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ORIGINAL ARTICLE

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Pontine axonal injury after brain trauma and nontraumatic hypoxic-ischemic brain damage

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Abstract Experimental studies have shown that diffuse axonal injury is usually induced by positive or negative acceleration mechanisms. In order to determine the reliability of axonal injury (AI) as a marker of this type of traumatic insult, we compared cases of trauma-induced focal cortical hemorrhage without dural involvement (n = 67) with cases of trauma-induced subdural bleeding without cortical hemorrhage (n = 26). Both groups exhibited a wide range of post-traumatic survival times. The injuries in the first group were caused mainly by direct impact to the head, those in the second by acceleration/deceleration mechanisms. The investigations were based primarily on immunohistochemical demonstration of antibodies targeted to β-amyloid precursor protein (β-APP) in the pons as a marker of AI and the results were assessed semiquantitatively. No significant differences were found between the two groups. In both groups AI was detected in 80–100% of cases with survival times of more than 3 h and two thirds of all positive cases showed pronounced positivity. Additional comparison of cases of brain death due to mechanical trauma (n = 14) with cases of brain death due to non-mechanical trauma (n = 18) also disclosed no significant intergroup differences. Finally, investigations of the pons in cases of non-traumatic death due to cerebral hypoxia/ischemia (n = 51) demonstrated AI with the same frequency as in the other groups, although the expression tended to be less pronounced. Our results confirm that β-APP expression in the pons is a reliable indicator of AI but does not discriminate between injuries caused by traumatic strain or shearing mechanisms and secondary damage due to cerebral hypoxia/ischemia or edema. In the large majority of cases with prolonged post-traumatic survival, it can therefore be assumed that AI in the pons is the consequence of primary and/or secondary events or a combination of both, as is common in non-missile head injury survived for more than 90–120 min. Therefore, positive differentiation of the type of biomechanical event based on this criterion alone is not possible.

Key words Axonal injury · Midbrain · Biomechanics · Specificity · Diffuse axonal injury

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Introduction

The phenomenon of diffuse degeneration of the white matter in cases of non-missile head injury was described by Strich (1956) as resulting predominantly from external force (Adams et al. 1982; Gennarelli et al. 1982; for review see Unterharnscheidt 1993; Graham and Gennarelli 1997), although it appears to show little relationship to the severity of injury (Gennarelli 1996). Gennarelli et al. (1981) were able to show that diffuse axonal injury (DAI) as the first indicator of white matter involvement is induced by a shear-strain mechanism after non-impact accelerations lacking the compounding effects of direct impact injuries. In 1993 Maxwell and his team could demonstrate DAI in a subhuman primate model using angular acceleration (Maxwell et al. 1993). In a porcine model (Meaney et al. 1995) and a rat model (Lighthall et al. 1989; Dixon et al. 1991), DAI was produced as an acceleration-deceleration response to impulsive head rotation. In addition, Maxwell et al. (1996) induced axonal injury (AI) by stretching the optic nerve of adult guinea pigs. Though all of these experiments were intended as models of AI, they obviously also provide additional information

Table 1 The case material according to age and gender

Diagnosis group	Age (years)							Sex		
	<3	3–14	15–29	30–59	>60	min	max	f	m	N
Closed Head Injury										
Cortical hemorrhages	1	5	6	43	12	7 m	92 y	25	42	67
Subdural. hematomas	1	0	0	18	7	4 m	85 y	9	17	26
Brain Death										
Mechanical trauma	0	1	4	7	2	13 y	65 y	3	11	14
Non-mechanical trauma	2	2	7	6	1	4 m	72 y	3	15	18
Hypoxia/Ischemia	12	4	10	22	3	11 d	83 y	17	34	51
Total cases	16	12	27	96	25	11 d	92 y	57	119	176

on the physical pathogenesis of this phenomenon, as was demonstrated by Adams and coworkers (1986) in cases of traumatic brain injury in humans.

Based on these and comparable findings, the phenomenon of DAI is currently thought to depend on acceleration and the progression from sagittal through oblique to lateral rotational acceleration is particularly associated with more severe DAI (Gennarelli et al. 1987). As the severity of the rotational forces increases, the more probable it is that central areas of the brain will be involved (Gennarelli et al. 1981; Blumbergs et al. 1995). A direct impact to the head is likely to cause an extraaxial collection, whereas acceleration-deceleration injuries more frequently cause diffuse cerebral damage (Miller et al. 1978; Adams et al. 1982). Falls from a standing position are only rarely associated with DAI (Adams et al. 1982; Lobato et al. 1983).

These observations suggest that neuropathological investigations should be able to demonstrate qualitative and quantitative differences in the human brain dependent on the type of biomechanical process. We therefore studied a selected case material to determine whether AI can be attributed to specific types of external forces and thus allow conclusions regarding the nature of the biomechanical cause.

AI was demonstrated in paraffin sections using antibodies targeted to β-amyloid precursor protein (β-APP) (Gentleman et al. 1993; Sherriff et al. 1994). This recently developed method has proved to be both specific and highly sensitive. Moreover, β-APP antibodies appear to target only injured axons (Povlishock and Christman 1995). To our knowledge, this method has never before been used to establish correlations between AI and the type of biomechanical insult.

The study was confined to the pons, which is one of the most vulnerable regions of the brain with an especially high rate of AI (Blumbergs et al. 1995; Gentleman and Graham 1997). The pons appears to be particularly well-suited for this retrospective study because in nearly all cases of closed traumatic brain injury it is located far from the impact of a direct blow to the head (and brain) and therefore it may give evidence of a “diffuse” type of axonal injury. Otherwise, the changes are nonspecific, as different mechanisms can induce axonal damage including shift, distorsion, raised intracranial pressure, deformation as a result of acceleration/deceleration or a combination of these. We investigated whether the distribution and amount of AI is the same or different depending upon whether the principal pathology is due to either impact or acceleration/deceleration or a nondisruptive process.

Materials and methods

Case material

The age and sex of the case material are summarized in Table 1. A total of 176 brains were examined which could be divided into the following diagnostic groups:

Group 1: Fatal cortical (i.e. contusional) hemorrhage – without subdural hematoma (n = 67): the types of injury are listed in Table 2.

Group 2: Fatal subdural hematoma - without cortical hemorrhage (n = 26): the types of injury are listed in Table 3.

Cases with total brain necrosis as well as with brain herniation and high ICP were not included in these two groups.

Group 3: Brain death after mechanical closed head injury (n = 14).

Group 4: Brain death without mechanical closed head injury (n = 18).

Table 2 Cases of traumatic cortical hemorrhage according to type of external force

Causes of traumatic cortical hemorrhages	N
Unknown	4
Fall	34
Traffic accident	22
Blow	7
Total cases	67

Table 3 Cases of subdural hematoma according to type of external force

Causes of subdural hematomas	N
Unknown	5
Fall	1
Traffic accident	5
Blow	13
Blow and fall	2
Total cases	26

Table 4 Cases of brain death (total circulatory arrest within the brain parenchyma) according to cause

Causes of brain death	N
Mechanical trauma (total cases)	14
Cortical hemorrhages	6
Subdural hematoma	5
Extradural hematoma	3
Non-mechanical trauma (total cases)	18
Drowning	5
Intoxication	4
Bleeding	3
Hanging	3
Cardiac arrest	2
Asphyxia/aspiration	1

Table 5 Cases of cerebral hypoxia or ischemia and reperfusion according to cause

Causes of hypoxia/ischemia	N
Drowning	13
Hanging	13
Cardiac arrest	8
Asphyxia/aspiration	8
Strangulation (manual/ligature)	6
Bleeding	2
Intoxication	1
Total cases	51

The diagnosis of "brain death" was based on clinical criteria. The cases of mechanical closed head injury resulting in brain death involved dural hematoma (n = 8) and cortical hemorrhages (n = 6). The cases of non-mechanically induced brain death involved cessation of cerebrovascular blood flow or a total, irreversible cut-off of the oxygen supply to the brain evoked by a variety of causes. The types of injury are listed in Table 4.

Group 5: Fatal cerebral hypoxia/ischemia (n = 51): the types of injury are listed in Table 5.

In contrast to the cases of brain death (groups 3 and 4), these cases were characterized by subsequent reperfusion and therefore did not exhibit total brain necrosis or elevated ICP, but, of course, a wide range of irreversible structural damage was manifested.

All brains were studied macroscopically and microscopically and documented photographically. In most cases a forensic neuropathology report had been made regarding the cause of death, causal relationships, survival time and type of trauma. This report was based on findings at autopsy, including macroscopic and microscopic examination of other body organs and the skull and took into account clinical data as well as findings by the public prosecutor's office and police. In every case the occurrence of AI was correlated with the post-traumatic survival time.

Histological evaluation

Each brain was fixed in toto for at least 2 weeks in buffered formaldehyde prior to macroscopic examination. Blocks of brain tissue were cut from at least eight brain regions (frontal lobe, neostriatum, thalamus, hippocampal area, cerebellum, superior pons, inferior pons, medulla oblongata) embedded in paraffin and the paraffin sections subjected to a variety of staining procedures.

For the present study, investigations were carried out on microscopic sections obtained from the rostral and caudal planes of the pons and, in some cases, on sections from the dorsal midbrain. In addition to hematoxylin and eosin, β-APP immunostaining was done according to the method of Sheriff et al. (1994). The sections were subjected to microwave pretreatment and the mouse monoclonal antibody against β-APP (clone 22 C 11, Boehringer AG, Mannheim, Germany) was applied at a dilution of 1:50.

The ABC method (horseradish-peroxidase, Dako GmbH, Hamburg, Germany) was used with the secondary antibody (biotinylated rabbit-anti-mouse, Dako GmbH, Hamburg, Germany) diluted 1:200. Peroxidase reactivity was demonstrated with diaminobenzidine (Boehringer AG, Mannheim, Germany) and the reaction product was intensified with 0.5% CuSO4 for 5 min.

Grading and statistical evaluation

β-APP positivity was registered in cases in which single immunoreactive axons, axon fragments or axon bulbs ("retraction balls") were repeatedly and unequivocally detected in one of the sections through the rostral or caudal plane of the pons. The following additional classification was made, blind to any clinical details, macroscopical findings and, in particular, to survival time:

(0) No recognizable expression in the midbrain.

(+) Isolated or disseminated single β-APP-positive axons, fragments or bulbs.

(++) β-APP-positive axons, fragments or bulbs occur distinctly in groups or are distinctly and diffusely distributed.

The percentage of cases where β-APP was detected was determined for the different survival times and the confidence intervals calculated. Statistical comparison was made using the test of equality and of two percentages according to Sikal and Rohlf (1969).

Results

Group 1: Fatal cortical hemorrhage without dural hematoma

The results of the evaluation are shown in Fig. 1. β-APP-positive axons were detected in the pons of approximately 80% of cases with a survival time exceeding 3 h. A pontile hemorrhage was present in only 21% cases, all of which expressed AI.

Topographically, AI was centered on the midline structure, with a perivascular accentuation. It was also located in the medial leminisci and cortico-spinal tracts as well as in the dorsolateral quadrants of the pons. There was no clear correlation between the presence of AI and biological age or gender. Axon bulbs were more common in cases with prolonged post-traumatic survival than in cases with brief survival.

Group 2: Fatal subdural hematoma without cortical hemorrhage

The findings are summarized in Fig. 2. Nearly 100% of cases with a survival time exceeding 3 h but of not more than 4 days were β-APP positive. Cases with survival times exceeding 4 days had a slightly lower, but still high, rate of β-APP positivity of approximately 80%. It is striking that in a high percentage of cases survival times of

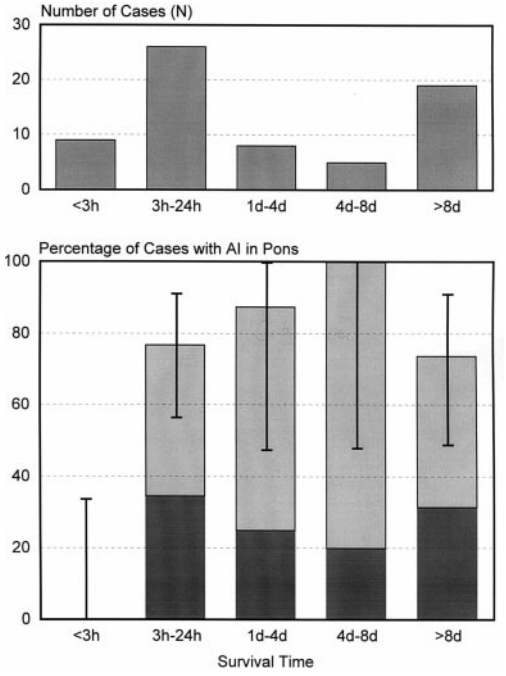

Fig. 1 Frequency of diffuse axonal injury in the pons in cases with fatal cortical hemorrhage dependent on survival times. The top figure shows the total number (n) of cases investigated, the lower figure the mean percentage of all cases expressing AI (total the columns +/++) in the pons, as well as the confidence interval; the black parts of the columns demonstrate the mean percentage of cases with slight β-APP expression (+)

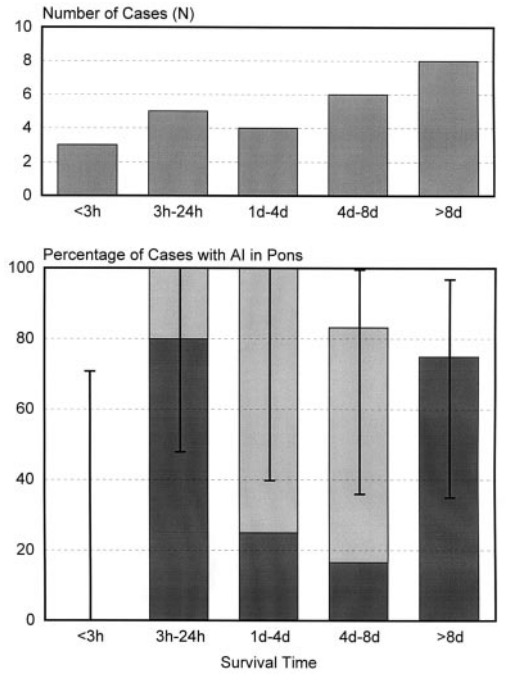

Fig. 2 The frequency of diffuse axonal injury in the pons in cases with fatal subdural hematoma without cortical hemorrhage dependent on survival times (for details see legend to Fig. 1)

3–24 h and over 8 days were associated with comparatively slight β-APP expression.

Statistical comparison of groups 1 and 2

Comparison of the two groups (cortical hemorrhages and subdural hematomas) revealed no significant differences in the frequency of AI.

Groups 3 and 4: Brain death caused by mechanical and non-mechanical trauma

The correlation between β-APP expression in axons and the time spent on a respirator is given in Fig. 3 and clearly shows that AI was present in a high percentage of cases with irreversible cessation of brain reperfusion (brain death). Following mechanically induced brain death (group 3), AI could be demonstrated in more than 80% of cases with a survival time under 4 days and the percentage was somewhat lower after longer survival times.

In group 4 (intracranial circulatory arrest following a non-mechanical event), the total number of cases with β-APP-positive axons in the pons was somewhat lower, attaining a maximum of 80%. Statistical comparison disclosed no significant differences either between the two groups or between the survival time in each group.

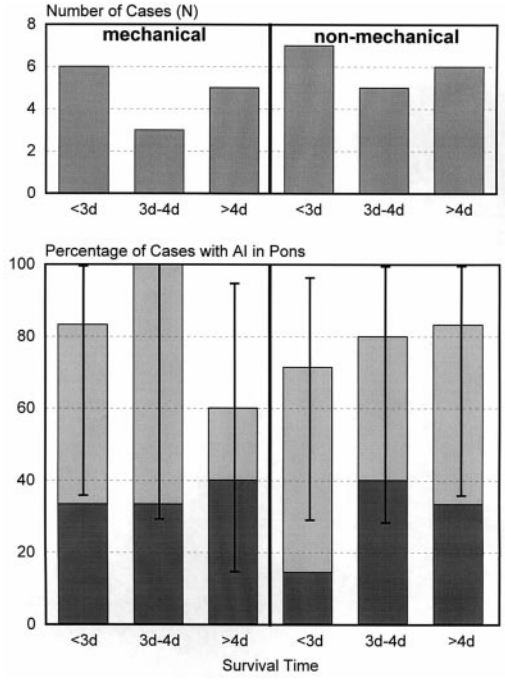

Fig. 3 Cases with brain death induced by mechanical trauma (left part of the figure) and non-mechanical trauma (right part of the figure) dependent on time on respirator (for details see legend to Fig. 1)

Group 5: Fatal brain hypoxia and/or ischemia

The findings are summarized in Fig. 4. In this group cases with a survival time under 3 h also showed no β-APP-pos-

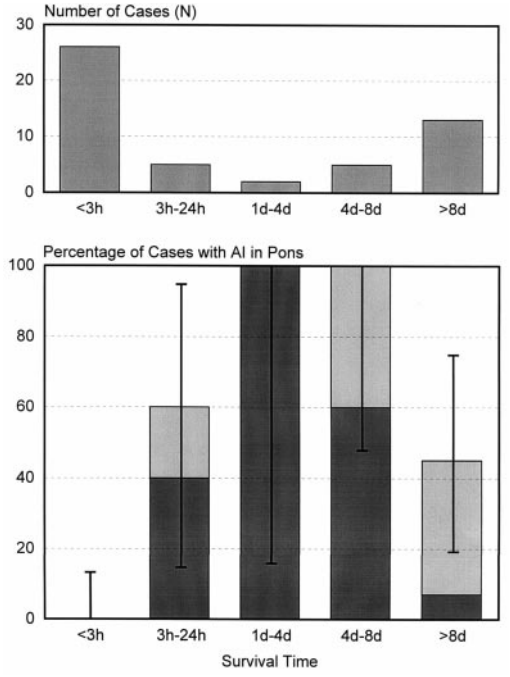

Fig. 4 Cases with fatal brain hypoxia/ischemia and reperfusion dependent on survival time (for details see legend to Fig. 1)

itivity in the pons, 60% of cases with a post-traumatic survival time of up to 24 h expressed β-APP which increased to 100% for cases surviving for 24 h–8 days. All the cases which expressed a β-APP positive reactivity in the pons were additionally marked by a structural alteration due to the preceding hypoxic process. It is noteworthy, however, that in a relatively high percentage of these cases the intensity of AI expression was rather less than it was in cases of traumatic injury.

Discussion

Our findings allow the following discussion and conclusions:

1. AI could not be demonstrated by β-APP in the pons within the first 3 h after traumatization by an external force. Simultaneous investigations on brain tissue damaged postmortem could also detect no AI which indicates that β-APP-positivity in axons and bulbs is the result of a vital reaction (cf. McKenzie et al. 1996; Oehmichen et al. 1997) requiring a minimum posttraumatic survival of about 3 h. Beside the emigration of leukocytes (Oehmichen 1990) and the expression of tumor necrosis factor-α (Kita et al. 1997) the demonstraton of axonal injury may be a further marker of vitality (Oehmichen et al. 1998). This finding agrees with those of other authors, who even detected AI in a few cases with a survival time of only 1.75 h (Blumbergs et al. 1995).

2. AI could be demonstrated in the pons using β-APP in 80–100% of cases of closed-head injury with a survival time of more than 3 h. This was equally true for cases of subdural hematoma without cortical hemorrhages and for cases of cortical hemorrhages without subdural hematoma. Both the extent of AI and the proportion of positive cases in each group were comparable. Statistically significant differences between the two groups were not found.

Isolated subdural hematoma without cortical hemorrhage is generally caused by acceleration, sometimes with rotational or translatoric components (Krauland 1961). In contrast, the majority of isolated cortical hemorrhages result from impact, with acceleration components clearly in the background. Our own qualitative and quantitative comparison, however, disclosed no real difference between these two groups with regard to the occurrence of AI as detected by β-APP staining. This finding alone indicates that no conclusions can be drawn regarding the type of injury based on the presence of AI in the pons.

The overlapping character of the cause of both groups of traumatic injury (cortical and subdural hemorrhages) may be an explanation for the lack of a significant difference. But a clear discrimination of these groups according to the biomechanic basis of trauma, e. g. either an isolated focal impact or an isolated acceleration mechanism, is possible only in very few real (human) cases or, of course, in animal experiments. An additional analysis of the biomechanic events and the clinical data of the few AI negative traumatic cases in our case material gave no further evidence of a special type of trauma.

The phenomenon of AI in both the traumatic groups may be explained by a primary mechanically induced damage of the axons in the pons. Another explanation may be a secondary, possibly non-disruptive damage of the brain stem by mass effects of the subdural hematomas.

It also agrees with the observations of other authors that pure shear and tensile forces do not evoke AI in all cases of mechanical impact, which means on the other hand that AI is not the immediate consequence of traumatic tissue tearing in all cases. The assumption that only the tensile forces of injury immediately tore the axons, causing them to retract and form reactive axonal swelling, or “retraction” balls, can thus be regarded as definitively disproved. As described by Maxwell and coworkers (1997) as well as by Povlishock and coworkers (Povlishock and Christman 1995; Povlishock and Jenkins 1995; Povlishock 1997), AI is mostly a delayed consequence of a complex axolemmal and/or cytoskeletal change evoked by a traumatic episode, which then leads to cytoskeletal collapse and impairment of anterograde axoplasmic transport ultimately progressing to axonal swelling and disconnection.

3. To determine whether AI is specific for primary mechanical brain damage and whether - and to what extent - secondary factors influence the development of AI, we compared cases of brain death resulting from mechanical injury and cases of brain death resulting from non-mechanical injury. Although the extent of the AI was consistently lower in the latter group of brain death than in the first two groups suffering injury from an external force,

the percentage of all cases with AI was almost identical (see also Jellinger and Seitelberger 1970).

This finding shows that detection of AI in the pons does not allow determination of whether the AI resulted from the primary mechanical injury or from an overlying (and masking) secondary event (Olsson et al. 1996; Graham 1996). This view is supported by our investigations of cases of isolated fatal brain hypoxia and/or ischemia without traumatization caused by an external force.

4. The possibility that primary mechanical damage to axons is masked by secondary events such as hypoxia, ischemia or edema received additional support from the following findings:

Topographically, AI was located predominantly in areas of the pons which also exhibited secondary hemorrhages, namely in the region of the fibrae pontis intermediae and the leminisci mediales. The AI aggregated in perivascular neuropils and in the inferior colliculi of the brain stem, the latter being an area especially vulnerable to hypoxic damage.

It is further known that secondary events such as hypertension, hypoxia and global ischemia can impair the bioenergetic and electrophysiological status of the brain and lead to neuronal damage (Jenkins et al. 1988, 1989 a,b). There is evidence that the traumatized brain is hypersensitive to delayed (i.e. secondary) cerebral ischemia. It thus seems quite possible that secondary events can evoke not only neuronal damage but also AI, which is characterized in part by a change in the permeability of previously damaged axons (Graham and Gennarelli 1997). This conclusion is supported by the hypothesis of Povlishock and coworkers (Povlishock and Jenkins 1995; Povlishock 1997) that mechanical impact results in physical brain deformations that are sufficient to alter ion channel permeability and result in the transient loss of neuronal ion homeostasis.

Secondary injuries, however, require time and it is not yet known how early secondary hypoxic AI can occur. Our own results indicate that this also takes about 3 h. It follows that if an antibody targeted to β-APP is applied in cases of secondary AI, the AI expression will tend to increase in proportion to the survival time, i.e. that the number of axons or axon fragments expressing AI will increase with time. This appears to agree with observations on AI following hypoxia (Fig. 3 - right columns, also Fig. 4) and even in cases of cortical hemorrhage inflicted by external force, the number of cases with AI in the pons rose with increasing post-traumatic survival time. Our case material was too small, however, to allow detailed conclusions especially with regard to the hours immediately following injury.

5. In the individual case involving head injury and a survival time exceeding 3 h, secondary events cannot be definitely ruled out. If AI can be caused by a combination of entirely different factors (mechanical, hemodynamic or biochemical - hypoxic and metabolic), then it should be impossible to reliably determine the type of external biomechanical force causing closed head injury.

But as infeasible as it is to distinguish in the pons region between the consequences of a primary external force and those of secondary alterations such as edema and hypoxia, it is even less possible to make this distinction in the cerebral region of maximum external force. The secondary changes will probably occur more dramatically at the site of maximum external force rather than in the pons.

6. This investigation was limited to AI expression in the pons region. The results, however, provide no further information on the phenomenon of the diffuse distribution of AI, so-called DAI, which is understood as a diagnostic entity. The topographic distribution of AI along the midline structures of the whole brain should give diagnostic evidence of the type of mechanical effects on axons expressing β-APP (Graham and Gennarelli 1997).

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ANNOUNCEMENT

In connection with the European grant to STADNAP under the Thematic Network Contract No. SMT4-CT97-7506, applications are requested from laboratories who wish to extend their level of expertise in forensic DNA testing and who consider that they could benefit from a period of training at one of the member laboratories of STADNAP. Priority will be given to laboratories who consider that the level of expertise is lower than the currently accepted standard for forensic DNA testing within European member states. The urgency of training and the promotion of younger scientists will also be given priority. Applications for short term secondments should be submitted in writing to:

STADNAP secondment programme WP3
c/o Prof. Dr. B. Brinkmann, Manger WP3
Institut für Rechtsmedizin der W.W.U.
Von-Esmarch-Strasse 62, D-48149 Münster, Germany

stating details of the proposed secondment and of the justification for sponsorship. Applicants should include their CV and publication list as well as a letter of acceptance from the host laboratory. Applications should be received by 31st July 1999.

The amount of funding will depend on the number of successful applications and will be decided by a unanimous vote of the members of the selection committee of WP3 on behalf of STADNAP.