SHORT REPORT

The structural basis of moderate disability after traumatic brain damage

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Abstract

The objective was to discover the nature of brain damage in survivors of head injury who are left with moderate disability. Macroscopic and microscopic examination was carried out on the brains of 20 persons who had died long after a head injury that had been treated in a neurosurgical unit. All had become independent but had various disabilities (moderate disability on the Glasgow outcome scale). Most deaths had been sudden, which had led to their referral from forensic pathologists. Post-traumatic epilepsy was a feature in 75%. An intracranial haematoma had been evacuated in 75%, and in 11 of the 15 with epilepsy. Diffuse axonal injury was found in six patients, five of the mildest type (grade 1) and one of grade 2. No patient had diffuse thalamic damage but one had a small focal ischaemic lesion in the thalamus. No patient had severe ischaemic brain damage, but three had moderate lesions which were bilateral in only one. No patient had severe cortical contusions. In conclusion, the dominant lesion was focal damage from an evacuated intracranial haematoma. Severe diffuse damage was not found, with diffuse axonal injury only mild and thalamic damage in only one patient.

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According to the Glasgow outcome scale¹ a patient who fails to make a good recovery from traumatic brain injury may remain vegetative, severely disabled, or moderately disabled. We have recently analysed the neuropathology of brain damage in vegetative² and severely disabled³ patients and now describe the structural damage underlying moderate disability in 20 patients who survived for between 1 and 47 years after injury.

Materials and methods

The Department of Neuropathology in this Institute has for many years had an arrangement with the Procurators Fiscal and departments of pathology in this region whereby intact brains from patients known to have been managed in the Department of Neurosurgery

for a head injury are sent for detailed neuropathological examination and subsequent report to the forensic pathologists. Although most of these brains come from patients who have died soon after injury we have, because of our research interest, encouraged the sending of brains from patients who have died long after their injury. For the present study we have identified from our data base of over 1300 cases of blunt head injury collected between 1968 and 1998—used in numerous previous studies—a group of patients who had recovered with only moderate disability before dying of any cause, often one remotely connected to their injury.

All brains were fixed in 10% formal saline for a minimum of 3 weeks before dissection, after which a full macroscopical and microscopical examination was undertaken in each case.⁴ In addition to conventional histological techniques, an immunocytochemical method was used to identify reactive microglia (CD68, 1: 200; Dako developed with vectastain ABC kit and visualised with diaminobenzidine). Blocks for microglial studies were taken from the cerebral hemispheres (bilateral parasagittal, bilateral internal capsules, and corpus callosum) and the brain stem. Contusions were assessed quantitatively using the total contusion index. This index takes into account the depth and extent of contusions in all regions of the brain: 0 means that there were no contusions, a contusion index of less than 9 is indicative of minimal contusions whereas one of more than 37 is indicative of severe contusions.⁵ Diffuse axonal injury, in which there is widespread damage to axons throughout the brain at the time of the original injury, was graded as previously described.^{6,7} In grade 3 (most severe) there are in addition focal lesions in the corpus callosum and in the dorso-lateral segment(s) of the rostral brain stem; in grade 2 there is a focal lesion only in the corpus callosum; and in grade 1 there are no focal lesions. Because of the long period of survival in every case, the diagnosis of diffuse axonal injury depended on the microglial reaction rather than the identification of actual abnormalities in axons. Despite the long periods of survival, there was in every brain an obvious residual microglial response, particularly in the cerebral hemisphere where contusions were most severe and adjacent to ischaemic brain damage, and to the sites of intracranial haematomas. In relation to these

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Table 1 Circumstances of death and history of epilepsy and alcohol misuse in 20 patients who survived moderately disabled for 1 year or more after a head injury

Patient	Circumstances of death	Epilepsy	History of alcohol misuse
1	Dead in toilet	+	+
2	Pancreatitis/cirrhosis	+	+
3	Lung cancer	+	+
4	Coma in street- head injury	0	0
5	Dead by bed- vomit	+	+
6	Dead at home	+	+
7	Heart failure	+	+
8	Dead in bed	+	0
9	Portal hypertension	+	+
10	Dead at home-GI haem	0	+
11	Fall - ruptured liver	+	0
12	Fall - liver failure	0	+
13	Dead at home-heart attack	+	+
14	Dead in seizure	+	0
15	Dead at home-overdose?	0	+
16	Dead at home	+	+
17	Dead at home	+	+
18	Post-op thromboembolism	0	0
19	Dead at home-heart attack	+	0
20	Dead at home-heart attack	+	0

haematomas, descending degeneration of wallerian type was often identifiable in the corresponding pyramidal tract. For the presence of diffuse axonal injury to be recorded we required there to be excessive bilateral (symmetric or asymmetric) proliferation of microglia associated with the presence of discrete clusters of microglia in the parasagittal white matter, in the internal capsule, and in long tracts in the brain stem.⁸

Ischaemic brain damage was graded severe if it was diffuse or multifocal or took the form of infarcts within entire specific arterial territories, and moderate when it was limited to arterial boundary zones alone or in combination with subtotal arterial territory infarcts.⁹ Pressure necrosis in one or both parahippocampal

gyri was taken as evidence of there having been raised intracranial pressure.¹⁰ Only haematomas more than 35 ml were recorded.

The definition of moderate disability is that the person is sufficiently independent to live on his own but has some persisting physical or mental impairment. The classification of these patients into this category depended on review of the medical records by the neurosurgical author (BJ). Although these notes were often very limited, there was always clear evidence that the patient had been living independently.

Results

The reason that many of these cases reached us was because they had sudden deaths that led to investigation by the Procurator Fiscal (table 1). Post-traumatic epilepsy was a feature in 15 patients (75%) and this was the main disability. In 11 of these patients with epilepsy an acute intracranial haematoma had been evacuated. In seven of the cases of epilepsy the patient had been found dead at home and some of these could be regarded as cases of sudden unexplained death due to epilepsy (SUDEP).¹¹⁻¹³ Of the five patients without epilepsy four had mental disabilities and one had hemiparesis. Alcohol misuse was a feature in 13 patients (65%) and in 10 patients there was both epilepsy and alcohol misuse.

The principal findings are given in table 2. There were 17 men in the group and survival ranged from 1 year to 47 years. The commonest cause of the injury was a fall (70%). Some clinical details are missing but of the 12 with a note about a lucid interval all but two were known to have talked soon after their injury,

Table 2 Principal features in 20 patients who survived in a moderately disabled state for 1 year or more after a head injury

Patient No	Age at death (y)	Sex	Cause	Survival	Lucid	Skull fracture	Brain weight (g)	IC Haem	ICP+	TCI	DAI	IBD	Abnormalities in:				
													Neocx	SCWM	Thalamus	Brain stem	Hydrocephalus
1	47	M	Fall	1 y	No	No	1310	ICHe	No	22	No	No	C	No	No	No	No
2	40	M	Fall	1 y 6 m	T	No	NK	ICHe	Yes	12	No	+	AT	F	No	L	No
3	44	F	Fall	1 y 6 m	T	NK	1245	No	No	10	No	No	C	No	No	No	No
4	67	M	Fall	2 y	T	Yes	1560	SDH	No	18	No	No	C	No	No	No	+++ B
5	44	F	Fall	2 y	P	Yes	1010	SDHe	Yes	10	No	+	C:AT	F	F	M	+ U
6	49	M	Fall	3 y	T	No	1440	No	No	6	No	No	C	No	No	No	++ B
7	54	M	Fall	3 y	P	Yes	1190	ICHe	Yes	27	1	No	C	D	No	No	+ U
8	51	M	Fall	3 y	T	Yes	1220	ICHe	No	14	1	No	C	D	No	No	No
9	48	M	Fall	3 y	NK	NK	1450	SDHe	No	12	No	No	C	No	No	No	No
10	59	M	Fall	4 y	NK	NK	1290	ICHe	Yes	15	No	No	C	No	No	No	++ B
11	48	M	Fall	4 y	T	Yes	1100	SDHe	No	12	1	No	C	D	No	No	+ U
12	37	M	Fall	4 y	NK	Yes	1100	ICHe	Yes	27	No	No	C	No	No	No	+ U
13	38	M	NK	4 y	NK	NK	1460	No	No	16	No	No	C	No	No	No	No
14	19	M	Assault	5 y	T	Yes	1680	SDH	No	6	No	No	C	No	No	No	No
15	35	M	Fall	11 y	No	NK	NK	No	No	1	2	No	C	D	No	No	No
16	60	M	NK	12 y	NK	Yes	1300	SDHe	No	10	1	No	C	D	No	No	++ B
17	58	M	RTA	16 y	T	Yes	1400	EDH	No	12	1	No	C	D	No	No	+ U
18	54	M	NK	16 y	NK	NK	1320	ICblr	No	10	No	No	C	No	No	No	No
19	48	M	RTA	22 y	NK	NK	1570	SDHe	No	6	No	No	C	No	No	No	No
20	55	F	Fall	47 y	NK	NK	1040	No	No	2	No	+	C:BZ	F	No	No	No

RTA=road traffic accident.

Lucidity: T=Total; P=Partial.

IC Haem=intracranial haematoma.

SDH=subdural haematoma; EDH=extradural haematoma; ICH=intracerebral haematoma; ICblr=intracerebellar; e=evacuated.

ICP +=Raised intracranial pressure.

TCI=Total contusion index.

DAI=Diffuse axonal injury: 1 and 2 indicate grade.

IBD=Ischaemic brain damage: +=moderate; BZ=arterial boundary zones; AT=arterial territories.

Neocx=Neocortex: C=surface contusions.

SCWM=Subcortical white matter: D=diffuse; F=focal.

Thalamus: F=focal damage.

Brain stem: M=focal damage in midline; L=lateral damage.

Hydrocephalus: +=slight ventricular enlargement; ++=moderate; +++=severe.

B=bilateral; U=unilateral; NK=not known.

and nine (75%) of the 12 patients where information was available had a fracture of the skull.

Surface contusions were present in every case; in five they were minimal and in none were they severe. Diffuse axonal injury was identified in six cases—five were grade 1 and one was grade 2. There was a significant intracranial haematoma in 15 (75%) and all of these had been evacuated surgically. In five patients there was pathological evidence that the intracranial pressure had been high during life and in two of these (patients 2 and 5) there were small focal lesions in the brain stem of the type associated with shift and herniation of the brain. There were no cases where ischaemic brain damage was classified as severe but in three there was moderate damage of this type; in two it affected arterial territories and in one case there were bilateral lesions in arterial boundary zones. Abnormalities in the subcortical white matter were diffuse in the six patients with diffuse axonal injury, and small and focal in the three patients with ischaemic brain damage. In one of the patients with ischaemic damage there was a small focal abnormality in the thalamus. In no patient were there diffuse abnormalities in the thalamus. Brain weights were within normal limits and in five there was unilateral ventricular enlargement in relation to loss of ipsilateral brain tissue. In four patients there was bilateral ventricular enlargement and patient 4 was thought clinically to have normal pressure hydrocephalus. In patient 16 there were also the features of Wernicke's encephalopathy. In patient 15 who had grade 2 diffuse axonal injury there were small bilateral gliding contusions of the type often encountered in association with diffuse axonal injury.⁷

Discussion

The great majority of the 20 moderately disabled patients had injuries that were brought about by falls (14; 70%). As expected after such injuries most had talked immediately after their injury and there was a high incidence of intracranial haematoma (75%). Diffuse axonal injury was identified in six patients (30%) but in five of these it was grade 1 (the least severe form). Further evidence that the axonal injury was not severe was that in no case was there evidence by conventional microscopy of transneuronal changes in the thalamus—a standard feature in patients with the more severe grades of diffuse axonal injury who had survived for more than 2 or 3 months after their injury. Ischaemic brain damage occurred in only 15% and was bilateral only in patient 20, where the abnormalities in arterial boundary zones suggested that the patient had experienced an episode of hypotension and cerebral perfusion failure shortly after the injury. Brain weights were within normal and generalised ventricular enlargement was present in only four cases. The only patient with severe generalised hydrocephalus was thought clinically to have normal pressure hydrocephalus (patient 4). In the other five cases with an enlarged ventricle this was asymmetric and related to focal loss of brain tissue. The absence of any progressive fall in

the weights of the brains or generalised increase in the size of the ventricular system indicates that progressive cerebral atrophy was not a feature in these patients.

There has been much interest in the long term outcome in those contact sports in which there is relatively minor but repeated head injury. These include boxers, a proportion of whom develop dementia pugilistica, often with parkinsonian features.¹⁴ The neuropathology in such patients comprises some features in common with Alzheimer's disease^{15, 16} providing additional support for the significant association between a history of head injury with loss of consciousness, and the risk of subsequent Alzheimer's disease.¹⁷ If a head injury does precipitate Alzheimer's disease then a potent acute phase molecule such as IL1 and the upregulation of neuronal β -APP are necessarily involved¹⁸ probably in genetically susceptible (APOE ϵ 4 positive) people.¹⁹ The case material in this report is part of a much larger study investigating the cellular and molecular relation between head injury and subsequent neurodegenerative disease, which will be reported when the study is complete.

These findings suggest that moderate disability after a head injury is related mainly to focal brain damage often associated with the surgical evacuation of an intracranial haematoma. In 75% of the patients in this series post-traumatic epilepsy was a major component of the disability and 11 of these 15 patients had had an intracranial haematoma. It seems from this study that epilepsy can be an important factor contributing to late but premature death in patients left moderately disabled after a head injury—some of these coming into the category of sudden unexplained death from epilepsy (SUDEP).^{11–13}

One particular reason for these neuropathological studies was to establish whether or not the brains of patients who remained vegetative, severely disabled, or moderately disabled after a head injury showed a similar range of structural damage but of decreasing severity. Some types of brain damage were common to all, but diffuse damage (the severer grades of diffuse axonal injury and hypoxic brain damage) and thalamic damage predominated in vegetative survivors whereas focal damage (intracranial haematoma in particular) predominated in patients who remained severely or moderately disabled.³ But a third of the severely disabled patients had either severe diffuse axonal injury, or thalamic damage, or both.

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NEUROLOGICAL STAMP

Jean Martin Charcot (1825–93) and Jean Baptiste Charcot (1867–1936)

Jean Martin Charcot spent more than 30 years of his career at the Salpêtrière and established the great school of neurology there. Charcot's interest in neurology was slow to evolve. He was inspired largely by his contemporary, Duchenne. Charcot was also a contemporary of Broca. Freud was among his pupils. Charcot's famous lessons dealt with all matters of neurological importance, including cerebral localisation in 1875 and 1876. Early in his career he also made several contributions to general medicine. His particular interests included hysteria and hypnotism.

Charcot convincingly demonstrated cortical motor centres in humans. He delineated the brain's vascular supply and with his intern Charles Bouchard described military aneurysms. Amyotrophic lateral sclerosis, which he also described, is still referred to as Charcot's disease in many parts of the world. He noted that in infantile paralysis the spinal lesions were limited to the anterior horns of the grey matter. With Marie he described the peroneal form of muscular atrophy. He had clear views on the differentiation of hysteria from epilepsy, neurosis from psychoses, and multiple sclerosis from paralyse agitante. Charcot created the term Parkinson's disease (*la maladie de Parkinson*). Charcot also focused considerable attention on differentiating the tremor displayed by patients with Parkinson's disease from that of patients with multiple sclerosis. In his analyses of head tremor he asked patients to wear a lightweight wand attached to a head band to magnify the tremor. To improve evaluation in his gait laboratory the patients walked on paper after dipping their feet in ink. He

described locomotor ataxia, gastric crises, and the joint lesions of syphilis. In 1960 France issued a stamp picturing Charcot and the Salpêtrière (Gibbons 1492, Scott B344).

His son, Jean Baptiste Charcot, was the illustrious son of an illustrious father. He graduated as a physician from the University of Paris in 1895 and served as house physician to his father at the Salpêtrière before moving to the Pasteur institute. In 1901 he deserted medicine to become an Arctic and Antarctic explorer sailing in his famous polar ship *Pourquoi pas?* ("Why not?"). He perished tragically in a gale off northern Iceland in 1936. Charcot Island in Antarctica was named by him in honour of his father. He has also been philatelically honoured as an Arctic and Antarctic explorer. This is one of the few instances of father and son, both physicians, receiving postal recognition for quite different achievements. Jean Baptiste Charcot and the *Pourquoi pas?* are shown here on a stamp of the French Southern and Antarctic Territories issued in 1961 on the 25th anniversary of his disappearance (Stanley Gibbons 24, Scott 21).

There have been at least two biographies written about J M Charcot, one of the founders of neurology. They are Guillemin G. *J-M Charcot: his life-his work* (translated by P Bailey) London: Pitman Medical Publishing Company, 1959) (In French: *JM Charcot, sa vie-sa œuvre*. Paris: Masson, 1955) and Goetz CG, Bonduelle M, Gelfand T. *Charcot. Constructing neurology*. Oxford: Oxford University Press, 1995.

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