hours [6], based on our results and the data available in the literature it is an indisputable fact that DVI is a very severe injury of the head where the majority of the cases die within the first few hours.

Fractures of the skull bones were analyzed as a most appropriate prove of the direct impact of high intensity force to the head. Eight of the cases with diagnosed DVI had fractures of the skull, of which four cases featured extensive fractures both on the calvaria and the base of the skull. In two cases – case No. 42 and case No. 44, fractures of the skull bones were not detected, but extensive fractures of the face bones were detected that confirm the impact of a high-intensity force in the facial area. The fact that fractures of the skull bones were recorded in 90 % of the cases with diagnosed DVI is a reliable indicator that DVI occurs as a result of a direct impact of a high-intensity dynamic force on the head. This is different from DAI, which is an injury typically occurring as a result of the impact of acceleration and deceleration forces and can be produced even without a direct impact on the head, which was experimentally proved on primates [7, 8]. This means that in real life even a direct impact of a force with a lesser intensity on the head can be sufficient to cause acceleration-deceleration and the occurrence of DAI. This is why DAI as an entity is detected even in cases where there are no skull bone fractures (Table 4).

Previously mentioned assumption is important from the aspect of the correlation between the occurrence mechanisms of DVI and that of DAI, particularly due to the fact that the DVI occurrence mechanism has not been unravelled yet.

Some authors equalized the DVI and DAI occurrence mechanisms with a conclusion that both lesions are triggered by the same mechanism, pointing out that the degree of axonal and vascular lesion is determined by the intensity of the acceleration of the head [9].

These authors suggest and open the possibility for the existence of a spectrum, or at least a continuum between these two entities, which would indicate that these are not two separate entities but different degrees in the spectrum of one and the same type of trauma. The same research paper reports that DVI as an entity is restricted to traffic accident cases.

Our results undoubtedly indicate the presence of DVI not only in traffic accident cases, but also in cases of a falling from height – case No.31, 32, 41 (see picture). The fact that precisely the same types of traumatising events lead to the occurrence of DAI [2, 10] points to the possibility of a correlation between these two entities.

Another fact contributing to this is that in our surveyed material, of the 11 DVI cases, 3 (27%) were diagnosed with DAI also, two of whom were diagnosed with the existence of a lesion in the corpus callosum, which is graduated as DAI2 by the grading system of Adams [11], while one case was diagnosed with the microscopic examination of immunohistochemically stained samples. This one case was the only DVI case with a survival time of 4-5 hours, which means that the survival time was long enough for the axonal damage to be visualised with the applied immunohistochemical method where visualization can be achieved in cases with survival time of at least 2-3 hours [5, 12, 13]. This raises the question whether it would have been possible to prove the concurrent existence of DAI in other DVI cases if they had lived long enough?

Whether DAI is contained in DVI and is its constituent part, which would mean that the axons are more vulnerable than the brain blood vessels, and whether the occurrence of DAI requires the same type of force as DVI, only with lesser intensity?

These questions deserve a serious scientific approach and carrying out of extensive studies with a large number of samples. At this moment, what we know as a fact is that, unlike DAI that was clearly proved and produced in experiments with subhuman primates, DVI has hitherto not been produced in the same manner; unlike Pittela's study in which all DVI cases were diagnosed with DAI, our results indicate that DAI is present in 27% of the DVI cases, which means there is diversity regarding the yielded results; unlike DVI, which is practically always accompanied by fractures of the head bones confirming the direct impact of a high-intensity force, in DAI cases these are less frequent.

Therefore, we believe that one cannot talk about a continuum or a spectrum in which DAI and DVI would represent merely different degrees of manifestation of the impact the same forces. It is more likely that beside the impact of acceleration and deceleration forces, which is why DAI occurred in some of the DVI cases, acceleration was not sufficient and that the direct impact of a force upon the head plays a great role in a process of the occurrence of DVI.

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