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Aquaporin-4: A Predictor and Therapeutic Target for Permanent Paraplegia after Endovascular Thoraco-abdominal Aortic Aneurysm Repair☆

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WHAT THIS PAPER ADDS

Aortic aneurysm repair interrupts blood flow to the spinal cord and may cause an ischaemic cord injury that can induce paraplegia. Biomarkers and therapies that prevent this devastating complication are lacking. This study found aquaporin-4 (AQP4) to be approximately fourfold higher in the cerebrospinal fluid of patients who became permanently paraplegic post thoraco-abdominal aortic aneurysm (TAAA) repair *vs*. those who recovered from or did not develop paraplegia, highlighting its potential as a prognostic indicator. Pre-operative AQP4 inhibition preserved spinal neurons and glia in the dorsal horn and intermediate zones of white matter and protected against paraplegia in a rat model of ischaemic spinal cord injury. These insights identify AQP4 levels in cerebrospinal fluid as a biomarker, heralding paraplegia post-TAAA repair and prophylactic inhibition as a potential therapeutic target.

Objective: Endovascular thoraco-abdominal aortic aneurysm (TAAA) repair can impair spinal cord perfusion, leading to paraplegia. The mechanisms driving this devastating complication are poorly understood. This study aimed to interrogate the cerebrospinal fluid (CSF) proteome in patients after TAAA repair to identify biomarkers that herald permanent paraplegia. It also aimed to investigate a potential therapeutic target identified by proteomics using an *in vivo* model of ischaemic spinal cord injury (iSCI).

Methods: CSF was collected for proteomic analysis from patients before and following TAAA repair. A differentially expressed protein identified in human paraplegic subjects was subsequently interrogated in a rodent model of iSCI. The protein composition of CSF was analysed using tandem mass tag proteomics. Neurological examinations were carried out by a blinded neurologist and T2 weighted magnetic resonance imaging (MRI) was used to measure spinal cord volume and oedema. A rodent model of iSCI was used to investigate a clinically relevant therapeutic target informed by proteomic findings.

Results: CSF analysis was taken from 37 patients, all of whom had aneurysm repair using a custom branched and or fenestrated device (median age 73.5 years, range 67 − 78 years; 27 men, ten women; Crawford classification: six type I, 11 type II, 15 type III, three type IV, and two type V). Five patients remained permanently paraplegic and seven recovered from transient paraplegia. The CSF of patients who remained paraplegic contained approximately fourfold more aquaporin-4 (AQP4) (41.8 ± 19.2 ng/mL, $n = 5$) than those who recovered from paraplegia (10.8 ± 1.3 ng/mL, $n = 7$; $p = .005$) or did not develop paraplegia (10.8 ± 1.2 ng/mL, $n = 25$; $p = .004$). Permanently paraplegic patients had CSF AQP4 levels > 15 ng/mL and this was associated with greater cord oedema on T2 weighted MRI (1.77 ± 0.19 *vs*. 1.03 ± 0.36; $p = .032$). In a rodent model of iSCI, AQP4 inhibition preserved spinal neurons and glia in the dorsal horn and intermediate zones of white matter ($p = .004$) and protected against ischaemia induced paraplegia ($p < .001$).

Conclusion: The AQP4 level in the CSF of a patient represents a prognostic marker of permanent paraplegia after TAAA repair and highlights a novel therapeutic target. These findings represent a conceptual advance in the management of iSCI.

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INTRODUCTION

Paraplegia is a devastating neurological condition that has a profound effect on a patient's independence and quality of life.[1–3] The individual and societal impacts include a person's withdrawal from the community or workforce and yields a significant economic burden. The cost of caring for a paraplegic patient in the first year has been calculated at approximately €480 000 and €67 000 per annum thereafter.[4,5] The mechanisms driving paraplegia after an ischaemic spinal cord injury (iSCI) remain poorly understood. There is also a paucity of clinical indicators that predict those at risk,[6] and lack of therapies to mitigate or reverse the neurology after its onset.[7]

Perfusion of the spinal cord is maintained by an extensive blood supply that includes the intercostal and lumbar vessels, which directly originate from the aorta.[8–10] Endovascular thoraco-abdominal aortic aneurysm (TAAA) surgery, performed to prevent death from rupture, involves relining the aorta and excluding blood flow to the aneurysmal segment using stent grafts. However, these stents can also cover multiple intercostal and lumbar vessels, reducing blood flow to the spinal cord and potentially causing paraplegia in an unpredictable fashion.[11,12]

It was hypothesised that endovascular TAAA repair induces a hypoxic insult by reducing blood flow to the spinal cord, which results in breakdown of the blood—spinal cord barrier, releasing proteins into the local cerebrospinal fluid (CSF). This study investigated whether any of these proteins could serve as a clinically useful biomarker in the CSF that heralded permanent paraplegia after endovascular TAAA repair. Further mechanistic insights and the therapeutic utility of one protein of interest, aquaporin-4 (AQP4), was subsequently interrogated in an animal SCI model.

MATERIALS AND METHODS

Ethical approval for this study was granted by the Proportionate Review Sub-committee of the NRES Committee London — City & East (IRAS project 97052). Patients undergoing endovascular TAAA repair who had a prophylactic pre-operative CSF drain inserted were recruited into the study.

Study population

Any patient undergoing elective TAAA repair with a fenestrated or branched device where a prophylactic spinal drain was planned because of a high risk of spinal cord ischaemia was offered participation in the study. Emergency endovascular repairs as well as open repairs were not included, in order to maintain a homogeneous study population. Patients were divided into three cohorts based on neurological outcome after TAAA repair: (1) no evidence of paraplegia ($n = 25$); (2) developed post-operative paraplegia but recovered ($n = 7$); and (3) developed post-operative paraplegia and remained paraplegic ($n = 5$).

Endovascular aneurysm repair and spinal drainage

Fenestrated or branched stent grafts were used for endovascular TAAA repair. CSF was collected from prophylactic spinal cord drains. All drains were inserted into the subarachnoid space between L2/L3 or L3/L4, and CSF samples were collected pre-operatively and 24 hours post-drain insertion. A minimum of 20 mL of CSF was taken at each time point. Samples from traumatic spinal insertions and those that contained frank blood were excluded. CSF samples were immediately processed upon collection by centrifugation at 400 × *g* for 5 minutes with supernatants aliquoted, snap frozen, and stored at −80 °C until required for proteomic analysis.

Neurological assessment

Daily neurological examinations of sensory and motor function were recorded using the American Spinal Injury Association (ASIA) score.[13] Motor capacity was graded using the Oxford classification ranging from zero (total paralysis) through to a maximum score for each myotome of five (active movement against resistance). Formal diagnoses of spinal cord ischaemia and paraplegia status were only made by a consultant neurologist blinded to the study. A patient was diagnosed as permanently paraplegic if they were unable to walk, including using a walking stick, or were bed or chair bound. All subjects were followed up for at least one year post-operatively. Patients who developed neurology underwent T2 weighted magnetic resonance imaging (MRI) of the spinal cord within 24 hours of onset of symptoms and signs to confirm the presence of spinal cord infarction and rule out a compressing spinal cord haematoma.

T2 weighted magnetic resonance and spinal cord dimensions

Patients who developed neurology in the post-operative period underwent T2 weighted MRI (turbo spin echo sequence) with identical slice selection (same protocol using same machine within same hospital) of the spinal cord to confirm the presence of spinal cord infarction and rule out a compressing spinal cord haematoma. Neuroradiologists analysing all MRI scans were blinded to the clinical outcome of the patients. The volume of the spinal cord was measured using the equation: $\pi \times r1 \times r2 \times h$.[14] The formula $\pi \times r1 \times r2 \times h$ represents an approximation

for the surface area or volume of a conical frustum where $\pi \approx 3.14159$, r1: Radius of the top (smaller) base, r2: Radius of the bottom (larger) base. h: Vertical height between the two bases. Measurements of the spinal cord volume used coronal, sagittal, and transverse planes at the level of the ischaemic lesion. Control subjects, in whom no infarction was identified, were age and weight matched patients complaining of lower limb weakness and or sensory disturbance who had not had any vascular intervention or spinal cord ischaemic insult. Analysis of MRI of the spinal cord was made from T10 — L2, or until the level at which the conus medullaris ended. Differences in spinal cord volumes were represented as fold change relative to the mean spinal cord volume measured in control patients. MRI assessments were performed by two consultant level neuroradiologists blinded to the study and the patient's neurological status.

Animal studies

A comprehensive summary of the techniques used pertaining to the animal studies and the surgical techniques are described in detail in the Supplementary Methodology.

Statistics

Human data. Enzyme linked immunosorbent assay (ELISA) and MRI cord volume data were analysed by Kruskal—Wallis tests, as a normal distribution was not assumed. The proteomics data were analysed in R (R Foundation, Vienna, Austria).

Animal data. Animal histological data were analysed by one way ANOVA, as the Shapiro—Wilk test proved a normal distribution. Significance was taken as $p < .01$ for analysis of the proteomic data and $p < .050$ for all other analyses. Data were analysed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA) and R (R Foundation).

Full methodological information of the proteomics, bioinformatics, neurobehavioural analyses, and histological techniques is described in the Supplementary Methodology.

RESULTS

Over a three year period, 161 TAAA repairs were carried out, of which 155 were repaired using custom made branched and or fenestrated stent grafts. CSF was collected from 37 of these patients upon prophylactic pre-operative drain insertion and 24 hours after drain insertion (median age 73.5 years, range 67 — 78 years; 27 men, ten women; Crawford classification: six type I, 11 type II, 15 type III, three type IV, and two type V; Supplementary Figure S1). The decision to use a prophylactic CSF drain was based on a pre-operative assessment by the surgical team that the patient was at high risk of SCI (Supplementary Figure S2). Demographics, extent of aortic coverage, and nuances related to surgery were comparable between groups (Supplementary Table S1).

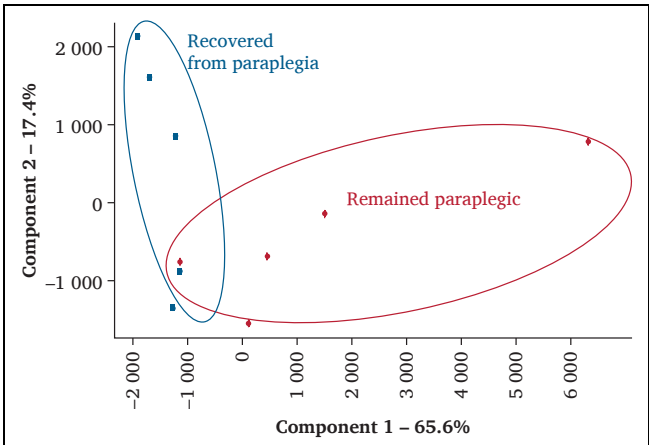

Figure 1. Principle component analysis comparing the cerebrospinal fluid proteome of permanently paraplegic patients (red circles, $n = 5$) and patients who recovered from paraplegia (blue circles, $n = 5$). All samples were taken 24 hours after surgery and before knowing which patients would eventually recover from paraplegia. Clear clustering of proteome content noted related to whether the patient recovered from paraplegia (blue oval) or remained paraplegic (red oval).

Permanent paraplegia in patients undergoing thoracoabdominal aortic aneurysm repair is associated with raised levels of glial and astrocytic proteins in the cerebrospinal fluid

Tandem mass tagged proteomics of CSF obtained before and 24 hours after surgery in five patients from each group identified a total of 1 038 proteins. Patient details of the proteomic analysis are shown in Supplementary Table S2. Despite a near identical pre-operative CSF proteome, principal component analysis of post-operative protein composition (Fig. 1) demonstrated a distinct cluster separation between the patients with permanent paraplegia compared with those who recovered from paraplegia, as well as a marked difference from patients who did not develop post-operative neurology. Furthermore, a total of 110 proteins were found to be statistically significantly more expressed ($p < .050$) in the paraplegic cohort *vs*. those who recovered from paraplegia and the group of patients with no neurological impairment post-operatively (Supplementary Figures S2 and S3). All proteomic findings were validated by immunoassay (ELISA) and performed blinded to the outcomes of the proteomics (Supplementary Figure S4). More specific comparison of the proteome between patients who recovered from paraplegia and those who became permanently paraplegic only revealed differences in the levels of 28 proteins (all $p < .010$), with all but one demonstrating statistically significantly higher levels in the CSF of the permanently paraplegic cohort (Fig. 2).

Patients with permanent paraplegia have raised post-operative cerebrospinal fluid levels of aquaporin-4 and develop spinal cord oedema

Volcano plot analysis of differential protein expression in the post-operative CSF of permanently paraplegic *vs*.

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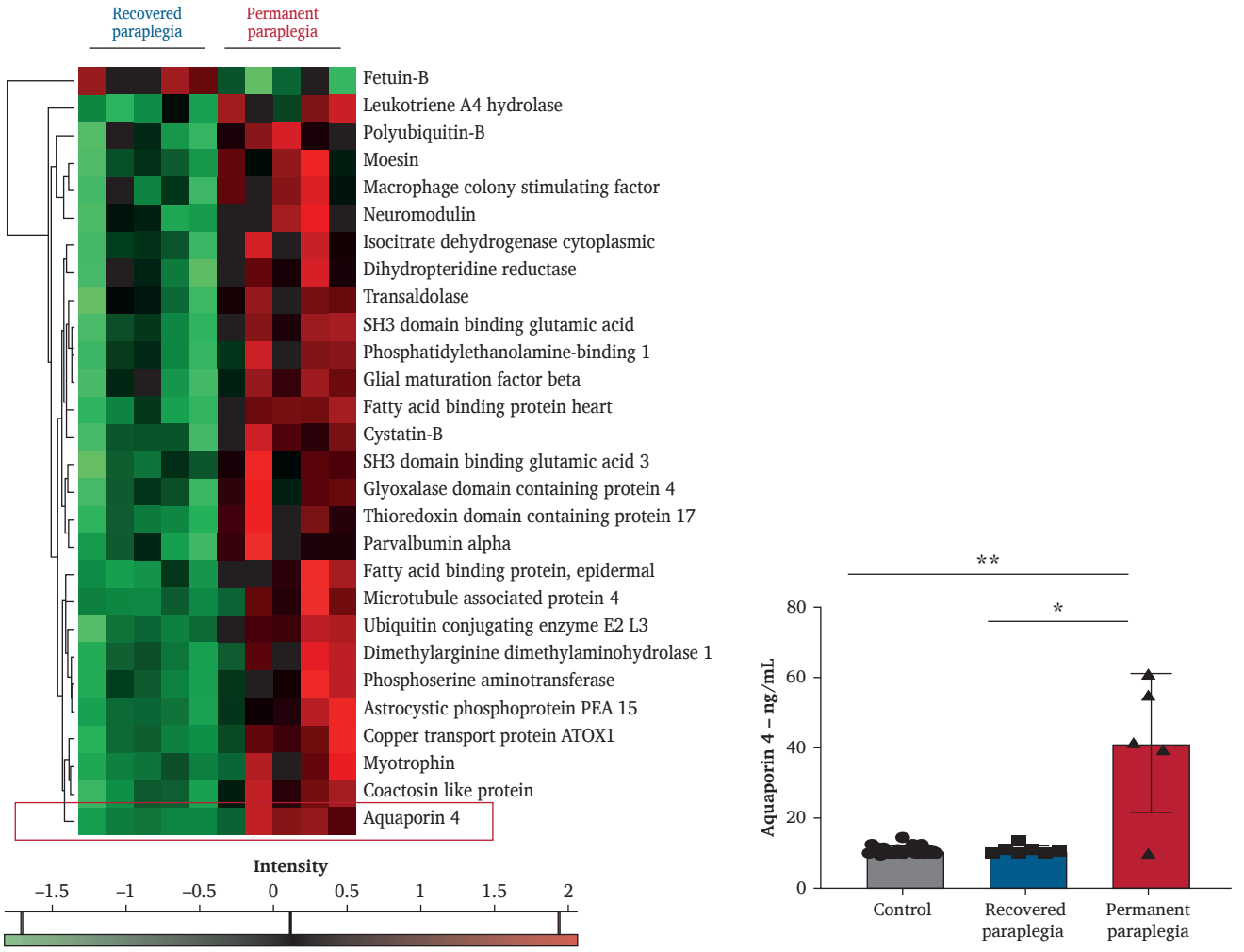

Figure 2. Heat map contrasting permanently paraplegic ($n = 5$) and recovered paraplegic ($n = 5$) cohorts, identifying differential expression of 28 proteins (Student t test, $p < .01$). Levels of all but one (fetuin-B) of these proteins were raised in the cerebrospinal fluid (CSF) of patients rendered permanently paraplegic. The soluble aquaporin-4 levels in CSF were then validated by enzyme linked immunosorbent assay (ELISA), and were higher in patients with permanent paraplegia (41.8 ± 19.2 ng/mL, $n = 5$) *vs.* recovered paraplegia (10.8 ± 1.3 ng/mL; $p = .01$, $n = 7$) and those without post-operative neurology (10.7 ± 1.2 ng/mL; $p = .004$, $n = 25$). Error bars represent one standard deviation. $^{*}p < .05$, $^{**}p < .01$; p values are two sided.

recovered paraplegic patients identified the astrocytic proteins glial fibrillary acidic protein (GFAP) and AQP4, cytoskeletal microtubule protein MAP-4, and the proteins involved in enzymatic conversion of glutamate synthetase and L-asparaginase as the top five proteins with the highest levels in CSF from patients with permanent paraplegia (Supplementary Figure S5; Supplementary Table S2). Hierarchical cluster analysis identified AQP4 as one of nine proteins that were consistently higher in post-operative CSF of patients with permanent paraplegia. AQP4 was not identified by proteomics in patients who recovered from paraplegia or in the pre-operative samples of patients who would go on to develop permanent paraplegia (Supplementary Figure S6). The proteomic findings of raised AQP4 levels were validated by ELISA, which demonstrated levels of AQP4 in the CSF of permanent paraplegics (41.8 ± 19.2 ng/mL, $n = 5$) were approximately fourfold greater than those in the CSF of patients who recovered from paraplegia (10.8 ± 1.3 ng/mL, $n = 7$; $p = .005$) or did not develop paraplegia at all (10.8 ± 1.2 ng/mL, $n = 25$; $p = .004$) (Fig. 2). The amount of AQP4 in post-operative CSF samples reflected the severity of neurological injury, with concentrations > 15 ng/mL predicting permanent paraplegia, with a specificity of 100% (confidence interval [95% CI] 88.78 — 100.0%) and sensitivity of 80.0% (95% CI 28.36 — 99.49%; Supplementary Figure S7). At this cutoff, the positive predictive value was found to be 100%, negative predictive value 96.9%, and accuracy 97.2%.

This study therefore investigated the T2 weighted spinal cord MRI of control patients made up of age, height, weight, and sequence matched patients *vs.* patients with permanent paraplegia, to assess whether a greater level of AQP4 in CSF was associated with a greater degree of cord oedema. It found that an almost twofold greater lesion

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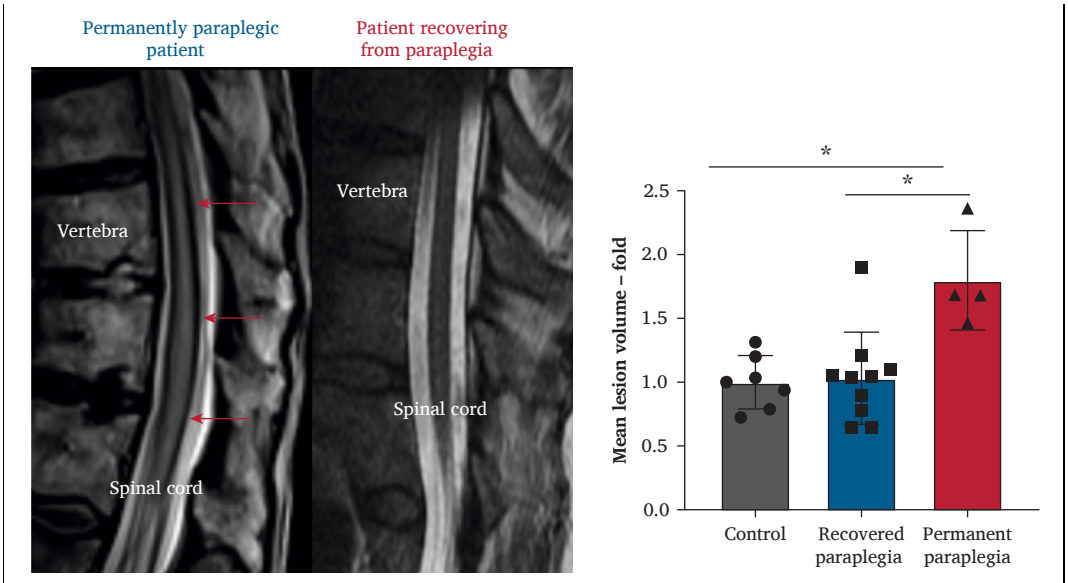

Figure 3. Representative sagittal and axial images of thoracic T2 spinal cord magnetic resonance imaging (MRI) lesional volumes in patients with permanent and recovered paraplegia, respectively. The red arrows demonstrate the oedema within the spinal cord found in a patient who would remain paraplegic, which is not demonstrable in the patient who would recover from paraplegia. In this case the oedema is notable from L3 to the conus medullaris. The patient who recovered from paraplegia has no evidence of an infarct. The bar chart demonstrates mean fold differences in lesional cord volumes using T2 spinal cord MRI. Fold changes expressed relative to matched controls (control $n = 7$, recovered paraplegia $n = 10$, permanently paraplegic $n = 4$). Greater cord volumes noted in permanent paraplegia attributed to oedema ($p = .032$). Error bars represent one standard deviation. $^{*}p < .050$; p values are two sided.

cord volume, relative to the control cohort, was apparent in patients who remained permanently paraplegic compared with those who recovered from paraplegia (1.77 ± 0.19 *vs*. 1.03 ± 0.36; $p = .032$) (Fig. 3). There was no difference between the cord volume of control subjects and those who recovered from paraplegia. This suggests that significant cord oedema only occurred in patients who developed permanent paraplegia, all of whom had a CSF AQP4 level > 15 ng/mL.

Inhibition of aquaporin-4 ameliorates paraplegia in a rodent model of spinal cord ischaemia

This study then aimed to investigate whether AQP4 inhibition had a neuroprotective effect after spinal ischaemia. An intraperitoneal dose of 2-(nicotinamide)-1,3,4-thiadiazole (TGN-020, 200 mg/kg), a potent AQP4 inhibitor,[15] was administered before induction of spinal cord ischaemia in a rat model. In this model, an intra-aortic occlusive balloon was used to interrupt blood flow to the spinal cord, causing reproducible paraplegia (Supplementary Figure S8).[16]

An injection of TGN-020 or saline was administered 15 minutes before the induction of spinal ischaemia. Neurobehavioural analysis showed functional gait preservation in rats pre-treated with TGN-020 compared with control animals injected with saline ($p < .001$ two way ANOVA) (Supplementary Figure S9).[17,18] The treated rats demonstrated superior fine stepping movements at all time intervals: 24 hours (4.55 ± 0.25 *vs*. 3.52 ± 0.87; $p = .004$), 48 hours (4.63 ± 0.77 *vs*. 3.65 ± 0.16; $p = .006$), and 72 hours (4.75 ± 0.27 *vs*. 3.77 ± 0.52; $p = .006$). Open field neurobehavioural analysis quantified by the Basso, Beattie, and Bresnahan score also demonstrated preserved continuity of gait post-cord ischaemia in treated rats compared with controls after induction of ischaemic cord injury ($p < .001$ two way ANOVA) (Supplementary Figure S10), with treated animals showing statistically significant differences at all time intervals: 24 hours (14.5 ± 1.8 *vs* 9.0 ± 3.9; $p = .004$), 48 hours (15.8 ± 2.5 *vs*. 9.8 ± 3.5; $p = .007$), and 72 hours (16.5 ± 2.3 *vs*. 10.7 ± 3.5; $p = .009$).

Immunohistochemical analysis of rat spinal cords showed that rats treated with TGN-020 had greater preservation of GFAP in white matter regions containing the lateral corticospinal (0.49 ± 0.30 *vs*. 0.16 ± 0.17; $p = .0425$), rubrospinal (0.47 ± 0.32 *vs*. 0.17 ± 0.14; $p = .049$), and reticulospinal tracts (0.47 ± 0.31 *vs*. 0.15 ± 0.17; $p = .039$) (Supplementary Figure S11). A clear loss of spinal interneurons in the dorsal horn and in the intermediate zone was noted in paraplegic animals, with only minimal neuronal loss seen in the TGN-020 treated group. There was also a statistically significantly greater area of neuronal nuclei staining in spinal grey matter after AQP4 inhibition, suggesting a greater degree of intact grey matter neurons also ($p = .004$) (Fig. 4).

DISCUSSION

This study highlights a distinct cluster separation in the CSF proteome of patients who develop permanent paraplegia after SCI induced by aortic aneurysm repair compared with

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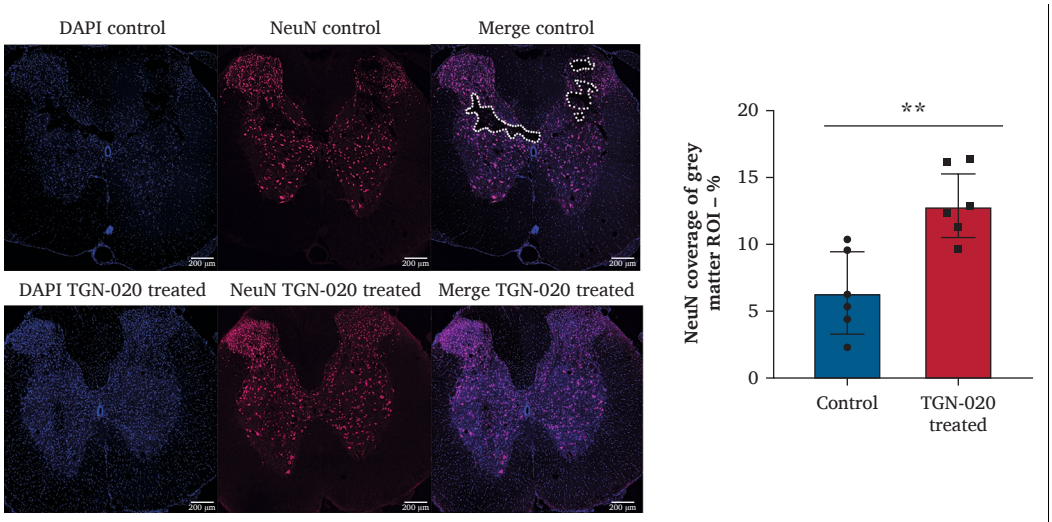

Figure 4. Example of the neuronal (NeuN) staining in (I) control and (II) 2-(nicotinamide)-1,3,4-thiadiazole (TGN-020) treated rats. Consistently there was a notable loss of spinal interneurons in dorsal horn and intermediate zone in controls (marked with dotted line). The bar chart demonstrates the greater of preservation of NeuN staining in TGN-020 treated rats compared with controls (12.8 ± 2.4 *vs.* 6.32 ± 3.1; $p = .004$). Error bars represent one standard deviation. $^{*}p < .050$; $^{**}p < .01$; p values are two sided. DAPI = 4-6 diamidino-2-phenylindole; ROI = region of interest.

those exhibiting transient or no paraplegia. The most striking differences were in the composition of proteins derived from astrocytes and the glial limitans.

The development of cytotoxic oedema in the spinal cord is reported to be an AQP4 mediated process.[19] An ischaemic insult to the central nervous system (CNS) is thought to cause failure of energy dependent mechanisms of cation extrusion, leading to the accumulation of sodium and other cations from the extracellular space in neurons and astrocytes.[20] This is followed by an influx of anions to maintain electrical neutrality and this osmotic gradient drives the influx of water, resulting in intracellular expansion, known as cytotoxic oedema.[20] This cellular damage leads to breakdown of the blood—brain and blood—spinal cord barrier, resulting in leakage of plasma proteins into the extracellular space and CSF (vasogenic oedema).[21] AQP4 is the most abundant osmoreceptor in the mammalian spinal cord and one of a family of membrane transport proteins expressed on astrocytes, glia limitans, and ependymal cells, which are key regulators of CSF production.[22] AQP4 was one of nine proteins identified by hierarchical clustering, with higher levels consistently found in the post-operative CSF samples of patients with permanent paraplegia and not identified in the CSF of patients who recovered from paraplegia or did not develop post-operative neurology. The CSF AQP4 proteomics findings were confirmed by immunoassay in a larger patient cohort, in which concentrations $>$ 15 ng/mL demonstrated 100% specificity, supporting its potential utility as a prognostic biomarker. Whilst this threshold yielded a sensitivity of 80%, analysis of the paraplegic group may have been skewed by the incorporation of one outlier patient who died on post-operative day five from cardiogenic shock when still paraplegic. The proteome of this patient was more in keeping with patients who went on to recover from paraplegia. As all other patients were assessed after a minimum of 24 months post-surgery, it is unknown whether this patient would have recovered on follow up, and therefore belonged to the recovery group rather than the permanent paraplegia group.

There is currently no biomarker that informs the functional outcome of spinal cord infarction, with some series describing post-operative neurological impairment in up to a third of TAAA repairs.[23,24] Of the post-operative salvage measures available, elevation of the mean arterial pressures and prolonged CSF drainage can lead to secondary complications, including neuraxial haematoma, subarachnoid haematoma, and meningitis.[23,25,26] Therefore, in the case of TAAA surgery, a biomarker could more safely inform of the risks in pursuing such rescue measures. CSF AQP4 may therefore offer a means of stratifying the likelihood of neurological recovery and informing whether post-operative rescue measures are likely to be beneficial or expose patients to additional risk without clear benefit.[23,26]

AQP4 is implicated in the regulation of oedema across the blood—brain barrier.[22,27] Hypoxia stimulates the expression of AQP4,[28] which in turn promotes cytotoxic brain oedema in animal models of cerebral stroke.[29] Furthermore, AQP4 null mice demonstrated improved survival and reduced infarct volume in a cerebral stroke model.[30] Pre-treatment with an AQP4 antagonist in the same model reduced cerebral oedema.[15] Perivascular expression of AQP4 has been proposed as a regulator of water flux in pathophysiological conditions, such as the reperfusion phase after cerebral ischaemia.[31] More recently, trauma induced cord hypoxia has been shown to trigger an AQP4 mediated increase in the flux of water into

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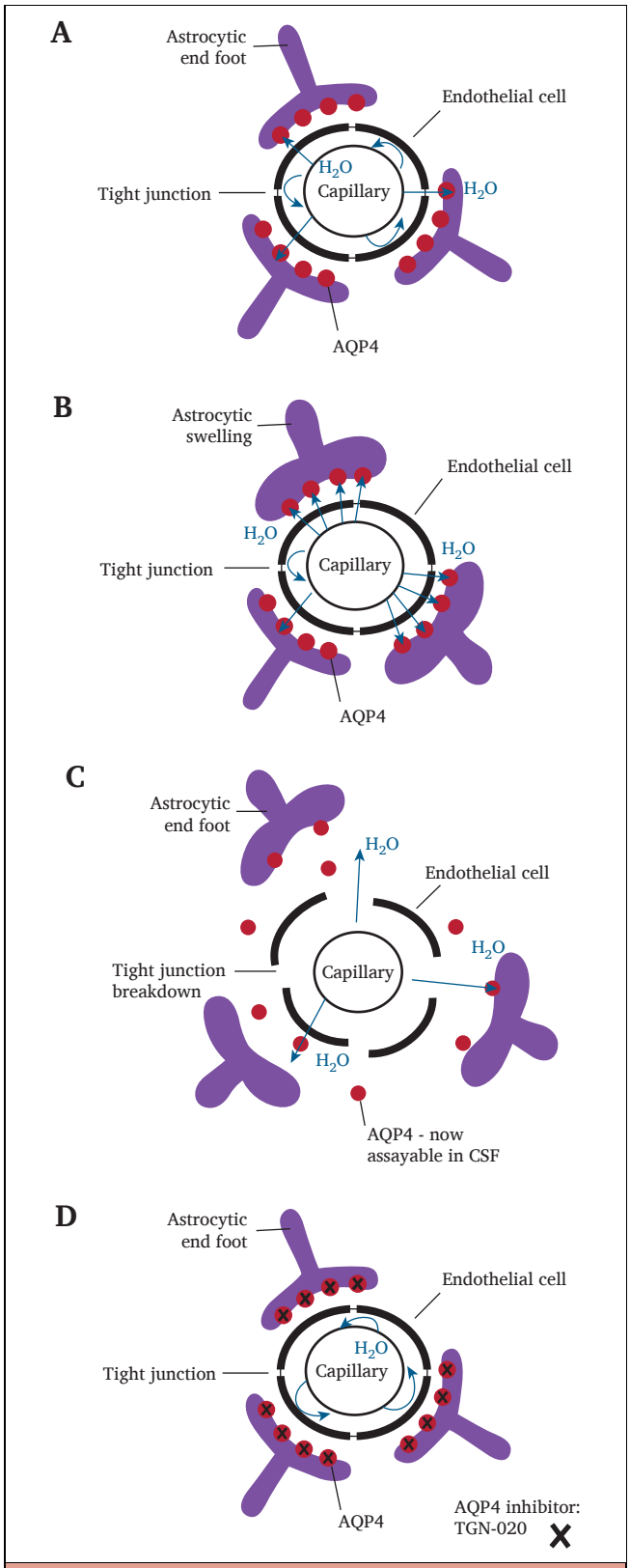

Figure 5. (A) Under physiological conditions, aquaporin-4 (AQP4) is bound to astrocytic end feet and regulates transcellular water movement. The interface between the endothelial tight junctions and capillaries maintains the blood–spinal cord barrier. (B) After an ischaemic insult, AQP4 on astrocytic end feet mediates water flux into astrocytes causing pathological swelling (cytotoxic oedema). (C) Progressive swelling eventually causes disruption of the blood–spinal cord barrier allowing extravasation of water into the extracellular lumen (vasogenic oedema). At this stage AQP4 is dissociated from astrocytic end feet and becomes assayable in cerebrospinal fluid (CSF). (D) Pre-surgery therapeutic inhibition of AQP4 (with TGN020) prevents the onset of cytotoxic oedema, which in turn prevents development of vasogenic oedema, ameliorating the extent of spinal cord injury. AQP4 remains bound to the astrocyte and its expression is significantly less than in cases of permanent paraplegia.

astrocytes, while its inhibition prevented cord oedema, whilst targeting the calmodulin mediated cell surface localisation of AQP4 has also been recently suggested as a means to manage CNS oedema.[19]

This study therefore hypothesised that an ischaemic insult to the spinal cord after TAAA repair leads to an influx of water into the spinal cord, mediated by astrocytic AQP4. This hypothesis appears to be supported by the MRI analysis of spinal cord oedema, showing an almost two-fold greater volume in patients with permanent paraplegia *vs*. age, height, and weight matched controls. Patients who recovered from paraplegia had a cord volume comparable to controls. All patients used for this analysis who remained paraplegic had CSF AQP4 levels of $\geq$15 ng/mL, whilst those who recovered all had AQP4 levels of $<$ 15 ng/mL. Given the limited number of events, however, this cutoff value should be regarded as hypothesis generating and requires external validation in larger, independent cohorts of patients with paraplegia.

This study then established whether AQP4 antagonism *in vivo* would protect the spinal cord during the hypoxic insult induced during aneurysm repair. Pre-operative prophylactic inhibition of AQP4 with TGN-020 ameliorated paraplegia after an ischaemic insult in a clinically relevant rat model of SCI. This was evidenced by both preservation of neurobehavioural function and histologically with reduced injury to the spinal interneurons in dorsal horn and intermediate zone, and preservation of astrocytes in several essential descending motor pathways.

Several limitations must be considered when interpreting the present study development of paraplegia post iSCI is a multifactorial process, impacted by variables such as episodes of hypotension and blood haemoglobin concentration. The incremental prognostic value of CSF AQP4 when considered alongside established clinical and procedural variables warrants further evaluation, and additional studies in larger cohorts with a greater number of paraplegia events are required to validate its role as a biomarker. The cutoff of 15 ng/mL for AQP4 is hypothesis generating and requires external validation, even though the performance of the threshold seemed strong in the present cohort. The patient cohorts used for this study were not matched and this may have introduced selection bias. It should also be mentioned that AQP4 could be elevated in any biological activity where the blood–brain or blood–spinal cord barrier is injured and AQP4 is shed from the astrocytes, not only after cord ischaemia. A larger cohort with a greater number of permanent paraplegia events would have enabled multivariable logistic regression

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analysis to better account for potential confounders, including unmeasured physiological and anatomic factors that may contribute to differences in CSF AQP4 expression.

All patients requiring a prophylactic spinal drain were offered entry to the study and a blinded assessor determined whether they developed post-operative neurological impairment. Matching could have been used to ensure equal ages or equal aortic coverage, for example, but this requires a much larger, multicentre cohort of patients. The analysis included one patient classed as permanently paraplegic but who died in the early post-operative period from myocardial infarction. This patient may have recovered from paraplegia and appeared to have a proteomic signature more in keeping with recovery but was recorded as permanently paraplegic.

Additionally, given the limited number of MRI studies available in patients with permanent paraplegia, these imaging findings should be regarded as supportive correlates of CSF AQP4 release, consistent with dissociation of AQP4 from astrocytic end feet and associated oedema, but not definitive evidence of causality. Finally, the rodent model used does not fully recapitulate the permanent paraplegia that is a consequence of aneurysm repair in patients and highlights the need for a clinical study to explore the therapeutic value of pre-emptive AQP4 inhibition. Attempts were made to standardise the location of balloon inflation, but it is very difficult to ascertain the exact location and extent of balloon inflation without the use of fluoroscopy.

CONCLUSION

These findings suggest that the level of soluble AQP4 (sAQP4) in CSF acts as a novel, sensitive biomarker that informs early neurological prognosis after SCI. This represents a significant conceptual advance of translational importance, as it could lead to stratified and targeted treatments aimed at preserving spinal cord function after an ischaemic insult. It is believed that this is the first study to indicate an association between permanent paraplegia and raised levels of sAQP4 in CSF post ischaemic insult. Interrogation of these findings in a pre-clinical experimental rodent model showed that AQP4 inhibition ameliorates the neurological sequelae of this insult in keeping with other rodents models of AQP4 knockout mice post middle cerebral artery ligation.[30] Taken together, the present data, informed by the proteome of patients who sustained spinal cord infarction and followed by the results of inhibition studies in a clinically relevant *in vivo* model of spinal ischaemia, yield a proposed mechanism for the development of ischaemic cord injury post TAAA repair, as well as a novel therapeutic target (Fig. 5).

No therapy has yet been developed to prevent or protect the spinal cord before the onset of an ischaemic insult. TGN-020, the AQP4 inhibitor in this study, has been used in patients.[32,33] Whilst the authors accept that optimisation studies would be required to address questions regarding the side effect profile, the timing of the administration, and the feasibility of intra-thecal delivery of TGN-020, its therapeutic use benefits from the fact that, unlike in stroke where the timing of the cerebral ischaemic insult is unpredictable, the ischaemic insult to the spinal cord in elective TAAA repair is known. TGN-020 could be administered intrathecally to the area of the spinal cord exposed to ischaemia and would readily lend itself to a clinical study assessing its utility in patients undergoing endovascular TAAA repair.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2026.01.033.

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