Original Paper

Parkinsonism associated with prolonged unresponsive wakefulness syndrome after blunt head injury: a clinico-pathological study

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Abstract

Objective: Survival after traumatic brain injury (TBI) and posttraumatic parkinsonian-like symptoms is increasing, in particular in those patients developing during disease course an unresponsive wakefulness syndrome (UWS) previously termed persistent vegetative state.

Material & methods: 100 patients with disorders of consciousness after a blunt TBI ranging from deep coma to defective states / minimal cognitive state survived between 12 and 900 days. 15 patients developed parkinsonian symptoms, which were correlated with their neuropathological changes.

Results: The patients, surviving either UWS recovery (n = 10) or defective minimally conscious state (MCS) (n = 5), clinically presented with severe (n = 7), moderate (n = 5), or mild (n = 3) parkinsonian symptoms mainly comprising symmetrical rigidity, amimia, hypo- / akinesia and convergence disorder, which in six patients were associated with unilateral or bilateral resting tremor. Following levodopa treatment, 11 patients showed mild to moderate improvement and four patients almost complete improvement of UWS, parkinsonism or both. Neuropathology revealed in most cases supratentorial traumatic lesions such as contusions, cerebral hemorrhages and diffuse white matter lesions. In addition to lesions in the basal ganglia and hippocampus, all cases displayed older lesions in the dorsolateral or lateral parts of the pons and in lower midbrain with various involvement of substantia nigra. The periaqueductal gray and upper midbrain tegmentum were however preserved. The pattern of brainstem lesions correlated with the sequelae of transtentorial shifting due to increased intracranial pressure.

Conclusions: These and other rare observations following blunt TBI confirm the importance of the pattern of secondary brainstem lesions for the development and prognosis of UWS and rare parkinson-like symptoms.

Keywords: Blunt traumatic brain injury, Prolonged unresponsive wakefulness, Chronic vegetative state, Posttraumatic parkinson-like symptoms, Brainstem lesions, Neuropathology

Introduction

Survival rates after blunt traumatic brain injury (TBI) and chronic posttraumatic disorders of consciousness (DOC) are increasing [1]. In view of recent advances in the prognosis of TBI and related DOCs and their impact on diagnostic accuracy, prognosis and treatment [2, 3], the European Task Force on Disorders of Consciousness proposed the term "unresponsive wakefulness syndrome" (UWS) [4–8] for the challenging neurological conditions previously termed "apallic syndrome" [9, 10] or "persistent vegetative state" (PVS) [11, 12]. The functional outcomes following severe TBI are summarized in Fig. 1. With increased survival rates after severe TBI, the incidence of posttraumatic parkinsonism (PTP) has increased [14]. PTP is commonly caused by injuries from accidents (mainly motor vehicle accidents and falls) with loss of consciousness and latency to symptom onset of one to six or more months, although up to 42 % of patients did not report loss of consciousness [14]. In the fully developed "apallic syndrome", akinesia, amimia and increased muscle tonus with cogwheel phenomenon are almost obligatory and associated with spasticity and disorders of optomotoric akin to decerebration rigidity, while tremor is usually absent [10]. On the other hand, some patients with DOC following severe TBI have been reported to have parkinsonian symptoms [15]. Both PVS and minimally conscious state (MCS) following severe TBI can include features of akinetic mutism and parkinsonism that may share midbrain network dysfunctions [16, 17]. Extrapyramidal symptoms with bradykinesia, rigidity and resting tremor are the hallmark features of PTP, whereas postural instability was reported only in 15 % of cases [18].

Neuroimaging shows either a subdural hematoma causing transient compression obstruction of the basal ganglia or hypointense lesions confined to the basal ganglia [14] or were negative [15]. In a prospective study of patients with posttraumatic movement disorders, basal ganglia were the most common sites affected (66.7 %), followed by thalamus and brainstem (16.7 % each), while diffuse white matter (WM) involvement was the most common radiological lesion in patients with tremor [19]. In a man aged 37 years, parkinsonian features following a blunt TBI were associated with hypo-

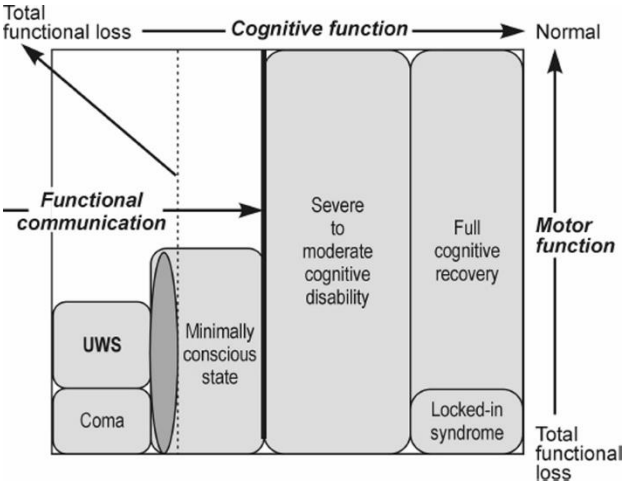

Figure 1. Conceptual overview of functional outcomes following severe traumatic brain injuries (modified from [13]). *Functional communication* refers to the most basic skills of communication that become better with improvement of the unresponsive wakefulness syndrome (*UWS*) (*horizontal arrow*). The *ellipse* between UWS and minimally conscious state reflects rare patients with fragments of behavior that arise spontaneously and not in response to stimulation. *Locked-in syndrome* is a rare neurological disorder in which patients can think and reason. They cannot speak but they can move their eyes up and down and blink.

substantia nigra (SN) region [20]. In three patients, a posttraumatic rigid-akinetic syndrome resembling Parkinson disease appeared after a delay of one to five months after TBI. These patients displayed traumatic changes in the substantia nigra (SN) according to neuroimaging, and responded to levodopa [21]. According to a recent review, 53 % of PTP cases had a confirmed lesion; 53 % of the latter was located in the SN, 22 % more broadly in the midbrain [14].

Neuropathological studies of PTP after blunt TBI emphasized the importance of brainstem lesions secondary to increased intracranial pressure (ICP) [22–25] and extensive damage of the cerebral WM due to diffuse axonal injury [26–28], associated with hippocampal lesions and bilateral necrosis in thalamus and other basal ganglia [29]. Among 35 patients who survived blunt TBI for one month and up to eight years, thalamic lesions were seen in up to 96 % of cases, while diffuse axonal injury and ischemic brain lesions were seen in 14 % to 71 % of cases [30]. Brain-injured patients with DOC showed lesions of thalamus and basal nuclei that were confirmed by MRI [31] or proton magnetic spectroscopy [32]. Thalamic lesions were associated with thalamo-cortical disconnectivity [33] and disordered

brain networks [34, 35], whereas brainstem lesions after severe TBI were of prognostic value [36]. Disruption of the ascending arousal network in the brainstem tegmentum causes DOC after acute TBI [37]. Neuroimaging studies suggested an important role for the default mode network to discriminate the UWS from MCS [8, 38], while abnormalities in the brainstem were confined to the TBI group [39]. Brainstem injuries detected by MRI after severe TBI were shown to be of prognostic value [36]. Most recent studies provided evidence for a key difference in the left frontoparietal connectivity when contrasting UWS with MCS [40].

This paper presents the neuropathological findings in a series of 15 patients surviving after blunt TBI, showing either complete recovery or defective states of UWS, presenting with severe to mild, mainly symmetrical rigid-akinetic parkinsonian symptoms.

Material and methods

In a consecutive post-mortem series of 630 subjects who survived a blunt TBI, 100 subjects (59 males and 41 females, age from five to 85 years, mean age 41.5 years, 77 % traffic accidents, 23 % falls plus other causes) with prolonged DOC and a survival between 12 and 900 days showed various states of consciousness ranging from deep coma or acute midbrain syndrome (n = 6, survival 12–35 days) to full UWS state (n = 61, survival 12–257 days), partial recovery from UWS (n = 22, survival 21–900 days) to remission state or partial clinical improvement comparable to MCS (n = 11, survival 21–293 days, mean 93.5 days). The neuropathological findings of this group have been described previously [25].

The 100 patients who survived blunt TBI for periods between 22 and 900 days (mean 564 days) included 15 patients (13 males, 2 females aged 21 to 56 years, mean 41.4 years) who showed not only posttraumatic motor and postural disorders but also flexor and / or extensor spasms and oculomotor disorders (diplopia, convergence disorders) and who developed parkinson-like symptoms of moderate to severe intensity, mainly characterized by symmetrical hypo / akinesia, hypomimia / aminia and rigidity, with convergence disorders in 10 patients and unilateral or bilateral resting tremor in six patients.

The clinical data of these 15 patients were evaluated retrospectively from their clinical and intensive care records. Their state of consciousness was evaluated by intensive care specialists according to the Glasgow scales and their extrapyramidal symptoms by movement disorder specialists. Since a part of the patients died between 1966 and 1980, CT studies could only be performed in a few patients. In addition to supratentorial traumatic lesions, the patients showed recent uni- or bilateral necroses, hemorrhagic cysts, old necroses, and/or atrophy of striatum, globus pallidus and/or thalamus, unilateral or bilateral hippocampal lesions, extensive damage to the cerebral WM and uni- or bilateral lesions in the brainstem, usually in lateral or dorsolateral parts of the pontine tegmentum, cerebral peduncles and/or cerebellum. In some patients, cerebral blood flow measurements were performed with the ^{133}Xenon clearance method according to Ingvar & Lassen and gray matter hypoperfusion was correlated with the anatomical brainstem lesions [41].

Most of the patients with parkinsonian symptoms received levodopa treatment, initially per gastric tube and later on orally (levodopa / benserazide carbidopa 100 / 25 mg three times per day). Eleven patients showed partial improvement of the parkinsonian symptoms and less PVS, while four patients showed almost complete recovery of both syndromes.

Neuropathological examination was performed according to standard protocols, with macroscopic assessment of brain atrophy, focal supratentorial brain lesions, deep traumatic and posttraumatic brain lesions (residuals of subdural / epidural or subarachnoidal hemorrhages, cortical contusions / concussions or hematomas, etc.). Pressure necroses / hemorrhages in the parahippocampal gyri were taken as evidence that ICP had been increased. Macroscopic changes in brainstem and cerebellum were described in detail. Histological examination of multiple paraffin blocks was performed using routine stains (H&E, cresyl violett, Kluver-Barrera or Heidenhain stain, Bodian silver impregnation, Holzer stain for fibrillary gliosis and immunohistochemistry for glial fibrillary acidic

protein / GFAP). Amyloid-β, tau and synuclein pathologies were not specifically examined.

Results

The type, location and extension of the essential morphological changes are presented in Table 1. The key clinical and neuropathological data are presented in Table 2.

The 10 patients who survived for periods between 25 and 900 days with a partial recovery from UWS showed residuals of intracranial epi- or subdural hemorrhages (n = 4), cortical contusions / lacerations (n = 8), vascular / ischemic cortical necroses or WM hemorrhages (n = 1 each), diffuse WM changes (n = 6), lesions of the corpus callosum (n = 1), old hemorrhagic / ischemic lesions of the hippocampus usually with unilateral predominance (n = 9) or old hemorrhages and / or (cystic) necroses of the globus pallidus (n = 5) or less frequently of the striatum and / or the thalamus (n = 3/2). Among the latter patients, one case each also showed cystic necrosis of the globus pallidus with unilateral or bilateral lesions (small cysts, old hemorrhages, neuronal depletion) in the SN. The lesions mainly involved the lateral and dorsal parts of the SN (supply areas of small circumflexious rami) or oral and medial parts of the SN (supply areas of paramadian arteries). No definite lesions were seen around the walls of the third ventricle and in the periventricular gray matter. In one case, small cystic necroses and hemorrhagic residuals were detected in the dorsolateral midbrain tegmentum together with bilateral SN lesions. All the other cases showed superficial defects or hemorrhagic residuals in the lateral and dorsolateral pontine tegmentum. In one case each, myelin pallor and diffuse gliosis of the pontine basis and cerebellar lesions were present.

Table 1: Cerebral lesions in 15 patients with blunt traumatic brain injury showing distinct recovery states from unresponsive wakefulness syndrome (UWS) and parkinsonian symptoms

	UWS partial recovery	UWS defective state/MCS	Total
Number of patients	10	5	15
Survival (days)	25–900	22–293	
Deep coma (days)	3–12	3–10	
Intracranial, epi-subdural hemorrhage	4	2	6
No superficial brain lesions	2	0	2
Cortical contusions/lacerations	8	2	10
Vascular/ischemic cortical lesions	1	1	2
White matter hemorrhages	1	0	1
Diffuse white matter lesions	6	4	10
Lesions corpus callosum	1	0	1
Hippocampal/parahippocampal lesions	9	4	13
Necroses/hemorrhages striatum	3	2	5
Necroses/hemorrhages globus pallidus (total)	5	1	6
Necroses thalamus	2	0	2
Lesions globus pallidus + bilateral SN	2	1	3
Lesions globus pallidus + unilateral SN	1	1	2
Lesions floor 3rd ventricle, periaqueductal gray	0	0	0
Brainstem lesions (total)	10	5	15
Lesions midbrain tegmentum + SN	1	0	1
Lesions lateral/dorsolateral pons tegmentum	9	5	14
Diffuse gliosis pons	1	1	2
Cerebellar lesions	1	1	2

UWS: unresponsive wakefulness syndrome; MCS: minimal cognitive state; SN: substantia nigra

Table 2. Key clinical and neuropathological data

					UWS stage			Major secondary lesions		
Age sex	**Accident**	**Coma duration (days)**	**Survival (days)**	**Primary traumatic lesion**	**Partial recovery**	**Defect state**	**Parkinsonian symptoms**	**Hippocampus**	**Others**	**Brainstem lesion**
48 F	Car accident	8	111	Subdural h., concussions	+	–	Rigor, akinesia	++	Thalamus	Dorsolat. pontine tegmentum
74 F	Car accident	10	112	Subdural h., concussions	+	–	" - "	++	Cerebellum	" - ", SN
32 M	Motorcyclist, blow to fore-head	10	160	Epidural h.	+	–	" - "	++	Thalamus	Rostral pontine tegmentum, SN
21 M	Motorcyclist, hit by car	8	184	Concussions	+	–	" - "	++	Pallidum	Pontine tegmentum, SN
39 M	Drunken fall on occiput	8	228	WM lesions, frontal concussion	+	–	" - "	++	?	Dorsal pontine tegmentum
47 F	Fall from ladder	4	230	Concussions	+	–	" - "	++	Pallidum	Rostral pontine tegmentum, SN
32 F	Skiing accident	10	527	Epidural h.	+	–	" - "	++	Pallidum	" - "
20 M	Motorcyclist, hit by car	10	301	Concussions	+	–	" - "	++	Pallidum	" - "
36 M	Motorcyclist	30	301	Concussions	+	–	" - ", oculomotor palsy	++	Thalamus, pulvinar	Caudal midbrain + pontine tegmentum
59 M	Scooter ride	4	360	Skull fracture, concussions	+	–	" - "	++	Pallidum	" - "
39 M	Drunken fall	4	456	None	+	–	" - "	++	Thalamus	Midbrain, pontine tegmentum
30 M	Motorcyclist, hit by tram	5	236	None	–	+	" - "	++	Cerebellum, gliosis	Caudal midbrain tegmentum, SN, gliosis pontine brain
23 M	Motorcyclist, hit by car	6	260	WM lesions	–	+	+/–	++	–	Old hemorrhages, caudal midbrain tegmentum
72 M	Knocked over by car	8	290	Depressed skull fracture, concussions	–	+	+	++	–	Dorsolat. pontine tegmentum, SN
30 M	Motorcyclist, hit by car	4	301	Subdural h., concussions	–	+	+	++	Striatum, pallidum	Dorsolat. pontine tegmentum, SN, demyelination pontine basis

UWS: unresponsive wakefulness syndrome, h.: hematoma; WM: white matter; SN: substantia nigra

A 32-year-old woman victim of a skiing accident was treated by excavation of an epidural hematoma. She survived for 10 days in an acute coma and for 257 days in partial recovery from UWS. She had no further direct traumatic brain lesions. In addition to spastic hemiparesis, she developed symmetric rigidity, akinesia and amimia, but reacted to external stimuli and, finally spoke a few hardly understandable words. She died from pneumonia. Neuropathology revealed residuals of the epidural hematoma but no primary traumatic lesions, subarachnoid hemorrhage or cortical contusions. Yet, there were cystic necroses of the left central thalamus and contralateral medial hypothalamus next to the SN (Fig. 2A), compression necrosis of the left hippocampus/parahippocampus (not shown) and symmetric cystic necroses in the caudal midbrain colliculi (Fig. 2B) and extensive unilateral necrosis of the SN and pes pedunculi (Fig. 2C). The location of the most frequent brainstem lesions due to transtentorial shifting and compression as well as the corresponding arterial blood supply are shown in Fig. 2 D–F.

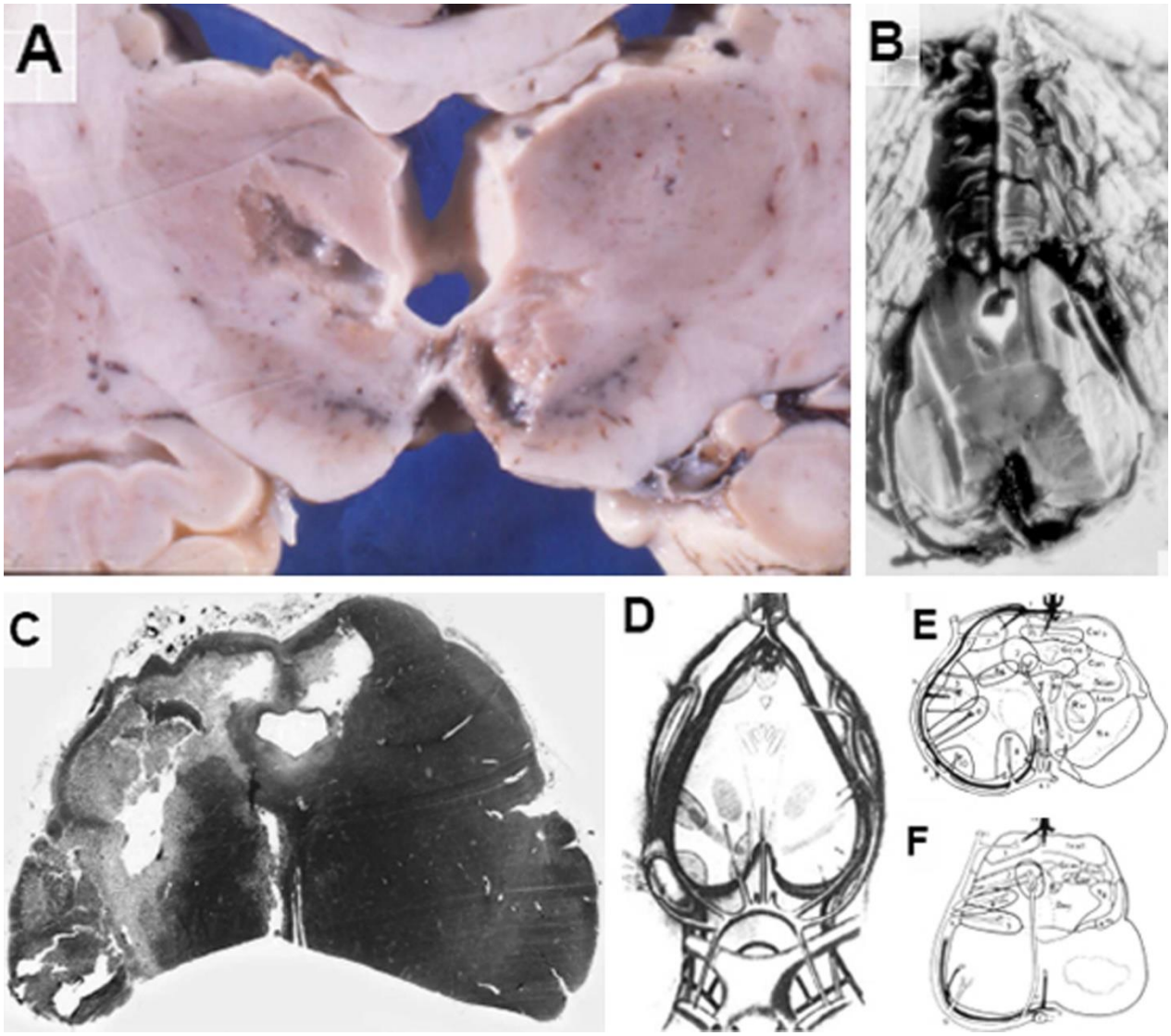

Figure 2.

A. Old cystic necroses in left medial thalamus and in contralateral medial hypothalamus next to medial SN. **B.** Old cystic necroses in lateral and contralateral paramedian tegmentum of caudal midbrain. **C.** Extensive cystic necroses in caudal midbrain colliculus and unilateral cystic necrosis of SN and pes pedunculi. Heidenhain stain. **D–F.** Schematics showing localization of compression lesions in the brainstem due to transtentorial herniation and their corresponding arterial blood supply (in bold). (B–F from [25] with permission from the publisher Taylor & Francis Ltd)

A 39-year-old man sustained a drunken fall on his occiput. No skull fracture, intracerebral hemorrhages or cortical contusions were found. Following a deep coma lasting four days, he died after 456 days in UWS with moderate clinical improvement, spasticity of his extremities, double vision (paresis of the right third brain nerve), bilateral rigidity, akinesia and hypomimia without tremors. Cerebral blood flow measurement at 100 days post TBI showed considerable reduction of gray matter perfusion, which significantly correlated with the anatomical brainstem lesion. After about 6 months, he was extubated, and later began to speak single words and to react to commands. CT showed cystic lesions in bilateral basal ganglia and dorsolateral brainstem. Levodopa was administered first through gastric tube and later on orally with levodopa / benserazide 100 + 25 mg three times per day. Levodopa treatment led to slow reduction of rigidity and amimia but did not change spasticity. The patient was transferred to a chronic care center, where his general state did not change considerably. He died from acute cardiac infarction. Neuropathology revealed no superficial traumatic residuals but diffuse WM lesions and old cystic necroses in globus pallidus and thalamus due to compression of the left anterior choroidal and right thalamo-perforant arteries. In addition to an old hemorrhagic infarction in the right occipital lobe, extensive lesions were found in the hippocampus/parahippocampus with unilateral predominance. There were small cystic necroses in the left dorsolateral midbrain tegmentum around the aqueduct, in the nucleus ruber and in the ipsilateral SN (Fig. 3A). Old hemorrhagic compression necroses in the pontine tegmentum surrounded the enlarged aqueduct (Fig. 3B), while extensive necroses were found in the pontine tegmentum affecting the rostral reticular formation and central tegmental tract (Fig. 3C). In the SN, small cystic lesions and focal loss of neurons were seen (Fig. 3D).

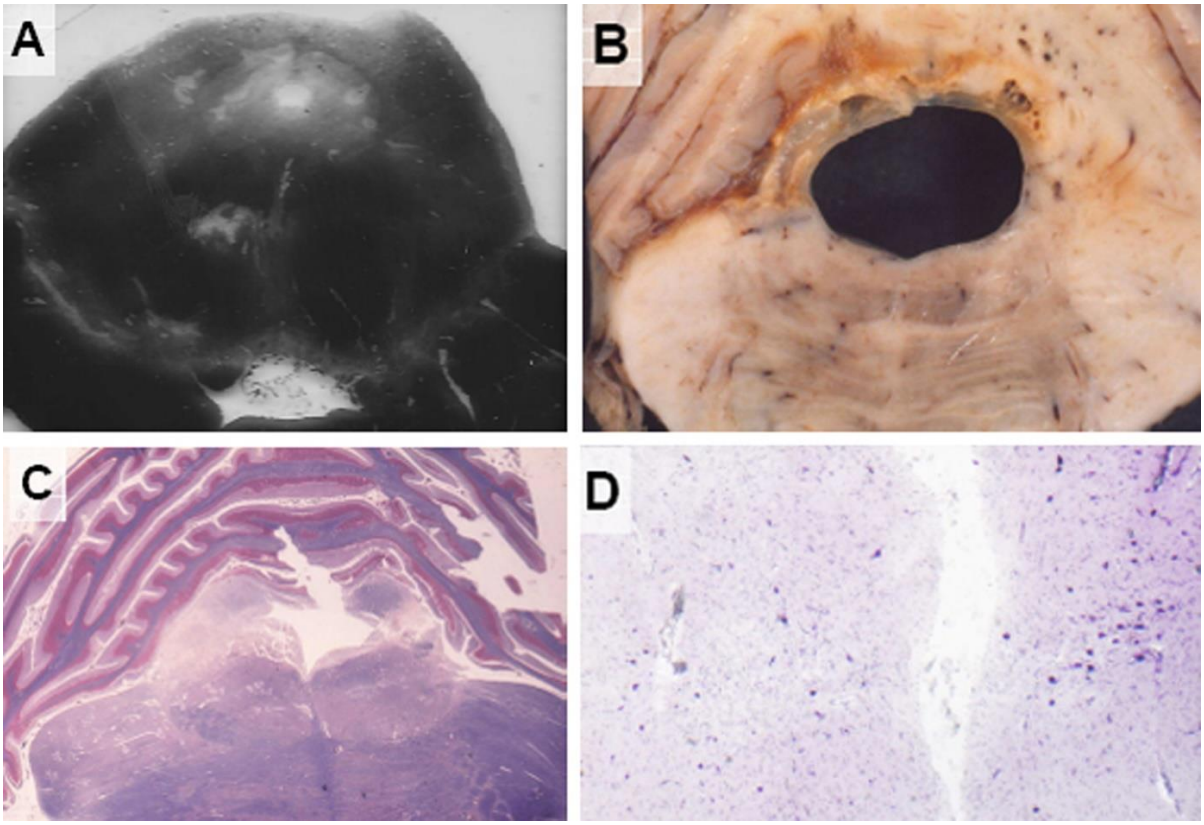

Figure 3.

A. Multiple small necroses in caudal midbrain tegmentum around aqueduct, in unilateral red nucleus and SN. Heidenhain stain. **B.** Old hemorrhagic compression necroses in pontine tectum and tegmentum, enlarged aqueduct. **C.** Old bilateral necroses in pontine tegmentum involving both the rostral reticular formation (nuclei pontis centralis oralis) and the central tegmental tract. Luxol fast blue. **D.** Cystic lesion and focal neuron loss in the SN. H&E stain.

A 36-year-old motorcyclist, hit by a car, received a blow to the right forehead, causing no skull fracture, intracranial hematoma or cortical contusions. He was in deep coma for around 30 days and died after 301 days, transition from UWS to Klüver-Bucy syndrome. In addition to left-sided spastic hemiparesis, he developed parkinsonian symptoms with almost bilateral akinesia, rigidity, hypomimia and slurred, hardly understandable speech. He was given levodopa via gastric tube and later on orally, which was followed by incomplete reduction of rigidity and akinesia without changes of spastic hemiparesis. He died from pneumonia. Neuropathology revealed neither skull fracture nor residuals of intracranial hemorrhage or cortical contusions, but diffuse WM changes, partial rupture of corpus callosum and severe hippocampal/parahippocampal lesions with left preponderance. The basal ganglia, walls and bottom of the third ventricle as wells as the periventricular gray matter and oral midbrain were preserved. Old hemorrhagic necroses involved however the dorsal and dorsolateral tegmentum (Fig. 4A and C). A small necrosis was seen in the right dorsolateral pontine tegmentum (Fig. 4B), while extensive compression necroses were seen in the right dorsolateral pontine tegmentum and adjacent cerebellar gyri (Fig. 4D). Pictures of the bilateral SN lesions have unfortunately been lost.

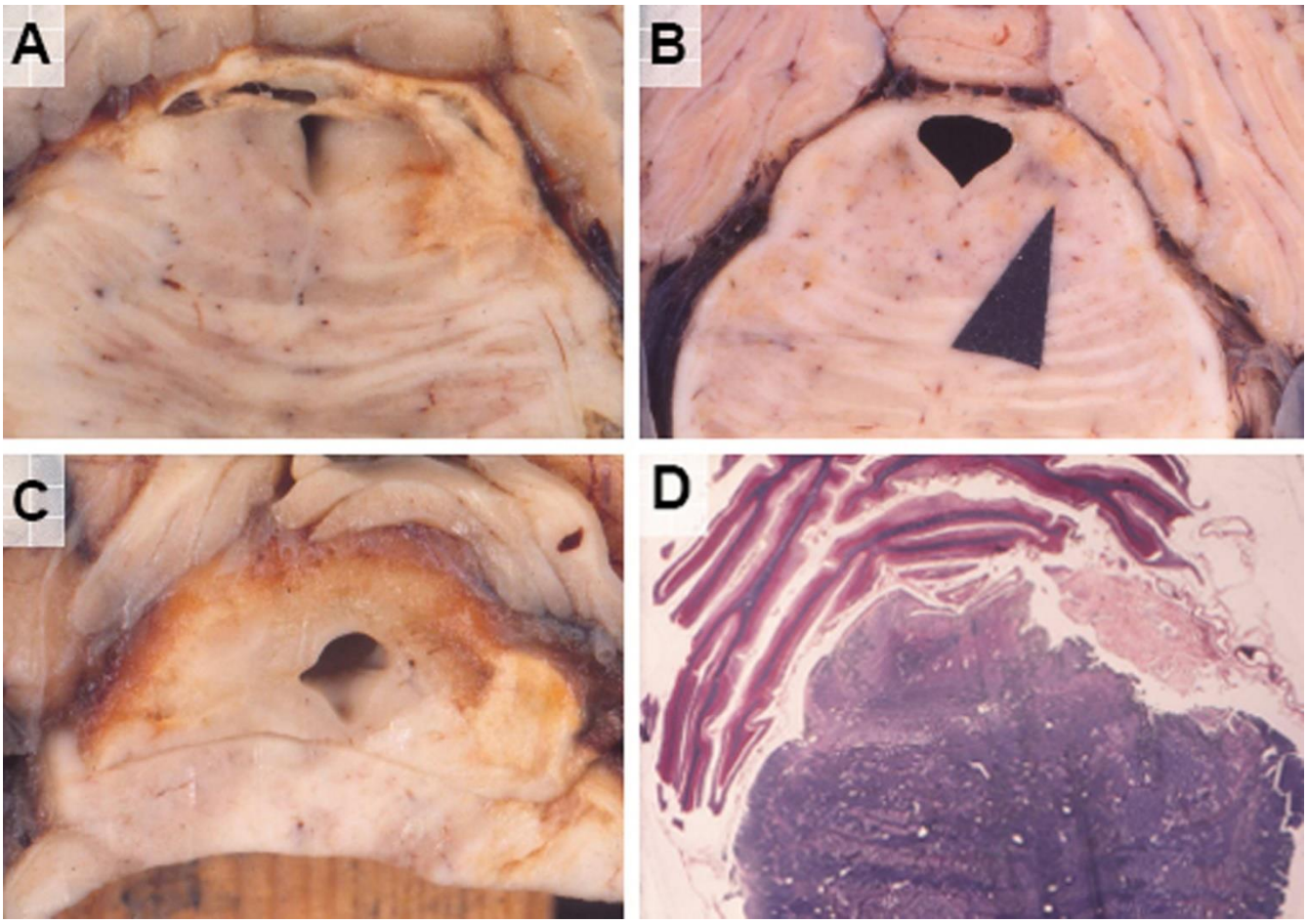

Figure 4.

A. Old hemorrhagic necroses in the dorsal and dorsolateral pontine tectum and tegmentum. **B.** Small necrosis in the right dorsolateral pontine tegmentum. **C.** Compression necroses of the right dorsolateral pontine tegmentum and the adjacent cerebellar gyri. Luxol fast blue. **D.** Extensive, mainly unilateral, old necroses of the dorsal and dorsolateral pontine tegmentum. Luxol fast blue. (A–C from [25] with permission from the publisher Taylor & Francis Ltd)

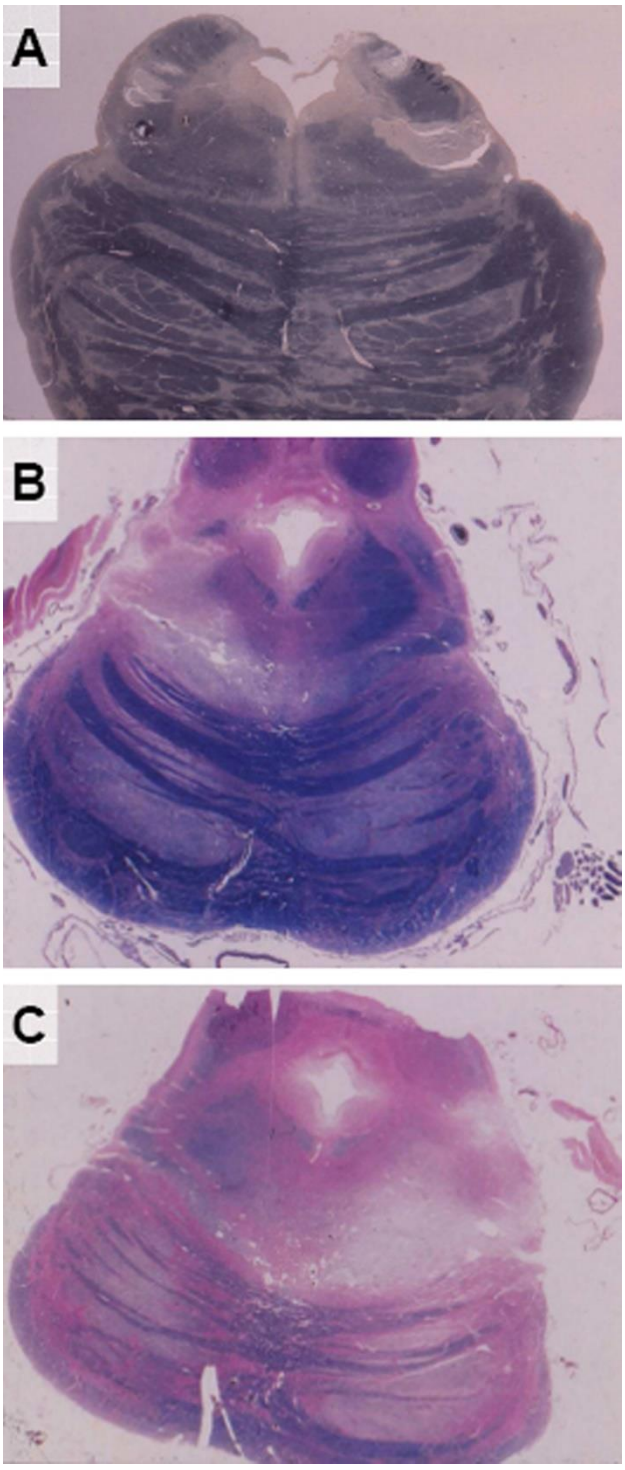

Figure 5.

A. Bilateral vascular compression necroses in the dorsolateral tegmentum of the upper pons and in the brachium conjunctivum. **B.** Unilateral vascular necroses of the dorsolateral tegmentum of the upper pons and bilateral incomplete degeneration of the pyramidal tracts. **C.** Necroses in the lateral and ventral pontine tegmentum and bilateral partial degeneration of the pyramidal tracts in the pontine basis. All Heidenhain stain.

Five subjects survived TBI for periods ranging from 22 to 293 days in various recovery states from UWS, presenting with MCS associated with spasticity and moderate to mild parkinsonian symptoms. Neuropathology revealed residuals of subdural hemorrhage (n = 1) and cortical contusions (n = 2), callosal damage (n = 1) and diffuse WM lesions (n = 3), uni- or bilateral lesions of globus pallidus and/or thalamus with or without lesions to the SN were seen in one case each, as well as hippocampal/parahippocampal lesions (n = 2). Brainstem lesions were restricted to old uni- or bilateral necroses in dorsolateral pontine tegmentum (Fig. 5A) that were associated with diffuse pontine gliosis in one case.

A 30 year-old man, a motorcyclist hit by a car, survived after evacuation of a subdural hematoma for 301 days, first 20 days in deep coma and subsequently with moderate improvement in UWS. In addition to right-sided spasticity, he developed almost symmetrical akinesia, bilateral rigidity and hypomimia with mild unilateral resting tremor. He died in 1968 hence no MRI was possible. He also received levodopa through gastric tube and later orally, which was followed by reduction of rigidity and hypomima without changes of spasticity. He died from pneumonia. Neuropathology revealed a brain fracture and residuals of subdural hematoma and superficial cortical contusions as well as bilateral partial necrosis of striatum and globus pallidus, diffuse WM lesions and considerable hippocampal lesions with left-sided predominance. The floor of the 3rd ventricle, the periaqueductal gray matter and the midbrain tegmentum were relatively preserved, while old necroses involved the dorsal and dorsolateral pontine tegmentum and the brachium conjunctivum (Fig. 5A). Another vascular necrosis in the dorsolateral tegmentum of the rostral pons (Fig. 5B) was associated with partial degeneration of the pyramidal tracts in the pontine basis (Fig. 5C).

Discussion

Parkinsonian symptoms are well recognized as a component of posttraumatic encephalopathy in boxers and in other sport-related traumatic brain injuries (TBI) [42–44]. The incidence of parkinsonism

after TBI (PTP) has been estimated to 3.07 % overall and to 11.59 % in TBI patients aged over 65 years [45]. Almost 100 years ago, the minimal criteria for the diagnosis of Parkinson's syndrome following acute head injury (PTP) were that (1) the trauma should be severe and should have led to concussion or unconsciousness, (2) there should be a close temporal relation between the acute trauma and the onset of parkinsonian features and the course of parkinsonian features should be uninterrupted [46].

The number of PTP cases after acute TBI in the earlier literature is limited [20, 47, 48]. A man aged 36 years with a skull fracture and unconsciousness for 24 hours developed over six weeks a predominantly right-sided, slowly progressive, levodopa-unresponsive parkinsonian syndrome. Neuroimaging disclosed a cerebral infarction in the left caudate and lenticular nucleus, suggesting impairment of nigro-striato-frontal circuits [49].

Other studies suggested that in PTP, supplementary motor area impairment seems important [50]. In a series of 54 patients who died in prolonged coma after closed TBI, a man aged 30 years died 301 days after a motorcycle accident in a partial recovery state from PVS, following a coma of 40 days. He had no skull fracture, cortical contusions or intracerebral hemorrhage but presented with parkinsonian features in addition to chronic decerebration. Autopsy revealed extensive brainstem lesions due to tentorial compression of the rostral brainstem as complications of increased ICP [22]. Matsuda and colleagues [51] reported three patients with PVS after severe TBI who, after recovering from prolonged loss of consciousness, presented parkinsonian features with mainly rigidity and hyperkinesia, which improved after levodopa treatment. T2-weighted MRI studies showed lesions in the dorsolateral midbrain and the cerebral peduncle, suggesting axonal injury involving the dopaminergic system (SN and ventral tegmental area). These findings implied that the midbrain was injured by tentorial compression induced by translatory and rotatory acceleration when the cranium was struck in its sagittal axis, or by posterolateral damage [52, 53]. This conclusion was based on neuroradiological and neuropathological studies on PVS after TBI, indicating that the most common structural lesions were diffuse axonal injury involving the corpus callosum, the thalamus and the dorsolateral aspects of the rostral brainstem [26, 54]. A study using voxel-based morphometry on structural MRI involving 61 patients with DOC of traumatic origin found widespread structural brain injury in the brainstem, midbrain, thalamus, hypothalamus, basal forebrain, cerebellum, and posterior corpus callosum. Potential structural differences were found between UWS and MCS, especially at the individual level [7].

Primary traumatic brainstem lesions after severe TBI inducing parkinsonian symptoms are either caused by hyperextension of the head, tearing forces or rotation mechanisms leading to contusions, fatal tears and hemorrhages of the rostral brainstem [55] or by shearing motion due to a rotatory mechanism and cavitation forces inducing hemorrhages and strains in the upper brainstem [23]. This is documented by two personal observations: first, a 19-year-old motorcyclist who died after 18 hours in deep coma after a rear-end collision crashing into a tree showed rupture of the diencephalon and hemorrhages in the SN; second, a 37-year-old man who survived 10 days in deep coma after a drunken fall with multiple fractures of the calvaria showed multiple cortical lacerations, deep diencephalic ruptures and hemorrhages in midbrain SN and rostral pons [56]. Rare cases of patients with traumatic SN lesions who survived for a longer time with or without developing a parkinsonian syndrome have been reported, such as a subject who survived a severe TBI with symmetric SN necroses for 32 years without parkinsonism [57].

The findings in the present study of patients who developed parkinsonian symptoms in the course of long-term UWS after blunt TBI and in an earlier study of a larger group of patients with prolonged UWS after severe TBI [25] are in favor of a secondary traumatic cause of morphological lesions related to prolonged posttraumatic UWS, recovery from UWS and defective states including posttraumatic parkinsonian symptoms. This conclusion is based on the following facts: (1) Translatory and rotational acceleration following TBI is usually followed by extensive cortical contusions/lacerations at the contralateral side of the focal impact, often associated with lesions or rupture of the corpus callosum, which was seen in only 13.3 % of cases in the present series. (2) Direct or "primary traumatic"

lesions to the rostral or caudal brainstem due to rotational shearing injury or rotatory acceleration forces are usually associated with acute death [56, 58, 59]. However, in rare patients with long survival following acute TBI, symmetrical necrosis of the SN without clinical parkinsonian symptoms has been reported [57]. In the majority of cases with prolonged survival in UWS and recovery states, the morphological lesions are restricted to the dorsal and dorsolateral pontine tegmentum, with preservation of the upper brainstem. (3) When comparing the frequency of brainstem lesions and morphological signs of increased ICP, there is strong association between both parameters. This is particularly true for the UWS group, when considering the presence of intracranial expanding lesions, the history of elevated ICP and the morphological sequelae of elevated ICP in various cerebral regions, e.g., compression necrosis in the hippocampus, which is seen in up to 80 % of fatal TBIs [25, 60–62]. Patients surviving TBI in deep coma, in addition to frequently showing both intracranial hemorrhages, cortical contusions (about 80 %) or hippocampal lesions (only 50 %), showed multiple brainstem lesions mostly involving the floor of the 3rd ventricle, the periaqueductal gray matter and the brainstem tegmentum, involving the ascending arousal system (AAS) or the ascending arousal network (AAN) [29, 37, 58, 63]. These lesions are frequently associated with diffuse axonal injury [28, 64, 65], disrupting the connection between brainstem, thalamus, forebrain, and substantially impairing the activation of the default mode network [66], the resting state and other functional networks [67]. While some patients will irreversibly remain in UWS, particularly due to severe damage to central areas of the upper brainstem, usually involving sequelae of increased ICP and transtentorial compression of the upper brainstem, other patients evolve to a minimally responsive condition or MCS [68, 69]. In these cases, brainstem lesions are usually restricted to dorsolateral/peripheral parts of the pontine tegmentum with preservation of the AAS [17]. As illustrated in a former and in the present case series, these patients, irrespective of occasionally frequent supratentorial lesions, may show involvement of the dorsolateral pontine tegmentum, the cerebral peduncles and the SN, with preservation of the central parts of the rostral brainstem. There is evidence that during recovery from traumatic coma, there is increase in brainstem-thalamic or AAN connectivity [70]. The distribution pattern of the brainstem lesions in the present series of posttraumatic UWS and residual parkinsonian symptoms, i.e., superficial softening in the dorsolateral tegmentum of the rostral pons and the velum medullare anterior, corresponds to the supply area of branches of the long lateral midbrain and pontine vessels, the superior cerebellar and posterior perforating arteries or of the basal and internal cerebral veins. Focal lesions in the dorsolateral pontine tegmentum affecting the superior cerebellar peduncle and the lateral lemniscus correspond to the supply areas of branches of long circumferential and superior cerebellar arteries or the drainage territory of precentral cerebellar veins as well as of the lateral sulcus veins. Occasional small scattered necroses and hemorrhagic scars in the pontine tegmentum result from obstruction of branches of circumferential vessels or the superior cerebellar artery (Fig. 2 D–F). These circulatory disorders result from compression of the brainstem tegmentum, leading from increased ICP to free tentorial edge / transtentorial shifting. The lesion pattern of posttraumatic parkinsonian symptoms and the therapeutic efficacy of long-term levodopa treatment suggest a dysfunction of the nigro-striato-cortical catecholaminergic system [14, 71], which may, however, progressively decompensate in some patients with long-lasting UWS after severe TBI.

The limitations of the present study based on archival material are threefold: the absence of MRI data and / or SPECT and PET data on striatonigral dysfunction [16], the lack of immunohistochemical data on Alzheimer-related lesions, in particular of analyses of p-tau and β-amyloid to exclude changes akin to chronic traumatic encephalopathy [72, 73] and the lack of data on amyloid precursor protein to detect axonal injury [74], which was partly detected in the present study by Bodian silver impregnation. Another limitation is the fact that disorders previously diagnosed as "apallic syndrome" or PVS had to be reclassified using current criteria (UWS).

The essential point of the present study is to demonstrate the morphological basis of rare parkinsonian symptoms in the course of UWS following fatal TBS. This endeavour appears important for

further clinical and prognostic studies aiming to improve assessment of brain (dys)functions in prolonged DOC / UWS. Here, modern neuroimaging and other markers may provide valuable signs, not only documenting changing nosology but also offering further insights into the pathophysiology of post-traumatic parkinsonism.

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Conflict of Interest Statement

The author declares that he has no conflict of interest.

Ethics approval

This is a retrospective analysis of archival material of anonymized patient data from the years 1958–1980, for which no later ethical approval could be achieved.

Abbreviations

CT - computer tomography, **DOC -** disorder of consciousness, **ICP -** intracranial pressure, **MCS -** minimally conscious state, **SN -** substantia nigra, **PTP -** posttraumatic parkinsonism, **PVS -** persistent vegetative state, **TBI -** traumatic brain injury, **UWS -** unresponsive wakefulness syndrome, **WM -** white matter.

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