Witness Statement Ref. No. 107/1

NAME OF CHILD: Adam Strain

Name: David Webb

Title: Dr

Present position and institution:

Consultant Paediatric Neurologist, Our Lady's Hospital, Dublin, Ireland

National Children's Hospital, Tallaght, Dublin, Ireland

Previous position and institution:
[As at the time of the child's death]

Consultant Paediatric Neurologist, Royal Belfast Hospital for Sick Children

Membership of Advisory Panels and Committees:
[Identify by date and title all of those between January 1995-present day]

None

Previous Statements, Depositions and Reports:
[Identify by date and title all those made in relation to the child's death]

Letter to George Murnaghan (12/12/1995) 059-061-147
Witness statement to PSNI (28/04/2006) 093-021

OFFICIAL USE:
List of previous statement, depositions and reports:

Ref:	Date:	
093-021	28.04.2006	Statement to PSNI

IMPORTANT INSTRUCTIONS FOR ANSWERING:
Please attach additional sheets if more space is required. Please identify clearly any document to which you refer or rely upon for your answer. If the document has an Inquiry reference number, e.g. Ref: 049-001-001 which is 'Chart No.1 Old Notes', then please provide it. If the document does not have such a number then please provide a copy of it

I QUERIES ARISING OUT OF YOUR PSNI STATEMENT

With reference to your PSNI Witness Statement dated 28th April 2006 (Ref: 093-021-060), please provide clarification and/or further information in respect of the following:

(1) *"I am a Consultant Paediatric Neurologist in Our Lady's Hospital for Sick Children and the National Children's Hospital in Dublin since 1997. Prior to my appointment to this position I was a Consultant Paediatric Neurologist at the Royal Belfast Hospital for Sick Children for two years."*

(a) Describe your work commitments to the Royal Belfast Hospital for Sick Children (RBHSC) from the date of your appointment as a Consultant Paediatric Neurologist and particularly over the period 26th November to 28th November 1995

November 26th Sunday – off call; Monday 27th, Tuesday 28th – on call

I began my appointment as a Consultant Paediatric Neurologist at RBHSC in August 1995. With Dr Elaine Hicks I provided a 1 in 2 on-call for Paediatric Neurology at the RBHSC providing in house consultation 24/7 for children with Neurological problems and 24/7 telephone contact for Paediatricians in Northern Ireland who required consultation on children with neurological problems.

On the Monday of November 27th 1995 I believe I was "on call" for Paediatric Neurology consultations that week. I undertook a Paediatric Neurology Outreach clinic once per month rotating between Derry Hospital and Craigavon Hospital and on November 27th I drove to Altnagelvin Hospital in Derry to attend my Paediatric Neurology outreach clinic which was an all day clinic. I cannot recall my commitments on Tuesday 28th November 1995.

(b) Describe what you considered to be your role in relation to and responsibilities towards Adam from his admission to PICU on 27th November 1995 until 28th November 1995 when ventilatory support for him was withdrawn

I considered my role and responsibilities in relation to Adam Strain to be to assess his level of consciousness and undertake clinical assessments of his brain-stem function. I was also asked to consider an explanation for his brain swelling which I understood from his medical team to be unexpected and unexplained.

(2) *"On 27th November 1995 I was contacted by the Nephrology Service to see a child named Adam Strain. I attended Adam at 7.30 pm on that date. Adam was a four year old boy with bilateral reflux nephrophaty and renal dysplasia who had received a cadveric renal transplant earlier that*

had been a completely unexpected finding as[sic] his cardio-respiratory monitoring had been normal throughout the operation"

(a) State the time at which you were first *"contacted by the Nephrology Service"*

I cannot be certain of the time I was first contacted by the Nephrology Service about Adam Strain but I imagine that this was some time after he had his CT brain scan done on the afternoon of November 27th 1995. (058-035-138)

(b)Identify the person that contacted you and state what you were told about Adam and his condition

I cannot be certain of who contacted me in relation to Adam Strain but this was most probably a member of the Paediatric Nephrology or Anaesthetic Team looking after him. I cannot be certain of the details of what I was told but I believe I was informed that Dr Savage had requested me to see a boy who had had a renal transplant earlier that morning and had not woken up following the procedure. He had been found to have fixed dilated pupils and papilloedema (optic nerve swelling) and had evidence of coning (brain herniation) on CT brain. He had received Mannitol without effect.

(c) Explain the source and basis for your statement *"This had been a completely unexpected finding"*

I do recall that Adam's brain swelling was considered to be unexpected by the Transplant, Anaesthetic and Nephrology teams as his cardio-respiratory monitoring had been satisfactory throughout the operation.

(3) *"My impression was that he had suffered severe acute cerebral oedema which was likely to have occurred on the basis of osmotic disequilibrium causing a sudden fluid shift ... When I said the cause of death was cerebral oedema on the basis of osmotic disequilibrium I am referring to abnormal fluid shifts between blood and surrounding tissue and in this case, between blood and brain cells in particular"*

(a) State what could have caused *"abnormal fluid shifts between blood and surrounding tissue and in this case, between blood and brain cells in particular"* in Adam's case.

I was not aware that Adam Strain was severely hyponatraemic following his operation. He was being cared for in an intensive care setting and was being ventilated after a kidney transplant. The predominant function of the kidney is to maintain normal fluid balance and blood biochemistry so in the absence of an abnormality that would have been known to the kidney transplant team I sought an alternative cause that could have explained brain swelling in a boy who was in renal failure and had undergone dialysis and renal transplant.

I found evidence for an osmotic disequilibrium syndrome that was thought to occur because of shifts in urea concentration between blood and brain and was associated with brain swelling. While this had been described following renal dialysis I speculated that it might have played some role in Adam's case. (1, 2,). Later References on the subject are also enclosed (3, 4, 5).

(b) State whether you have encountered similar circumstances or symptoms before or since Adam's death, and if so describe the circumstances and state the date of each such case.

I had not previously seen a child with cerebral oedema following renal transplant and I have not seen any further cases in the last 15 years.

(c) State with whom you discussed your finding of *"severe acute cerebral oedema which was likely to have occurred on the basis of osmotic disequilibrium causing a sudden fluid shift"*, when and to what effect

I wrote my comments on "osmotic disequilibrium" in Adam's clinical notes but I don't recall discussing my suggestion with any member of the team as there were no specific therapeutic implications that arose from this possibility. (058-035-140)

(d) Explain what you regard as the relationship, if any, between *"osmotic disequilibrium causing a sudden fluid shift"* and hyponatraemia

Hyponatraemia is a recognised cause of brain swelling and was most probably the main cause in Adam Strain's case. The mechanism by which hyponatraemia causes brain swelling appears to be quite complex but does involve "fluid shifts" by "osmosis" into brain cells with consequent swelling. Without knowing about Adam's hyponatraemia I was searching for an alternative cause for "abnormal osmosis" or osmotic disequilibrium.

(e) State whether you discussed Adam's fluid management with anyone and, if so:

- **identify the person(s) involved**
- **state when the discussion(s) took place**
- **describe their content**
- **state their effect**

I did not discuss Adam's fluid management with any member of the Medical or Nursing Team.

(4) ***"These tests are recorded on the papers of the original notes marked 139 and 140. These tests are done by two people. I was assisted by Dr O'Connor on the second occasion"***

(a) State whether you discussed Adam's condition and its cause with Dr. O'Connor and if so, when you discussed it and the views that were expressed

I cannot recall whether I discussed Adam's condition and its cause with Dr O Connor. I know that Dr O Connor was present for my second evaluation of Adam on the Tuesday morning (November 28th 1995) but I cannot recall the details of our discussion that morning. (058-035-142)

(5) ***"I had no contact with Adam before or during his operation"***

(a) Describe and explain the contact that you had with Adam between the end of his transplant surgery and the withdrawal of ventilatory support from him on 28th November 1995, including, when it took place, its nature and purpose

I undertook two clinical assessments of Adam's coma and brain stem function (058-004-009). The first

was undertaken on the Monday evening at 7.30pm and I believe was witnessed by Dr Campbell. The second was undertaken on the Tuesday morning and was witnessed by Dr O Connor. I cannot recall who else was present but on both occasions a member of the Anaesthetic team would have been present to assist in his "Apnoea Test".

The nature of my examination was to assess if Adam was able to respond to auditory tactile and painful stimulus. The purpose of this is to establish if the child is in coma. The remainder of my examination was focused on assessing the presence if any of brain stem function. This involved assessing pupil responses to light, corneal responses to touch with soft wool, movements of the eyes in response to the passage of ice cold water in both ears and airway protection responses to palatal stimulation.

I also confirmed that Adam had papilloedema (optic nerve swelling) in both eyes (an indication of a severe recent rise in intracranial pressure) and witnessed his apnoea test by the Anaesthetic team. The apnoea test is undertaken by withdrawing ventilatory support for a period of minutes to observe if the child breathes spontaneously. In the absence of breathing the child's blood level of carbon dioxide rises and this provides a potent stimulus to breath. The carbon dioxide blood levels are measured before and after the test to confirm an adequate stimulus has been provided.

I also reviewed Adam's CT brain scan undertaken earlier that day following his surgery and confirmed that this revealed evidence of downward brain herniation.

The purpose of my examination was to confirm to the transplant team that Adam's clinical condition fulfilled the criteria for brain stem death.

(b)State whether you had any discussions with Adam's family and if so, state when, where and what you discussed

I did not have any discussions with Adam's family.

II ADDITIONAL INFORMATION

(6) Describe in detail the education and training you received in fluid management (in particular hyponatraemia) and record keeping through the following, providing dates and names of the institutions/bodies:

(a) Undergraduate level

My undergraduate education was at University College Dublin Medical School and St Vincent's Hospital Dublin 1979 – 1985. Fluid management, biochemical derangements and hyponatraemia in particular were covered initially in Medical Physiology (1981) and subsequently in Final Year Medical School (1985).

(b) Postgraduate level

Training in fluid management and electrolyte disturbances continued during my postgraduate hospital appointments. These were at

St Vincent's Hospital Dublin, 1985 -1987.
The Coombe Women, Hospital, Dublin - Neonatal Unit 1987 - 1988
Our Lady's Hospital Crumlin, Dublin 1988
Southmead Hospital, Bristol 1988 - 1990
Royal United Hospital, Bath 1990- 1993
Southampton General Hospital 1993- 1994
Children's Hospital, Vancouver 1994 - 1995

In most post graduate hospital training posts fluid management was supervised by the Senior Non Consultant Hospital Medical Staff at Registrar and Senior Registrar level. I recall my most informative experience in fluid management was obtained during my work at The Coombe Women's Hospital, Dublin and Southmead Hospital, Bristol where I worked at a Neonatal SHO level supervising intensive care management of sick newborn infants on ventilation.

(c) Hospital induction programmes

I do not recall receiving a hospital induction course on fluid management.

(d) Continuous professional development

Fluid management is not a major part of the continuing professional development of a Paediatric Neurologist.

(7) Prior to 26th November 1995, describe in detail your experience of dealing with children with hyponatraemia, including the:

- **estimated total number of such cases, together with the dates and where they took place**
- **number of the children who were aged less than 6 years old**
- **nature of your involvement**
- **outcome for the children**

I am unable to recall the dates and location of previous children that I have seen with hyponatraemia but I estimate that the total number would have been less than 15 cases. My experience of dealing with children with hyponatraemia prior to 26th November 1995 would have been largely during my experience in neonatal intensive care positions, and the occasional older child with the Syndrome of Inappropriate Anti Diuretic Hormone secretion - (SIADH). I do not recall previously seeing any child with hyponatraemia coming to harm.

(8) Describe in your detail your experience, since 27th November 1995, in the care and management of children with hyponatraemia

As a Consultant Paediatric Neurologist I would rarely be involved in the care of a child with hyponatraemia. This condition is usually managed by the Paediatric Nephrologist or General Paediatrician. I was involved in the case of Claire Roberts who was admitted to The Royal Belfast Hospital for Sick Children On 21st October 1996 and died on 23rd October 1996. Claire was found to have died of cerebral odema due to meningo-encephalitis and hyponatraemia due to excess ADH production and status epilepticus. I can recall no other children coming to harm from hyponatraemia over the past 15 years.

(9)Describe in detail your role in the care and treatment of Adam prior to 26th November 1995, including:

(a) Date of each occasion and the procedure/surgery undergone by Adam

(b)The hospital concerned

(c) The fluid management regime employed on each occasion

(d)The lessons that you learned from your prior treatment of Adam

I had no role in the care and treatment of Adam Strain prior to 26th November 1995

(10) Identify any 'Protocols' and/or 'Guidelines' which governed Adam's renal transplant surgery

I have no knowledge of any protocols or guidelines which governed Adam's renal transplant surgery

(11) Identify precisely from Adam's medical notes and records the entries that you made or which were made on your direction and state below:

(a) When each of the identified entries was made

My notes on Adam Strain were made on the evening of November 27th 1995 after 7.30 pm and on the morning of November 28th 1995 after 9.10 am. (058-035-139, 140 and 058-035-142)

(b)The source of the information recorded in the entry

The source of information recorded in my entries would have been based on discussions with the medical and nursing staff caring for Adam in the Intensive Care Unit, my examination of Adam and my review of his CT brain scan.

(12) Provide any further points and comments that you wish to make, together with any documents, in relation to:

(a) The care and treatment of Adam from his admission for the renal transplant surgery on 26th November 1995 to his death on 28th November 1995

(b)Record keeping

(c) Communications with Adam's family about his care and treatment in respect of the renal transplant surgery

(d)Lessons learned from Adam's death and how that has affected your practice

(e) Current Protocols and procedures

(f) Any other relevant matter

I have no further comments to make on the care and treatment of Adam Strain.

References

1. Rosen SM, et al. Haemodialysis Disequilibrium. BMJ 1964,2672-675
2. Davenport et al. Management of patients with renal failure complicated by cerebral oedema. Blood Purif 1989;7(4):203-209
3. Silver SM et al. Brain swelling after dialysis: old urea or new osmoles? Am J Kidney Dis 1996 Jul;28(1):1-13
4. Trinh-Trang-Tan et al. Molecular basis for the dialysis disequilibrium syndrome: altered aquaporin and urea transporter expression in the brain. Nephrol Dial Transplant 2005 Sep;20(9):1984-8
5. Patel N et al. Dialysis disequilibrium syndrome: a narrative review. Semin Dial 2008 Sep-Oct;21(5):493-8

THIS STATEMENT IS TRUE TO THE BEST OF MY KNOWLEDGE AND BELIEF

Signed: D Nowell **Dated:** 12.4.11

periods of time without the risk of serious toxicity. The drug therefore is useful where a patient is infected by a penicillin-resistant staphylococcus and cannot be given one of the new penicillins because of drug-sensitization, or where resistance to one or other of the new penicillins has been demonstrated. Because there is now in certain hospital areas an additional risk of infection with erythromycin-resistant staphylococci the drug should also be considered in these circumstances. It may be that there is a theoretical risk of the ultimate emergence of cross-resistance between the macrolides and lincomycin as suggested by Barber and Waterworth (1964). At present, however, this does not appear to have clinical significance, and since lincomycin is not related chemically to the macrolides the possible danger may be minimal. From a clinical point of view the drug appears to be particularly valuable in the treatment of staphylococcal osteomyelitis and there is some theoretical and clinical evidence to support this (Holloway *et al.*, 1963; McDougall *et al.*, 1964). Further studies are at present being initiated to assess the value of lincomycin in experimental osteomyelitis in animals.

Summary

Twenty-four patients with various infections caused by Gram-positive organisms were treated with a new antibiotic, lincomycin hydrochloride. Treatment succeeded in 19 patients and there were no untoward side-effects or toxicity in the series.

We wish to thank Dr. R. G. Jacomb, of Upjohn Limited, England, for generous supplies of lincomycin hydrochloride. We also thank Miss Edith Wallace for technical assistance, and Dr. J. C. Gould, of the Western General Hospital, Edinburgh, for the *in vitro* studies of staphylococci in his laboratory.

References

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Haemodialysis Disequilibrium

S. M. ROSEN,* M.B., M.R.C.P., M.R.C.P.ED.; K. O'CONNOR,† B.SC.; STANLEY SHALDON,‡ M.A., M.D., M.R.C.P.

Brit. med. J., 1964, 2, 672–675

Several observers have noted a deterioration in the clinical condition of some patients during haemodialysis at a time when there is improvement in the blood biochemistry (Merrill, 1961; Kennedy, Linton, and Eaton, 1962; Sitprija and Holmes, 1962). The first evidence of this deterioration is increasing lassitude, headache, drowsiness, and confusion. In more severe cases there is an increase in blood-pressure, pulse rate, and respiratory rate. Fatalities may occur after cardiac arrest or pulmonary oedema. The syndrome is more severe when the plasma urea is very high before dialysis, and may last for 24 hours after the termination of dialysis.

Kennedy *et al.* (1962) noted that urea is removed more slowly from lumbar cerebrospinal fluid (C.S.F.) than from blood and suggested that the abnormal urea gradient thus established between C.S.F. and blood is responsible for this deterioration.

Investigations have therefore been performed to determine the relation between the concentration of plasma urea before dialysis and the size of the abnormal urea gradient established during dialysis, the duration of this abnormal urea gradient, and whether a similar phenomenon occurred with uric acid, creatinine, inorganic phosphorus, and bicarbonate. Observations were also made to correlate these changes in biochemical equilibrium with changes in the C.S.F.–plasma osmolality gradient.

Methods

Ten patients with acute renal failure were dialysed for periods of four to eight hours on a twin-coil kidney at blood-flow rates of approximately 200 ml./min. The rinsing fluid contained a concentration of 2% dextrose and 30 mEq/l. of bicarbonate ion. Simultaneous samples of lumbar C.S.F. and arterial blood were obtained anaerobically immediately before dialysis, immediately after dialysis, and 16 and 24 hours after dialysis. Analysis of lumbar C.S.F. and plasma was performed for concentration of urea by the urease method with nesslerization (Varley, 1962), uric acid (Henry, Sobel, and Kim, 1957), creatinine (Owen, Iggo, Scandrett, and Stewart, 1954), and inorganic phosphorus (Fiske and Subbarow, 1925). Osmolality of C.S.F. and plasma was determined from the depression of freezing-point, using the Fiske osmometer. *p*H and P_{CO_2} were estimated in blood and C.S.F. by means of the micro Astrup apparatus, and the concentration of bicarbonate ion was calculated using the equation $HCO_3 = \text{antilog}\ (pH - pK^1)\ (P_{CO_2} \times S)$. A value for S of 0.0304 was taken for plasma (Severinghaus, Stupfel, and Bradley, 1956) and a value of 0.0320 for spinal fluid (Shohl and Karelitz, 1926). pK^1 was calculated from the equations pK^1 plasma $= -0.062\ pH$ plasma $+ 6.56$ and $pK^1 = -0.143\ pH$ C.S.F. $+ 7.15$ (Cowie, Lambie, and Robson, 1962).

One sample of arterial blood and lumbar C.S.F. was also obtained anaerobically from fasting control subjects without renal dysfunction, and analysed by the above techniques.

Results

The relation of the urea gradient (C.S.F. minus plasma) to the concentration of plasma urea before dialysis is shown in

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Fig. 1. The plasma urea concentration at the beginning of dialysis ranged from 210 to 460 mg./100 ml. In all 10 cases the urea gradient before dialysis was negative, with values of between −10 and −30 mg./100 ml., the urea concentration in lumbar C.S.F. being lower than that in plasma. Immediately after dialysis the urea gradient became positive in all cases, ranging from +30 to +160 mg./100 ml. Moreover, the higher the plasma urea concentration the greater the urea gradient between C.S.F. and plasma at the termination of dialysis, even though no allowance has been made for variations in total urea pools between the different patients and differences in efficiency of dialysis.

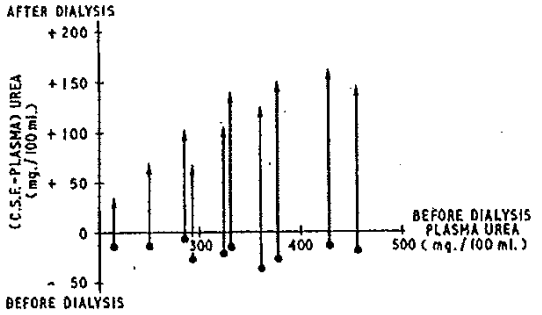

FIG. 1.—Relation of plasma urea before dialysis to urea gradient between C.S.F. and plasma before and after dialysis.

Serial observations on urea concentration in C.S.F. and plasma in one of these patients is shown in Fig. 2. At the start of dialysis the plasma urea concentration exceeds the C.S.F. by 16 mg./100 ml. At the end of a six-hour dialysis there is a reversal of the gradient, the C.S.F. concentration exceeding that of the plasma by 150 mg./100 ml. After the termination of dialysis the C.S.F. urea concentration continues to fall, but the plasma urea rises slowly, so that at 16 hours the gradient has diminished to +50 mg./100 ml. and at 24 hours has returned to its value before dialysis. Some patients who had a more rapid increase in blood urea after termination of dialysis re-equilibrated before 24 hours, and others who had a less rapid increase in blood urea took longer than 24 hours to re-equilibrate.

Fig. 3 shows the mean of the ratios

$$\frac{\text{urea concentration in C.S.F.}}{\text{urea concentration in plasma}}$$

in nine control subjects and the 10 patients who were dialysed. The mean of the ratios before dialysis was 0.91 (with a standard deviation of 0.08), and was not significantly different from that in the control series. Immediately after dialysis the ratio had increased to 1.99, and 24 hours after the termination of dialysis it had returned to the value before dialysis.

The mean of the uric acid ratios also increased during dialysis. However, 24 hours after the termination of dialysis the ratio had not returned to the level before dialysis (Fig. 4), showing that uric acid re-equilibrates more slowly than urea.

In the case of creatinine the mean of the ratios was 0.48 immediately before dialysis. This was significantly lower than that in the control series (Fig. 5). Immediately after dialysis the ratio increased to 0.89 and returned to 0.51 24 hours after the end of dialysis.

Haemodialysis causes a similar pattern of alteration to the ratio of inorganic phosphorus. The degree of alteration, however, is much less (Fig. 6). This was due to the fact that dialysis decreases the concentration of plasma inorganic phosphorus to a less extent than urea, uric acid, and creatinine.

The acid-base changes which occurred during haemodialysis are shown in Table I. The mean blood bicarbonate-ion concentration increased from 20.6 to 25 mEq/l., but the C.S.F. bicarbonate remained constant at 21.9 mEq/l. Twenty-four hours after dialysis the C.S.F. bicarbonate-ion concentration has increased to 24 mEq/l. although there has not been significant alteration in the blood bicarbonate. Thus there was a delay in the transfer of bicarbonate from blood to C.S.F.

The mean of the osmolality gradients between C.S.F. and plasma in a control series of nine is shown in Table II and can be compared with a series of patients with acute renal failure who underwent dialysis. The mean gradient (C.S.F. minus blood) before dialysis was −3 mOsm/kg., but immediately after dialysis had increased to +4.6 mOsm/kg. Twenty-four hours

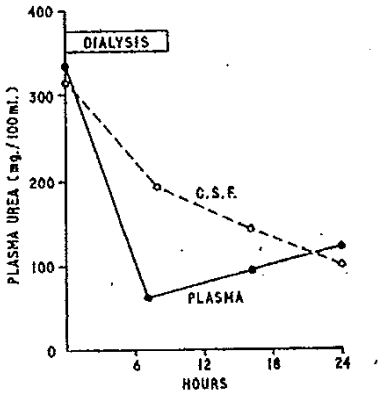

FIG. 2.—Serial observations on urea concentration in samples of C.S.F. and plasma obtained simultaneously from a woman aged 48 with acute renal failure, before, immediately after, and 16 and 24 hours after dialysis.

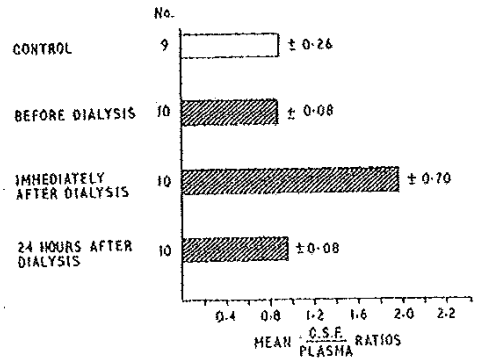

FIG. 3.—Mean of ratios of $\frac{\text{urea concn. in C.S.F.}}{\text{urea concn. in plasma}}$ in nine control subjects and 10 patients with acute renal failure before and after haemodialysis.

TABLE I.—*C.S.F./blood-acid-base Relationships*

Group	No. of Patients	HCO_3 (mEq/l.)		pH		P_{CO_2} (mm. Hg)	
		Blood	C.S.F.	Blood	C.S.F.	Blood	C.S.F.
Control	8	26·7	24·4	7·44	7·34	39	45
Before dialysis ..	10	20·6	21·9	7·41	7·25	33	40
Immediately after dialysis	10	25·0	21·9	7·50	7·24	31	38
24 hours after dialysis	10	25·1	24·0	7·49	7·37	33	40

TABLE II.—*C.S.F./blood Osmolality Gradient*

Group	No. of Patients	C.S.F.-blood (mOsm/kg.)
Control	9	− 0·4
Before dialysis	6	− 3·0
Immediately after dialysis	6	+ 4·6
24 hours after dialysis ..	6	− 2·6

after the termination of dialysis the gradient was −2.6 mOsm/kg. Thus dialysis had caused a net alteration of +7.6 mOsm/kg.

Discussion

Our results confirm that there is a delay in removal of urea from lumbar C.S.F. during haemodialysis with the creation of an abnormal urea gradient between C.S.F. and plasma. The size of this abnormal gradient in our series was proportional to the concentration of plasma urea at the start of dialysis. The precise duration of this abnormal gradient after the termination of dialysis varied on each occasion, but averaged 24 hours. Two factors are responsible for the speed of re-establishment of the normal urea gradient between C.S.F. and plasma. Firstly, the rate of rise of plasma urea, and, secondly, the rate of transfer of urea between C.S.F. and plasma. We tried to assess the latter factor by making serial and simultaneous observations on urea concentration in lumbar C.S.F. and plasma in patients who required prolonged haemodialysis for a period of 60 hours because of a very high catabolic rate. The results of these observations in one of these patients is shown in Fig. 7. During the first 36 hours of dialysis there was a persistent decrease in plasma urea concentration from 340 to 69 mg./100 ml. and the C.S.F. urea concentration decreased from 295 to 105 mg./100 ml. During the last 24 hours of dialysis the plasma urea concentration remained virtually constant, but sufficient urea did not pass from C.S.F. to plasma for re-establishment of the normal urea gradient. These results indicate that the rate of transfer of urea from lumbar C.S.F. to plasma is usually slower than the rate of rise of plasma urea in acute renal failure.

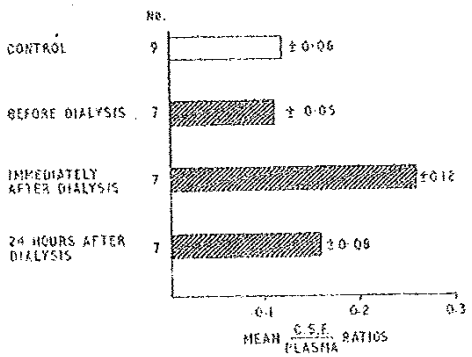

FIG. 4.—Mean of ratios of $\frac{\text{uric acid concn. in C.S.F.}}{\text{uric acid concn. in plasma}}$ in nine control subjects and seven patients with acute renal failure before and after haemodialysis.

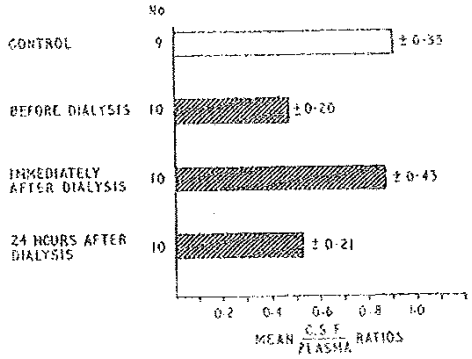

FIG. 5.—Mean of ratios of $\frac{\text{creatinine concn. in C.S.F.}}{\text{creatinine concn. in plasma}}$ in nine control subjects and 10 patients with acute renal failure before and after haemodialysis.

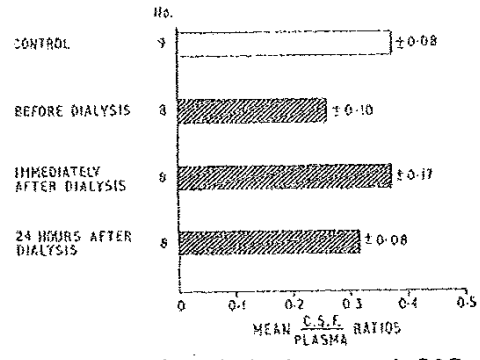

FIG. 6.—Mean of ratios of $\frac{\text{inorganic phosphorus concn. in C.S.F.}}{\text{inorganic phosphorus concn. in plasma}}$ in nine control subjects and eight patients with acute renal failure before and after haemodialysis.

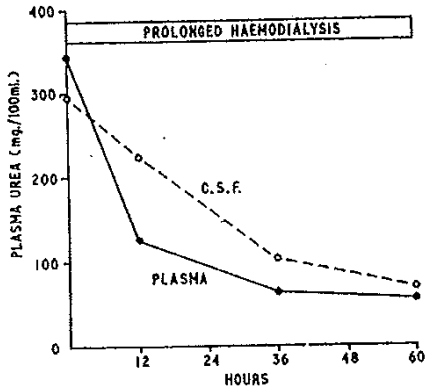

FIG. 7.—Serial observations on urea concentrations in samples of C.S.F. and plasma obtained simultaneously in a man aged 60 with acute renal failure who was dialysed continuously for 60 hours.

The mean alteration in osmotic gradient (C.S.F. minus plasma) caused by haemodialysis was 7.6 mOsm/kg. This is equivalent to a net alteration in transfer pressure of 100 mm. Hg. This would result in the transfer of water from plasma into C.S.F. with a subsequent rise in intracranial pressure and consequent symptoms.

Urea was the main substance responsible for the change in osmotic gradient, because the alteration in concentration of other substances was relatively small.

We did not measure C.S.F. pressures in our series, because the patients were often restless and conditions for measurement could not be standardized. However, Sitprija and Holmes (1962) have shown that there is a rise in the intracranial pressure of uraemic dogs after haemodialysis against a rinsing fluid free from urea. This rise in pressure did not occur if the rinsing fluid contained a concentration of urea equivalent to the plasma urea.

Prevention of symptoms due to biochemical disequilibrium may therefore be expected if biochemical gradients between C.S.F. and plasma are limited by dialysing for short periods of time and at frequent intervals. This can be effected economically by the use of indwelling catheters and storage of the dialysis circuit (Shaldon, Silva, and Rosen, 1964).

Summary

The size of the abnormal urea gradient between C.S.F. and plasma produced by haemodialysis is proportional to the concentration of plasma urea at the beginning of dialysis, and this abnormal gradient persists for approximately 24 hours after the termination of dialysis.

The delay in removal of urea from C.S.F. is associated with a change in the osmolality gradient between C.S.F. and plasma. This results in the passage of water into C.S.F., with consequent symptoms due to an increase in intracranial pressure.

It has also been demonstrated that haemodialysis creates a disturbance in equilibration of uric acid, creatinine, inorganic phosphorus, and bicarbonate between C.S.F. and blood.

It is therefore suggested that haemodialysis be performed at low levels of biochemical disturbance, for short periods of time, and at frequent intervals so that minimal biochemical disturbances be opened up between C.S.F. and blood and the dialysis disequilibrium syndrome be prevented.

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Medical Memoranda

Renal Vein Thrombosis in Acute Hyperparathyroidism

Brit. med. J., 1964, 2, 675–676

The diagnosis of primary hyperparathyroidism is usually suggested by the presence of renal stones or bone disease (Dent, 1962). Two cases are recorded here in which the presenting features were mental abnormalities associated with hypercalcaemia and rapidly progressive uraemia. In neither patient was there radiological evidence of bone disease or renal stones, and, though parathyroidectomy was undertaken as an emergency, both patients died and were found at necropsy to have renal-vein thrombosis. The absence of radiological bone or renal disease is uncommon in primary hyperparathyroidism, being found in 3% to 6% of cases (Keating, 1961 ; Hodgkinson, 1963).

CASE REPORTS

Case 1

A 38-year-old miner was admitted four times to hospital between April 1960 and June 1962 with vomiting and epigastric pain, and on each occasion the results of a barium meal were normal. He had nocturia, but his urine was protein free in 1961 and the blood urea was normal between bouts of vomiting. In June 1962 he became confused and was admitted for a short period to a mental hospital. In September 1962 vomiting recurred and the serum calcium was found to be 20 mg./100 ml. and the blood urea 192 mg./100 ml. Despite a maintained output of urine his blood urea rose and he was transferred to Hammersmith Hospital on 29 September 1962.

He was a well-built, febrile, stuporose man without corneal or tympanic membrane calcification or a palpable tumour in the neck. Clinically he appeared dehydrated: the blood-pressure was 100/70 mm. Hg. He had moist sounds at both lung bases. On admission the blood urea was 385 mg./100 ml., serum sodium 144 mEq/l. ; potassium 3.6 mEq/l. ; bicarbonate 28 mEq/l. ; calcium 19.2 mg./100 ml. ; inorganic phosphate 2.1 mEq/l. ; alkaline phosphatase 9 King-Armstrong units ; haemoglobin 13.0 g./100 ml. Radiology of the hands showed no evidence of hyperparathyroidism and there was no renal calcification or stone on the abdominal film, but the radiograph of the chest did reveal bilateral bronchopneumonic changes. The electrocardiogram showed deep S-T depression in all the chest leads.

Haemodialysis was performed on admission before surgical exploration of the neck. The blood urea fell to 175 mg./100 ml. but there was no significant change in the serum calcium. On 30 September 1962 a parathyroid adenoma measuring 1.5 × 1.5 × 0.5 cm. was excised by Mr. Selwyn Taylor from behind the left costochondral junction. By 2 October 1962 the serum calcium had fallen to 13 mg./100 ml. and the blood urea had risen to 475 mg./100 ml. when the patient suddenly died and could not be revived. His pneumonia had worsened but his daily output of urine had remained about 1 l.

The tumour consisted mainly of chief cells and areas of transitional clear cells. At necropsy both lungs showed bronchopneumonic changes. The right kidney weighed 230 g. and the left 192 g. In both kidneys the interlobar and arcuate veins were distended with recent dark thrombi and both main renal veins were occluded to just short of the inferior vena cava. Calcification was present in the renal tubules and also in small arteries in other organs. A few minute foci of osteitis fibrosa were seen in the sternum and spine.

Case 2

A 62-year-old clergyman had had impairment of memory and lack of concentration for one year. For one month before admission he had become more drowsy and confused, and he had developed dyspeptic symptoms and nocturia. On 10 August 1963 when he was admitted to hospital he was stuporose, dehydrated, and becoming progressively more uraemic, despite a daily output of urine of over 1 l. He was transferred to Hammersmith Hospital on 14 August.

He was a well-built man, with mild icterus and corneal calcification. His pulse rate was 110/minute and the blood-pressure was 100/70 mm. Hg. He had abdominal distension with scanty bowel sounds and tenderness in the right hypochondrium. He had no localizing neurological signs. Twelve hours after admission he developed thrombosis of the left femoral and external iliac veins. The blood urea was 275 mg./100 ml. ; serum sodium 137 mEq/l. ; potassium 3.0 mEq/l. ; bicarbonate 33 mEq/l. ; calcium 19.0 mg./100 ml. ; inorganic phosphate 2.9 mg./100 ml. ; alkaline phosphatase 13 King-Armstrong units ; serum bilirubin 2.8 mg./100 ml. ; amylase 375 Somogyi units ; haemoglobin 12.4 g./100 ml. A radiograph of the chest was normal, but abdominal films showed gaseous distension and fluid levels in the large and small bowel. There was no radiological evidence of hyperparathyroidism in the hands and no renal calcification or stones. The electrocardiogram showed S-T depression in all chest leads. The urine contained a trace of protein.

Emergency exploration of the neck was performed by Mr. Selwyn Taylor on 16 August and a tumour 2.8 × 2.8 × 1.5 cm. was excised

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Management of Patients with Renal Failure Complicated by Cerebral Oedema

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Key Words. Cerebral oedema · Continuous veno-venous haemofiltration

Abstract. Dialysis disequilibrium due to cerebral oedema still causes a significant degree of both morbidity and mortality. We discuss the management of 5 such cases and demonstrate the improved stability during treatment with continuous veno-venous haemofiltration. This may be due to the improved osmotic stability during haemofiltration with a resultant decrease in the osmotic gradient across the blood-brain barrier.

Introduction

Cerebral oedema can develop during routine haemodialysis in patients with chronic renal failure. An increase in brain parenchymal fluid has been demonstrated both by computerized tomographic (CT) [1] and nuclear magnetic resonance [2] scanning techniques and this is supported by post mortem studies of patients who died during haemodialysis treatment showing cerebral oedema and even tentorial herniation in some cases [3].

In patients undergoing regular haemodialysis, symptoms may be minimal consisting of restlessness and headache but occasionally nausea, vomiting, blurring of vision and even fitting may occur [4]. The majority of patients recover with appropriate medical treatment. However, a significant morbidity and mortality occurs in those patients who become comatose after fitting [5].

The pathogenesis of cerebral oedema during haemodialysis is not fully understood, but is related to an elevated cerebrospinal fluid pressure, a delay in the clearance of urea from the cerebrospinal fluid [6], and a fall in the cerebrospinal fluid pH [7]. Although the clearance of small molecules such as urea from the brain parallels that from the plasma, brain intracellular osmolality can increase due to changes resulting from the cerebrospinal fluid acidosis [8] as well as the production of idiogenic osmoles and to shifts of intracellular cations [9].

To prevent dialysis-induced cerebral oedema, shorter and more frequent haemodialysis treatments with a low blood flow rate or peritoneal dialysis have been suggested [10]. However, dialysis disequilibrium still remains a problem.

We reported our experience of haemodialysis in patients with neurological lesions

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and the successful outcome of using haemofiltration in the management of such patients with acute renal failure.

Case Reports

Case 1

A 45-year-old man with chronic renal failure due to glomerulonephritis commenced regular haemodialysis. He only weighed 45 kg and had a daily urine output in excess of 1 litre. In view of his endogenous renal function he was dialyzed twice a week for 3 h using a flat plate 1 m^2 cuprophan dialyzer (Gambro AB, Lundia, Sweden), his serum creatinine prior to haemodialysis ranged from 750 to 850 µmol/l. After 1 h of dialysis he regularly developed frontal headaches, felt nauseated, and would vomit if he had eaten or drunk anything prior to dialysis. At the end of dialysis, although he felt unwell, there were no focal neurological signs and he was neither hypoglycaemic nor hyponatraemic. After dialysis he was driven home, went to bed and by the next day his symptoms resolved. Investigation with a CT brain scan revealed bilateral porencephalic cysts (fig. 1). A repeat CT scan 4 h after a dialysis session did not show any enlargement of the cysts.

His symptoms persisted during 6 months of dialysis treatment despite various attempts to ameliorate them by re-using the dialyzer after reprocessing with sodium hypochlorite and formalin and using different types of dialyzer. Treatment was then changed to continuous ambulatory peritoneal dialysis. There has been no recurrence of his symptoms over a follow-up period of 18 months.

Case 2

A 29-year-old woman developed acute renal failure due to fulminant Goodpasture's syndrome. She was initially plasma-exchanged for 1 week to control pulmonary haemorrhage, but renal function did not recover. Arrangements were made for chronic haemodialysis and she was discharged on prednisolone 30 mg and cyclophosphamide 150 mg daily. Three days later she developed severe occipital headache and nuchal pain whilst receiving a blood transfusion during haemodialysis with a flat-plate 1-m^2 cuprophan dialyzer. The pain persisted overnight and she then developed increasing limb weakness starting in her legs. Although orientated and answering questions appropriately she had developed cortical blindness, quadriplegia and generalised hypertonia with bilateral knee and ankle clonus, and bilaterally upgoing plantars. A CT brain scan was performed which showed generalised oedema of the cerebral white matter (fig. 2). Prior to haemodialysis she was commenced on parenteral dexamethasone 4 mg 6 hourly. Fifteen minutes into dialysis using a 1-m^2 flat-plate cuprophan dialyzer (Gambro AB, Lundia, Sweden) with a blood pump speed of 200 ml/min she developed grand mal fitting. This persisted for 30 min despite intravenous diazepam and dialysis treatment had to be discontinued. She had become deeply comatose with fixed dilated pupils and was unresponsive to painful stimuli. On the following day she was haemodialysed for 4 h using a blood pump speed of 150 ml/min and was given an infusion of 100 ml of 20% mannitol during the first 15 min of dialysis. Despite these precautions she suffered a further 3

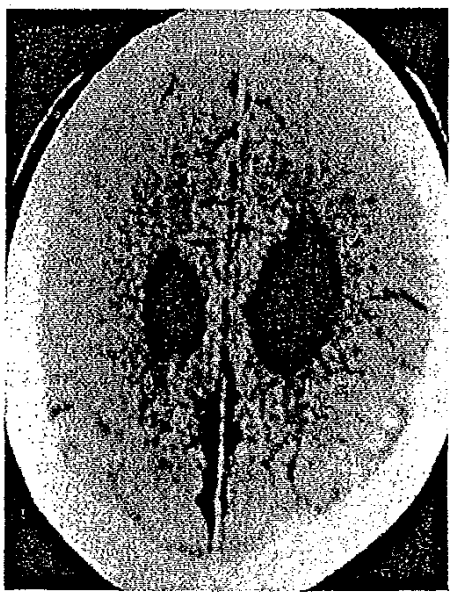

Fig. 1. Case 1 CT brain scan showing bilateral porencephalic cysts.

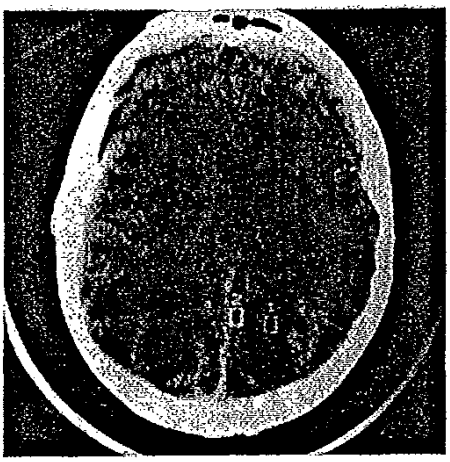

Fig. 2. Case 2 CT brain scan prior to haemodialysis showing diffuse oedema of the cerebral white matter.

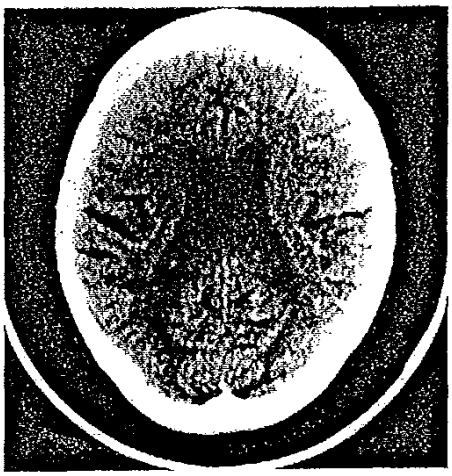

Fig. 3. Case 2 third CT brain scan showing complete resolution of cerebral oedema.

grand mal fits during dialysis. A neurologist reviewed the patient and noted decerebrate rigidity, askew doll's eye movements with a fixed and dilated right pupil.

Continuous veno-venous haemofiltration (CVVHF) was commenced using a Gambro FH55 haemofilter and a flow rate of 100–150 ml/min, to achieve an ultrafiltration rate of 1,000 ml/h. Anticoagulation was achieved with heparin at 10–13 IU/kg/h. Four days later she could answer questions appropriately and after a week there was some limb movement. She still had evidence of a mid-brain lesion with quadriplegia and impaired upward gaze. A repeat CT brain scan showed some improvement in the degree of cerebral white matter oedema. Over the next 2 weeks her condition slowly improved and CVVHF was discontinued after 3 weeks. A third CT brain scan showed marked improvement with resolution of the cerebral oedema (fig. 3). Four weeks after admission she was able to walk out of the unit and return home to resume regular haemodialysis without any permanent neurological damage. Twenty months later she remains at work whilst awaiting a renal transplant.

Case 3

A 47-year-old man who had recently returned from Uganda was admitted with a severe plasmodium falciparum parasitaemia (28% of red cells contained parasites). He was drowsy, disorientated but had no focal neurological signs and was in established oliguric acute renal failure. Initial treatment consisted of an exchange blood transfusion, intravenous quinine, dexamethasone and peritoneal dialysis. A CT brain scan on admission suggested some degree of cerebral oedema (fig. 4). He was markedly catabolic and despite peritoneal dialysis his plasma biochemistry became increasingly abnormal. Haemodialysis using a cuprophan 1-m^2 flat-plate dialyzer was started with a blood pump speed of 200 ml/min. However, after 30 min he became hypotensive (mean arterial blood pressure 54 mm Hg) and suffered both grand mal and focal seizures affecting the left arm. He became deeply unconscious and required ventilation. At no time was he hypoglycaemic or hyponatraemic. A further CT brain scan showed an infarct in the right parietal lobe (fig. 5). CVVHF was commenced using a Gambro FH55 haemofilter and a blood pump speed of 100–125 ml/min to achieve an ultrafiltration rate

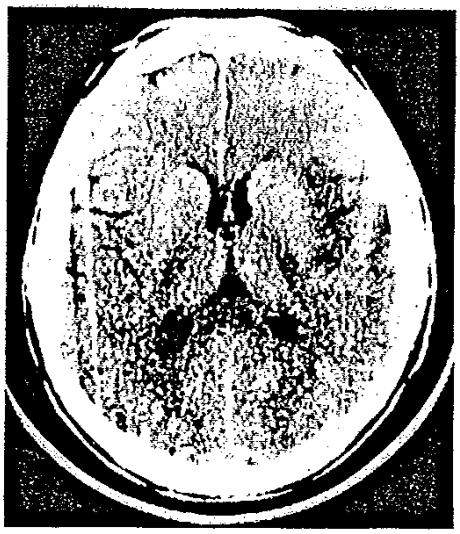

Fig. 4. Case 3 CT brain scan on admission showing some reduction in ventricular width and cortical haziness.

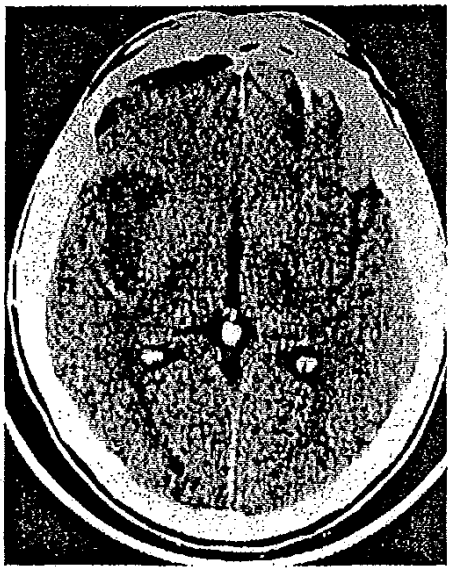

Fig. 5. Case 3 CT brain scan following haemodialysis showing an infarct in the right parietal lobe.

of 1,000 ml/h. Anticoagulation was with heparin at 10 IU/kg/h. He remained deeply unconscious for the next 2 days, but then began to move his right arm and leg spontaneously. After 5 days he was extubated and some left-sided movement was noted. His condition slowly improved and after 17 days CVVHF was stopped. He then received conventional haemodialysis until his renal function improved. He was discharged 6 weeks after admission, the only remaining neurological deficit being a loss of memory for events over the preceding 5 years. During clinic review over the next 6 months the memory deficit gradually resolved.

Case 4

A 52-year-old man was admitted with oliguric acute renal failure due to leptospirosis (IgM titre to *Leptospira icterohaemorrhagiae* positive at 1:5,120 dilution). On arrival he was jaundiced with conjunctival haemorrhages and small areas of purpura, in atrial fibrillation at a rate of 120 per min with a blood pressure of 140/90. He was haemodialyzed using a 1-m^2 flat-plate cuprophan dialyzer and anticoagulated with heparin. After 3 h of dialysis he suffered several grand mal fits and then had a respiratory arrest. He was neither hypoglycaemic nor hyponatraemic. Ventilation was required. Although a CT brain scan did not show any gross abnormality, a lumber puncture revealed a raised cerebrospinal fluid IgG value, IgG/albumin ratio 40% (normal $<16\%$), compatible with leptospiral encephalitis.

He was then haemofiltered for 5 days using a Gambro FH55 haemofilter with a blood pump speed of 100–125 ml/min to achieve an ultrafiltration rate of 1,000 ml/h, with heparin anticoagulation 8–11 IU/kg/h. Although he became polyuric, a further period of 4 days of CVVHF was required to maintain adequate serum biochemistries. His condition slowly improved and after 3 weeks ventilation was discontinued. His mental state improved with time and at discharge some 7 weeks after admission his only neurological deficit was a slightly spastic gait.

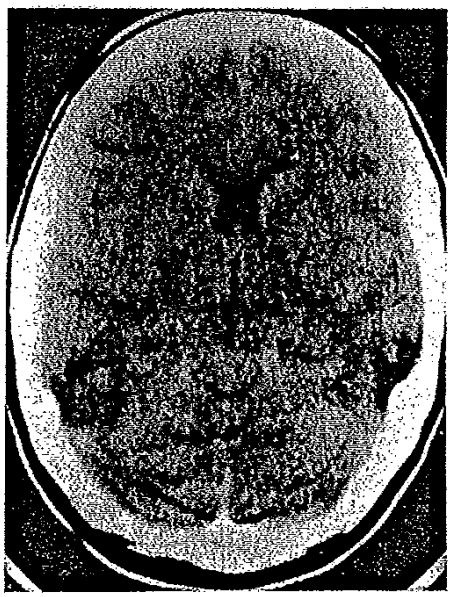

Fig. 6. Case 5 CT brain scan showing diffuse cerebral oedema and multiple infarcts in both parietal and occipital lobes.

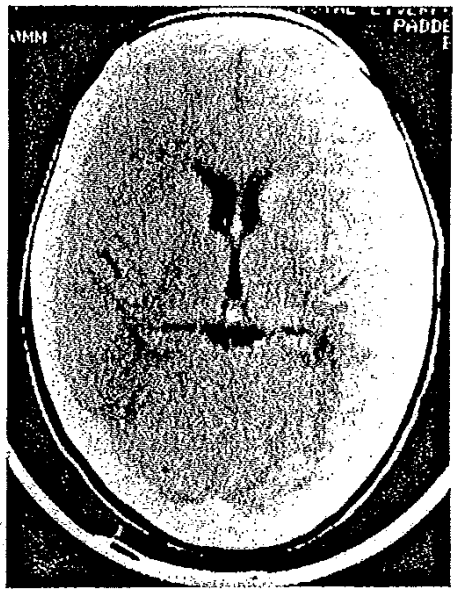

Fig. 7. Case 5 CT brain scan after treatment by CVVHF showing resolution of cerebral oedema and one small area of infarction in the right parietal lobe.

Case 5

A 26-year-old woman developed hepatorenal failure following a twin pregnancy complicated by antepartum haemorrhage and pre-eclampsia. She became drowsy and confused and then suffered a grand mal fit, was deeply unconscious and required ventilation. A CT brain scan showed generalised cerebral oedema and multiple infarcts in both parieto-occipital lobes (fig. 6). Treatment with CVVHF was commenced, using a 1.4 m^2 polyacrylonitrile membrane (Rhône-Poulenc, Paris, France) with a blood pump speed of 75–100 ml/min to achieve an ultrafiltration rate of 1,500 ml/h and anticoagulation was with heparin at 7–9 IU/kg/h. After 3 days of treatment she could flex to pain, and 2 days later could move her limbs to command. Ventilation was discontinued 4 days later and CVVHF stopped after a total of 14 days, when she was alert and orientated but generally weak. Bilateral foot drop had developed. A repeat CT brain scan showed improvement in the cerebral oedema although a small area of infarction persisted in the right parietal lobe (fig. 7). She required a further 6 haemodialysis treatments before her renal function improved to make dialysis unnecessary. Ten weeks after admission she was discharged home, with no neurological sequelae, to look after her twin babies.

Discussion

All 5 cases had evidence of neurological abnormalities prior to dialysis. The first patient with a structural brain abnormality although developing recurrent symptoms during dialysis did not fit. His symptoms may have been exacerbated by underdialysis, even though he had a urine output in excess of

1 litre and his predialysis serum creatinine was less than 900 µmol/l. However, he had no clinical evidence of peripheral neuropathy and nerve conduction studies performed on the lower limbs were within normal limits. His symptoms persisted despite trying to modify his dialyzer membrane by re-use and reprocessing and also the use of other more biocompatible membranes including polycarbonate and polyamide dialyzers. Only after changing therapy to continuous ambulatory peritoneal dialysis did his symptoms resolve.

However, in the 4 other cases the patients were too catabolic to permit treatment by peritoneal dialysis to have been used as a viable alternative. Three patients, the first with immune-mediated cerebral oedema due to an abnormal reaction to a blood transfusion with subsequent vasogenic cerebral oedema, the second and third with cerebral malaria and leptospiral encephalitis respectively, all did badly on conventional dialysis with a cuprophan dialyzer. All 3 fitted, two required ventilation and all became deeply unconscious. The fits recurred despite dexamethasone therapy in 2 patients and mannitol in the other. Dexamethasone, although producing clinical improvement in patients with cerebral oedema due to tumours, has not been shown to be effective in reducing the cerebral oedema by nuclear magnetic resonance imaging [11]. Similarly, mannitol has been shown to have little effect in reducing intracranial pressure when either the intracranial pressure has been elevated above 60 mm Hg or in patients with oliguric renal failure [12].

However, all 4 patients tolerated haemofiltration well without the use of dexamethasone, diazepam, or prophylactic mannitol. No patient was given paralysing agents or muscle relaxants during treatment with CVVHF, and only on one occasion was mannitol given when it was suspected clinically that the intracranial pressure had risen in patient 5 during the third day of treatment with CVVHF.

Patients undergoing haemofiltration have improved cardiovascular stability [13] compared to haemodialysis [14] due to maintenance of peripheral vascular resistance [15] and develop fewer symptoms during treatment [16]. The mechanism for the increased stability of those patients during haemofiltration has not been determined. We measured serum osmolality in 15 chronic haemodialysis patients both before and after a 4-hour haemodialysis session and showed that it fell significantly from 327 ± 3 mosm/kg (mean ± SEM) to 298 ± 2.6 mosm/kg, $p < 0.05$ (paired t test).

Serum osmolality was measured in 15 patients with acute renal failure treated by CVVHF at an ultrafiltration rate of 1,000 ml/h, there was no significant fall during the fist 4 h of treatment, the values were 315.5 ± 3.0 mosm/kg prior to and 314 ± 0.3 mosm/kg at 4 h respectively. This difference is not unexpected and confirmed previously published data [16] as during a 4-hour haemodialysis treatment between 120 and 150 litres of dialysate are used with an average creatinine clearance of 120 ml/min, whereas during 4 h of CVVHF only 4 litres have been exchanged with an average clearance of 20 ml/min.

During haemodialysis treatment the concentration of both urea and osmolality fall at a slower rate in the cerebrospinal fluid than in plasma [17], whereas during haemofiltration the transfer rate of urea from the cerebrospinal fluid is faster than during haemodialysis, resulting in a smaller gradient [16]. Similarly, during haemodialysis there is a preferential movement of solute from the

extracellular compartment resulting in a greater fall in plasma osmotic pressure [18], which may lead to the passage of water into the intracellular compartment resulting in cerebral oedema, whereas haemofiltration has been reported to result in a reduction in the extracellular volume without any change in the intracellular fluid volume [19].

It remains to be determined whether the reduction in osmotic gradients across the blood-brain barrier or the increased haemodynamic stability during CVVHF is responsible for the improved well-being of these patients thus treated compared to those treated by haemodialysis.

These cases suggest that CVVHF has an important role in the management of patients with acute catabolic renal failure complicated by raised intracranial pressure.

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IN-DEPTH REVIEW

Brain Swelling After Dialysis: Old Urea or New Osmoles?

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• The pathogenesis of brain swelling and neurological deterioration after rapid hemodialysis (dialysis disequilibrium syndrome) is controversial. The "reverse urea hypothesis" suggests that hemodialysis removes urea more slowly from the brain than from the plasma, creating an osmotic gradient that results in cerebral edema. The "idiogenic osmole hypothesis" proposes that an osmotic gradient between brain and plasma develops during rapid dialysis because of newly formed brain osmoles. In this review, the experimental basis for the two hypotheses are critically examined. Based on what is known about the physiology of urea and water diffusion across the blood-brain barrier, and empiric observations of brain solute composition after experimental hemodialysis, we conclude that the "reverse urea hypothesis" remains a viable explanation for dialysis disequilibrium and that rapid reduction of a high urea level in and of itself predisposes to this condition.

INDEX WORDS: Dialysis; disequilibrium syndrome; hemodialysis; brain; organic osmolytes; cerebral edema.

NEUROLOGICAL symptoms may develop when the blood urea nitrogen is lowered too rapidly by hemodialysis.[1] It is accepted that these symptoms, known as "dialysis disequilibrium," are associated with cerebral edema.* However, not everyone agrees as to what causes brain swelling after dialysis. The old neurosurgical practice of infusing urea intravenously to treat cerebral edema[2] led to the idea that dialysis disequilibrium was caused by slow diffusion of urea across the blood-brain barrier. After a rapid intravenous infusion, urea enters the brain slowly; the resulting urea (and osmotic) concentration difference draws water out of the brain.[3] Early clinical studies showed that after hemodialysis, the urea concentration was higher in cerebrospinal fluid than in plasma.[4] Thus, it was believed that by rapidly lowering the plasma urea concentration, dialysis caused cerebral edema in a manner that was analogous to but opposite of that of a therapeutic urea infusion (the "reverse urea effect"). This hypothesis was supported by the observation that dialyzed patients developed fewer electroencephalographic abnormalities when urea was added to the dialysate.[5]

Experiments by Arieff et al[6-8] in the 1970s seemed to discount the reverse urea effect as a cause of dialysis disequilibrium. These investigators concluded that urea is rapidly removed from the brain during dialysis and was not responsible for cerebral edema. Brain cell swelling was attributed to the formation of "idiogeneic osmoles," possibly organic acids, that formed in response to rapid hemodialysis. In contrast, more

* We use the terms *cerebral edema*, *brain edema*, and *brain swelling* interchangeably to describe a global increase in brain water content that affects both intracellular and extracellular fluid compartments. We use the term *brain cell swelling* to describe mechanisms that only affect the intracellular compartment.

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recent experiments by Silver et al[9,10] demonstrated that slow removal of urea from the brain could be an adequate explanation for dialysis-induced cerebral edema.

The purpose of this review is to reexamine the scientific evidence underlying the two theories of the pathogenesis of dialysis disequilibrium: the reverse urea effect (Table 1) and the "idiogenic osmole" hypothesis (Table 2). The conflicting experimental findings cannot be completely reconciled, but further analysis of these findings shows a significant amount of common ground. Although this review cannot end the controversy, it is intended to provide a perspective into the dynamics between brain and plasma urea, the concept of intracellular osmolality, and the role of brain organic osmolytes in uremia and in the dialysis disequilibrium syndrome.

EVIDENCE SUPPORTING THE REVERSE UREA EFFECT

Slow Diffusion of Urea Across the Blood-Brain Barrier

Transfer of urea across the blood-brain barrier takes place through the endothelial cells of brain capillaries. Their tight junctions, paucity of pinocytotic vesicles, and absence of fenestrae tend to create a major obstacle for the diffusion of water-soluble and polar solutes into the brain. Conversely, specific transcellular transport mechanisms promote transfer of a broad range of solutes between capillary plasma and cerebral interstitial fluid.[11-13]

Table 1. Arguments Supporting the Reverse Urea Effect

1. Urea diffuses much more slowly than water across the blood-brain barrier.
2. The concentration of urea in brain remains lower than that in plasma for several hours when the plasma urea level is elevated acutely. This creates an osmotic pressure difference across the blood-brain barrier that draws water out of the brain.
3. In acute experimental dialysis, a large brain-to-plasma-urea concentration difference develops that is associated with an increase in brain water content.
4. The postdialysis urea concentration difference is sufficient to explain the amount of water retained in the brain after dialysis.
5. Brain water after experimental dialysis does not increase if the rapid removal of urea is prevented by dialysis against a bath containing urea.

Table 2. Arguments Supporting the Idiogenic Osmole Hypothesis

1. Data supporting the reverse urea hypothesis should be viewed with suspicion because the concentrations of urea in brain and plasma are not equal in undialyzed animals.
2. Although urea is retained in the cerebrospinal fluid after dialysis, it is rapidly removed from cortical gray matter.
3. The brain-to-plasma concentration difference for urea that develops after dialysis is too small to explain the amount of brain swelling that occurs.
4. Direct measurements of the osmolality of brain tissue show that, after dialysis, brain osmolality is higher than plasma, a finding that cannot be explained by measured concentrations of urea and electrolytes in the brain (and is therefore attributed to the formation of idiogenic osmoles).
5. The intracellular pH of brain tissue decreases after dialysis, providing an explanation for the proposed idiogenic osmoles.

The transport characteristics of urea across the blood-brain barrier are perhaps the most widely studied of small organic solutes.[12,13] The ability of solutes to cross the blood-brain barrier, derived from intravenous injection and brain sampling for the solute in question, can be expressed by the blood-to-brain transfer coefficient (Ki). The units of Ki are milliliters of blood per gram per minute, making it a clearance term. The Ki for urea, measured with several methods, is approximately 5×10^{-3} mL/g/min, higher than that of mannitol, comparable to glycerol, and three orders of magnitude lower than that of water.[12,13] To conceptualize the meaning of this term, and its implications for the effects of dialysis on brain urea, consider a brain weighing 1 kg (with a water content of 800 mL). A Ki for urea of 5×10^{-3} mL/g/min would translate to 5 mL/min for the entire brain, indicating that close to 0.6% of brain water could be cleared each minute of its higher urea content and that it would take more than 2 hours to remove half of the brain's urea content.

Another way to examine the permeability of the blood-brain barrier to a given solute is to measure the effective osmotic pressure that solute can generate across this membrane. This factor can be expressed by the solute's reflection coefficient, that is, the ratio of its measured osmotic pressure to the ideal osmotic pressure predicted by the van't Hoff equation. Values range

from 0 to 1, with a value of 1 being completely impermeable.[14] The limited ability of urea to cross the blood-brain barrier is indicated by its reflection coefficient of 0.44 to 0.59 (v 0.48 for glycerol and 0.90 for mannitol). In contrast, the reflection coefficient of urea across heart capillaries is 0.1.[12,13]

Data also suggest a relative barrier for diffusion of urea within the brain. For example, Verkman and Fraser[15] studied brain synaptosomes (isolated membranes from presynaptic nerve terminals of cerebral cortex) and demonstrated that urea diffuses much more slowly across membranes than does water. Urea permeability in these preparations was 1.5×10^{-6} cm/sec, compared with 4.5×10^{-3} cm/sec for water. The permeability of synaptosomes prepared from uremic rats was not significantly different from normal.

In summary, urea diffuses across the blood-brain barrier and through brain tissue much more slowly than water does.

Discrepancy Between Brain and Plasma Urea Concentrations After Acute Perturbations

Studies in vivo have documented that urea diffuses slowly into the brain when plasma urea concentrations are increased acutely. Kleeman et al[16] found that 3 hours after injecting urea into rabbits, the ratio of urea concentrations between brain tissue (both white and gray matter) and plasma was approximately 0.5; in contrast, complete equilibration was achieved in muscle tissue within 1 hour.

The slow diffusion of urea across the blood-brain barrier, and the resulting urea concentration difference, has been exploited in the treatment of cerebral edema.[2,17] Experimental studies in animals without brain edema show that an acute intravenous infusion of urea causes brain dehydration that ultimately corrects in concert with near-equilibration of urea concentrations between plasma and brain over an 8-hour period.[3]

In summary, during urea infusion, urea diffuses slowly across the blood-brain barrier, resulting in a urea concentration that is higher in plasma than in brain. Therefore, with an acute increase in plasma urea concentration, urea acts temporarily as an effective osmole across the blood-brain barrier and draws water out of the brain.

Urea Retention in the Brain After Rapid Dialysis

Pappius et al were the first to study the pathogenesis of dialysis-induced cerebral edema in an experimental model.[18] After acute renal failure in combination with urea infusion, dogs with predialysis urea levels ranging between 140 and 280 mmol/L were hemodialyzed, reducing plasma urea levels by half in approximately 2 hours. The brain-to-plasma urea concentration ratio increased from close to unity predialysis to 1.27 in white matter and to 1.50 in gray matter at the end of dialysis (urea concentration was higher in the brain).† One hour after dialysis was stopped, both brain water content and the brain-to-plasma urea concentration ratio returned to baseline levels. Pappius et al concluded that these findings were consistent with the "reverse urea effect." Although these early studies were limited by a scatter in the predialysis urea levels and imprecise measurements of brain water, they are the only studies in which brain water and solute contents were measured serially both before and after acute dialysis.

In the 1970s, Arieff et al measured brain urea after dialysis in uremic dogs.[6-8] Six animals developed a marked increase in brain water content (14% in gray matter) after rapid hemodialysis during which plasma urea levels decreased from 72 to 24 mmol/L within 100 minutes. The apparent brain-to-plasma urea concentration ratio increased from 1.0 to 1.31 in gray matter and from 0.9 to 1.54 in white matter. These values underestimate the actual retention of urea because brain water content had increased, diluting its tissue concentration. Without the increase in brain water, the brain-to-plasma urea concentration ratio would have been 1.49 in gray matter and 1.71 in white matter. Although these investigators discounted the reverse urea effect as a cause of brain cell swelling after dialysis, their studies, like those of Pappius et al[18] confirmed that urea was removed relatively slowly from the brain during rapid hemodialysis and that this created a brain-to-plasma urea concentration difference.

In 1992, the pathogenesis of the dialysis disequilibrium syndrome was reexplored by Silver et al[9] in a model of rapid hemodialysis in the rat. Nine conscious rats underwent rapid (90 minutes) hemodialysis 42 hours after nephrectomy, reducing the plasma urea level from 72 to 34

† Measured concentrations of urea and other solutes in the brain must be interpreted cautiously because of uncertainty about how much of the water content of the brain serves as a solvent (see section below).

Table 3. Brain Solutes and Water Content After Hemodialysis in Rats

	N	Brain/Plasma Osmolality	Plasma Osmolality (mOsm/kg)	Predicted Brain Water* (L/kg dry wt)	Measured Brain Water* (L/kg dry wt)
Whole brain					
Uremic controls	15	1.08	361		3.67 ± .03
Rapid hemodialysis	11	1.00	334	3.89	3.89 ± .04
Urea hemodialysis	9	1.06	367	3.61	3.67 ± .04

* Predicted brain water is the tissue water content that would be expected under conditions of osmotic equilibrium based on the observed changes in tissue electrolyte and urea contents after dialysis. See Appendix for derivation of values.

Data from Silver et al.[9]

mmol/L and increasing brain water content by 6%. Brain urea was measured by an enzymatic assay, and the brain-to-plasma urea concentration ratio increased from 0.8 to 1.3. In quantitative terms, this concentration difference for urea could account for the measured increase in brain water (Table 3). These findings were confirmed in a similar group of studies by Silver in which urea and other organic osmolytes were measured by high-performance liquid chromatography. The brain-to-plasma urea concentration ratio increased from 0.65 to 1.32 in rapidly dialyzed rats, again enough to account for the observed brain swelling.[10]

In summary, all studies indicate that, after rapid experimental dialysis, a large urea concentration difference develops between the brain and plasma.

Brain-to-Plasma Urea Concentration Differences and Postdialysis Brain Edema

Because dialysis removes urea from the plasma more rapidly than urea can leave the brain, a difference in osmolality must develop very transiently across the blood-brain barrier. This difference is unlikely to be sustained because a difference of only 1 mOsm/kg H_2O generates a hydrostatic pressure difference of just under 20 mm Hg.[14,19] The brain-to-plasma urea concentration difference thus creates a powerful driving force for water movement into the brain. Although, as mentioned earlier, the capillary endothelium that forms the blood-brain barrier is not as permeable to water as are systemic capillaries,[13] water should still move across this barrier rapidly enough to achieve osmotic equilibrium between the brain and plasma within minutes.

In a mathematical model described by Fenstermacher,[13] a step increase in plasma osmolality from 300 to 350 mOsm/kg induced by a solute with a reflection coefficient of 1.0 (impermeable to brain) would result in a new plateau of lower brain water volume after approximately 40 minutes. In the experimental models described by Silver et al[9] and by Arieff et al,[6] plasma osmolality was decreased by approximately 20 to 40 mOsm/kg over the course of 1.5 to 1.6 hours because of lower plasma urea concentrations (a solute with a reflection coefficient of 0.4 to 0.6). Thus, it is reasonable to assume that brain and plasma osmolalities remain nearly equal during experimental dialysis. Although brain and plasma might not have been in absolute osmotic equilibrium at the end of dialysis in these models, a major difference in osmolality would not be expected.

If brain and plasma osmolalities are virtually equal, a sudden change in the osmolality of plasma must induce an identical change in brain osmolality. Based on this principle, we can estimate whether the change in brain water content observed during dialysis can be explained by the measured changes in plasma osmolality, brain urea, and brain electrolyte contents by applying the following formula:

Brain solute/Brain solvent water

= Plasma osmolality

Using this reasoning, Silver et al[9] found that enough urea was retained in the brains of rapidly dialyzed animals to explain most of the observed differences in brain water content (Table 3). At variance with the data and conclusions drawn from Silver et al's study[9] are the results from

Table 4. Brain Solutes and Water Content After Hemodialysis in Dogs

	N	Brain/Plasma Osmolality	Plasma Osmolality (mOsm/kg)	Predicted Brain Water* (L/kg dry wt)	Measured Brain Water (L/kg dry wt)
Gray matter					
Uremic controls	8	1.01	349		4.08 ± .10
Slow hemodialysis	6	1.01	304	4.04	4.09 ± .06
Rapid hemodialysis	6	1.08	306	4.33	4.63 ± .15
Urea hemodialysis	4	1.08	356	4.39	4.34 ± .03
High Na hemodialysis	4	1.08	336	4.12	3.96 ± .10
White matter					
Uremic controls	8	?	349		2.22 ± .06
Slow hemodialysis	6	?	304	2.32	2.36 ± .07
Rapid hemodialysis	6	?	306	2.40	2.47 ± .06
Urea hemodialysis	4	?	355	2.30	2.14 ± .03
High Na hemodialysis	4	?	336	2.11	2.14 ± .03

* Predicted brain water is the tissue water content that would be expected under conditions of osmotic equilibrium based on the observed changes in tissue electrolyte and urea contents after dialysis. See Appendix 1 for derivation of values.

Data from Arieff et al.[6]

Arieff et al.[6] These investigators found that post-dialysis urea contents were not large enough to explain the increase in brain water that they found in their rapidly dialyzed animals. To resolve this apparent conflict, we determined a "predicted" value for brain water in each of the experimental groups studied by Arieff et al by considering the measured changes in plasma osmolality, brain urea, and brain electrolytes reported by these investigators (Table 4). In these calculations, we assumed that brain and plasma osmolalities were equal and ignored values for measured brain osmolality for reasons to be discussed later. In gray matter, the predicted values for brain water range from 94% (rapid hemodialysis) to 104% (rapid hemodialysis against a high sodium bath) of the measured value. In white matter, the predicted values range from 97% (rapid hemodialysis) to 107% (rapid dialysis against a urea bath) of the measured value. Thus, in the rapid hemodialysis group studied by Arieff et al, measured brain water was more than expected, but in other groups brain water was less than expected; the variability in these results makes discrepancies between measured and calculated values difficult to interpret.

Two caveats are necessary to avoid overinterpreting the values presented in Tables 3 and 4. It is clear that urea is removed relatively slowly from the central nervous system when its concentration is lowered rapidly in plasma. It is also clear that brain water increases under these conditions. It may, however, be difficult to confidently ascribe observed changes in brain water content to retained urea in the brain. The difficulty stems in part from uncertainty about how much of cell water has ideal solvent properties. Experiments by Horowitz et al illustrate this problem.[20,21] These investigators microinjected [^{14}C]sucrose in gelatin into the cytosol of frog oocytes (chosen for study because of their large size and survival at low temperatures). After sufficient time for diffusion equilibrium, cells were quick frozen and microdissected, allowing measurements of the specific activity of [^{14}-C]sucrose in the gelatin and in various regions of the cytosol. In cytosol sampled near the cell nucleus, the specific activity of radioactive sucrose equaled that in gelatin and in a reference solution; however, in much of the remainder of the cytosol, the specific activity of sucrose was much lower (0.3), indicating that most of the water in this latter region did not behave as an ideal solvent.

Although mammalian brain cells and frog oocytes are obviously different, these data suggest that a degree of caution is required when measurements of urea (or other solute) contents are interpreted as concentrations in brain tissue. Determinations of urea concentration are based on the measured urea content (in millimoles per kilogram dry weight) and water content (in liters per kilogram dry weight) of the tissue. The latter

measurement (usually made by weighing the tissue before and after drying) includes both solvent and structural water; however, only the solvent portion is relevant to the osmotic activity of the measured urea.

Even if we could accurately determine the amount of solvent water in the brain, we could still only measure solute concentrations. Concentration cannot be equated with osmolality, a measure of activity that is altered by a number of factors, including the ionic strength of solutions.[19]

In summary, assuming that the brain and plasma are in osmotic equilibrium, measured brain solutes are sufficient to account for the observed changes in brain water found in the study by Silver et al.[9] In the study by Arieff et al,[6] measured solutes do not fully explain the severity of brain edema in rapidly hemodialyzed animals, but there is significant variability in their data: in other experimental groups, brain water contents are lower than would be predicted. However, all attempts to predict changes in brain water contents on the basis of changes in brain solute and plasma osmolality should be taken "with a grain of salt." A healthy skepticism is appropriate because brain and plasma osmolalities may not be absolutely equivalent, and, more importantly, because there are uncertainties about the amount of brain water that has ideal solvent properties and about the relationship between osmolality and concentration.

Brain Water Does Not Increase in Animals Dialyzed With a Bath Containing Urea

If slow removal of urea from the brain were responsible for dialysis-induced cerebral edema, one would expect that dialysis against an isoosmolar urea bath would prevent cerebral edema. In the studies of Silver et al[9] and of Zhou et al,[22] animals were dialyzed against a urea bath to prevent a decrease in the plasma urea level; in both studies, this maneuver alone prevented the development of cerebral edema, supporting the reverse-urea effect as a major cause of brain cell swelling after dialysis. In the studies of Arieff et al,[6] four animals were dialyzed against urea. Only one of the animals developed visible brain swelling, and in the group as a whole, the results were somewhat inconsistent: in white matter, the water content decreased by 4%, whereas in gray matter it increased by 6%; because white matter predominates, total brain water was probably unchanged.

ARGUMENTS FOR THE IDIOGENIC OSMOLE HYPOTHESIS

Studies Supporting the Reverse Urea Hypothesis Have Technical Problems

The studies of Silver et al[9] have been criticized[23] on technical grounds. Specifically, Silver's finding that undialyzed normal and uremic rats had brain urea concentrations lower than plasma seemed at variance with data obtained in dogs.

In fact, a steady-state concentration difference for urea between brain and plasma is the expected consequence of slow urea transport across the blood-brain barrier, and such a concentration difference has been reported by several investigators.[23,24-27] Studies using [^{14}C]urea demonstrate slow uptake of urea into the central nervous system (CNS). Johanson and Woodbury[26] measured the distribution of [^{14}C]urea in plasma, cerebrospinal fluid, choroid plexus, brain cortex, and skeletal muscle and found that equilibrium between cortex and plasma was reached only 8 hours after injection (v 0.5 hours in muscle) (Fig 1). The final concentration of [^{14}C]urea, compared with plasma, was 0.88 in cortex, and 0.71 to 0.72 in cerebrospinal fluid (CSF) and choroid plexus. Thus, even at steady state, the concentration of urea in brain water appears to be less than that of plasma. In these experiments, [^{3}H]H_2O entered the CNS more quickly than it entered muscle, equilibrating within 6 to 9 minutes. Thus, cerebral blood flow was not a limiting factor for urea equilibrium.

The steady-state urea concentration difference between brain, cerebrospinal fluid and plasma, although not obvious on the surface, can be explained by physiological events.[3,28] As CSF is formed at the choroid plexus, ions are secreted, water follows very quickly, and urea lags behind. Thus, newly formed CSF has a much lower urea concentration than do plasma and brain cells. Hence, some urea will also diffuse down its concentration difference, out of brain cells into the CSF. The limited permeability of urea at the blood-brain barrier prevents true equilibration between brain and plasma urea concentrations and allows a lower brain cell urea concentration to persist. At the arachnoid villi, the exit site where CSF returns to the body, bulk flow pre-

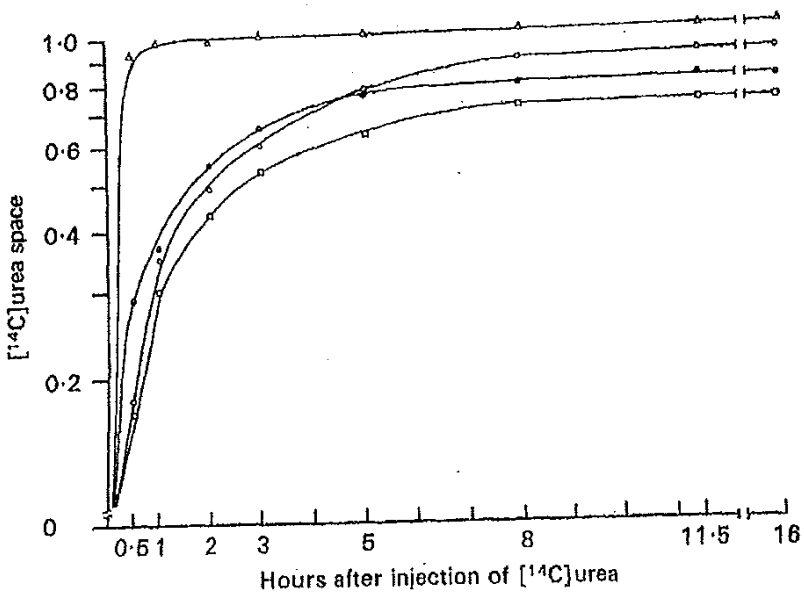

Fig 1. Time course of uptake of [^{14}C]urea by tissues and CSF of the adult rat. The ordinate indicates the ratio of counts of [^{14}C]urea per milligram plasma water to counts per milligram CSF or tissue. Each plot on graph for skeletal muscle (Δ), cerebral cortex (O), and choroid plexus (●) is a mean value for five or six rats; for CSF (□), each plotted mean value represents four or five animals. Standard errors are generally <5% of the respective means. (Reprinted with permission.[28])

dominates so that urea is "dragged" back into the circulation against its concentration difference. In experimental animals, this phenomenon (which occurs in the presence and absence of azotemia[29]) is not evident at birth, but develops by 4 weeks of age as the blood-brain barrier and choroid plexus mature.[30]

A number of studies have confirmed that apparent urea concentrations in brain can be lower than plasma in both normal and azotemic animals[24-27] (Table 5), although, as discussed earlier, all such studies suffer from uncertainty about the state of water in brain cells. Brain-to-plasma urea concentration ratios in dogs appear closer to unity than in other species (Table 5). Phylogenetic studies of urea transport in the CNS provide an explanation for this finding: the capillary exchange half-time is 15 minutes for the dog, compared with 30 minutes for the dogfish, and more than 60 minutes for the cat, monkey, and rat[31]; the half-time in humans is not known. More importantly, even if brain and plasma urea concentrations were equal after many hours of sustained azotemia, this observation would not militate against a disequilibrium after rapid changes in urea content. Indeed, measurements made after urea infusions lasting 4 hours or less have consistently shown that brain and plasma urea concentrations are not equal, even in the dog.[16,27]

In summary, the discrepancy between brain and plasma urea concentrations reported by Silver et al[9,10] is not a reason to reject the reverse urea hypothesis.

Urea Is Rapidly Removed From the Cerebral Cortex

As discussed above, Arieff et al[6] as well as Silver[9,10] reported a substantial apparent brain-to-plasma urea concentration difference after dialysis, particularly when dilution of retained urea by excess brain water is considered.

Urea Concentration Differences Are Too Small to Explain Brain Edema

Although apparent urea concentrations were higher in the brain than in plasma after rapid hemodialysis in the study of Arieff et al,[6] these investigators found that the difference was too small to completely account for the observed increase in brain water in rapidly dialyzed animals. Indeed, as shown in Table 4, the measured increase in the water content of gray matter after rapid hemodialysis is approximately twice the increase that would be predicted. Consequently, Arieff et al reasonably concluded that the reverse urea effect could not be responsible for brain edema after dialysis.

An alternative explanation for these findings should also be considered. A problem we find troubling is that a discrepancy between measured

Table 5. Brain and Plasma Urea Concentrations in Normal and Azotemic Animals

Species	Author	N	Experimental Conditions	Plasma [Urea] (mmol/L)	Brain Tissue	Brain/Plasma Urea Ratio
Rat	Llen et al[26]	8	Normal	5 ± 0.7	Whole brain	0.82 ± 0.15
	Silver et al[9]	12	Normal	6 ± 0.1	Whole brain	0.83 ± 0.12
	Silver et al[10]	11	Normal	8 ± 1	Whole brain	0.86 ± 0.27
	Trachtman et al[24]	6	Normal	8 ± 0.1	Whole brain	0.99 ± 0.05
	Llen et al[25]	5	Hypernatremia	15 ± 1.8	Whole brain	0.84 ± 0.11
	Silver et al[9]		42 hr postnephrectomy	70 ± 4	Whole brain	0.76 ± 0.06
	Silver[10]	10	42 hr postureteral ligation	111 ± 4	Whole brain	0.65 ± 0.12
	Trachtman et al[24]	5	48 hr postureteral ligation	90 ± 4	Whole brain	0.45 ± 0.05
	Johanson and Woodbury[26]	5	16 hr ^{14}C urea infusion	Not applicable	Gray matter	0.88
Cat	Bradbury and Coxon[27]	3	6 hr urea infusion	98 ± 4	Gray matter	0.81 ± 0.04
Rabbit	Kleeman et al[16]	7	Steady-state urea infusion	18 ± 2	Whole brain	1.07 ± 0.03
Dog	Papplus et al[18]	4	Normal	11 ± 3	Gray matter	0.87 ± 0.15
	Arieff et al[6]	10	Normal	5 ± 0.2	Gray matter	1.22 ± 0.13
	Bradbury and Coxon[27]	1	6 hr urea infusion	Not given	Gray matter	1.10
	Papplus et al[18]	20	Ureteral ligation and urea infusion	205 ± 81	Gray matter	0.98 ± 0.10
	Arieff et al[6]	8	3 days postureteral ligation	72 ± 5	Gray matter	1.00 ± 0.07
					White matter	0.91 ± 0.07

and predicted brain water contents was not limited to the rapidly dialyzed group (see Table 4); in other experimental groups, brain water increased by much less than would be predicted (ie, the discrepancy between measured and predicted values was in the opposite direction). The cause for this variability is unexplained but could reflect the methodological problems in obtaining samples of brain tissue when subfractionation is attempted (white v gray matter). Time was required to remove the top of the skull under anesthesia, occlude the vasculature, remove a portion of the brain, and then divide it into white and gray matter by blunt dissection. Because the water and fat contents are not identical in various regions of the brain, and because tissue trauma and ischemia can markedly alter brain water and solute contents by affecting the integrity of the blood-brain barrier, the sampling technique could result in significant variability of results. In the studies of Silver et al,[9,10] brain tissue was obtained by decapitation of unanesthetized rats so that an entire cerebral hemisphere was frozen within 15 seconds; in that study, no major differences between "predicted" and "observed" brain contents were identified (Table 3).

In summary, in contrast to the studies of Silver et al, Arieff et al found that measured brain solutes do not fully explain the large increase in brain water content that they observed after rapid experimental dialysis. The methods used by the two groups of investigators to sample brain tissue may account for the differences in results.

Direct Measurements of Brain Osmolality Show That New Osmoles Are Formed After Dialysis

Arieff et al[6] attempted to determine brain osmolality by measuring the freezing point depression of diluted and boiled tissue samples; only the data for gray matter were reported. As can be seen in Table 4, these investigators found brain and plasma osmolalities to be approximately equal in uremic controls and in slowly dialyzed animals. By comparing the product of brain osmolality and brain water (the measured brain osmolar content) with measured tissue urea and electrolyte contents, the investigators found that in uremic controls and slowly dialyzed animals, 65 to 75 mOsm/kg of tissue osmolality was unaccounted for. After rapid hemodialysis, the ratio between brain and plasma osmolalities was

1.08 (there was a 26-mOsm/kg difference in osmolality between plasma and brain), and 100 mOsm/kg of tissue osmolality was unaccounted for. Based on this finding, brain edema after rapid dialysis was attributed to the formation of new "idiogenic osmoles" in response to rapid hemodialysis at a concentration of 25 to 35 mOsm/kg.

Of note, postdialysis brain-to-plasma osmolality differences were not limited to rapidly dialyzed animals. Similar differences were observed in animals dialyzed against urea (brain-to-plasma osmolality difference = 38 mOsm/kg) or against a high sodium bath (osmolality difference = 27 mOsm/kg). In these latter groups, tissue urea and electrolyte contents are fully adequate to explain the measured changes in brain water without invoking "idiogenic osmoles" (Table 4). Thus, the brain-to-plasma osmolality difference in the rapidly dialyzed group was not unique, and brain-to-plasma osmolality differences in other groups were not associated with unexpectedly large increases in brain water.

Perhaps more important is the question of whether large osmotic concentration differences between brain and plasma could exist in vivo. Consider that a 26 milliosmolal difference would generate a hydrostatic pressure difference of over 500 mm Hg. Silver et al,[9] using a minor modification of the technique described by Arieff et al,[32] found the whole brain-to-plasma osmolality ratio to be 1.08 in undialyzed animals and 1.00 postdialysis—a difference that was not statistically different. Silver et al attributed the predialysis osmolality difference in their study to imprecision of the osmolality measurement in extracts of brain.

In summary, the idiogenic osmole hypothesis is based on the finding that large differences in osmolality exist between brain and plasma during dialysis. Such osmotic differences are highly unlikely and have not been reproduced by other investigators. We discuss the validity of these tissue osmolality measurements below.

Organic Acids as "Idiogenic Osmoles"

Arieff et al[7] examined the effect of hemodialysis on CNS pH; brain urea contents were not measured in this study. Documentation of both CSF and intracellular acidosis led to the hypothesis that organic acids form in response to rapid hemodialysis and that these acids (which are not lactate) in some way increase brain osmolality, thereby leading to cerebral edema. It is important to stress that for added acids to increase osmolality, the protons must be buffered by proteins and not by bicarbonate.[33] To determine whether protein or bicarbonate buffers predominate, one must know what changes occurred in tissue partial pressure of carbon dioxide (PCO_2).[34] To obtain this information, one needs to know the venous PCO_2,[33] a parameter that is not measured in any of the studies in which the intracellular pH was measured in the CNS. Therefore, one should be hesitant to infer that unidentified organic acids led to the formation of new osmoles in the brain. In addition, organic acids are not among the organic osmolytes have been recently been shown to play a major role in brain adaptation to osmotic stress.[35]

THE IDIOGENIC OSMOLE HYPOTHESIS; A CRITIQUE

Validity of Brain Osmolality Measurements

Investigators encounter great difficulties when they attempt to quantify the osmolyte content and osmolality in cellular fluid.[20,21,36-39] When studying the brain, the problems are even more complex because of cellular heterogeneity, a blood-brain barrier, white and gray matter, granules with bound materials, and the fact that the skull is a major obstacle for rapid tissue sampling without interventions. To be succinct, we highlight three major problems:

Sample dilution. In the technique commonly used to measure tissue osmolality, boiling water is added to quick-frozen brain tissue to inactivate proteolytic enzymes. The resulting tissue dilution (five parts of water to one part brain) introduces several potential errors. Dilution decreases the ionic strength of the preparation, which could lead to a small increase in the activity coefficient (and osmotic contribution) of the electrolytes in solution. Sweeney and Beuchat[19] have cautioned against techniques using simple multiplication to correct for dilution to obtain the apparent osmolality of the undiluted sample. A large dilution factor also exaggerates the inherent inaccuracy of available osmometers.

Bound osmoles in tissues. The preparation of tissue extracts before osmometry can potentially release a variety of solutes that are bound, and thus not normally free in solution. These include magnesium, the second most abundant cation in cells (bound in vivo to compounds such as adenosine triphosphate); ligands or ions bound to na-

tive tissue proteins; products released from disrupted digestive granules; and ion complexes that occur in neurosecretory granules.

Solvent versus structural water. As discussed earlier, not all of the water contained in the cell cytosol may act as ideal solvent water. Calculations performed by Srere[40] suggest that much of the water in mitochondria is not ideal solvent water; rather most is probably associated with polar groups in proteins. Preparation of tissue extracts disrupts these associations, adding more solvent water and decreasing the measured osmolality.[36]

Some of these problems would artifactually increase tissue osmolality, whereas others should decrease it. This may explain why the technique has yielded measurements of brain osmolality that are close to plasma osmolality.[32] However, reported values for brain have also had large standard errors—as high as 14 mOsm/kg. Reported brain-to-CSF osmolality ratios have ranged from 0.92 to 1.07, and a linear regression relating these two variables does not pass through the origin.[11,32]

Known Brain Organic Osmolytes Do Not Increase After Rapid Hemodialysis

The brain neither swells in response to hypotonicity nor shrinks in response to hypertonicity to the degree that would be expected of a perfect osmometer. The resistance of brain tissue to osmotic swelling and shrinkage cannot be completely explained by changes in brain electrolyte contents. In the past, changes in brain cell "idiogenic osmoles" were invoked to explain this phenomenon. It is now known that brain cells accumulate or extrude solutes known as organic osmolytes in response to osmotic stress. These solutes (amino acids, polyols, and methylamines), which can vary widely in intracellular concentration without interfering with protein function, are similar to those used by a wide variety of cells—ranging from prokaryotes to mammalian renal cells—for volume regulation.[35]

Major brain organic osmolytes in animals include myoinositol, taurine, glutamine, and glutamate. Accumulation of brain organic osmolytes in response to hypertonicity is relatively slow, occurring over the course of many hours. The process depends on transcription and translation of genes coding for transporters that promote cell uptake of these solutes.[41-43] For example, myoinositol accumulation by C6 glioma cells requires upregulation of a sodium-dependent uptake pathway. After exposure of the cells to a hypertonic environment, intracellular myoinositol levels begin to increase in 10 hours and peak in 24 hours in conjunction with increased activity of a phlorizin-inhibitable inositol transporter. Correction of hypertonicity leads to the relatively slow loss of organic osmolyte, in part because sodium-dependent myoinositol transporters stimulated by hypertonicity continue to be activated for several hours.

In studies of in vivo hypernatremia, cerebral levels of organic osmolytes increase but the process takes several days to reach completion.[25,44] During rapid correction of hypernatremia, cerebral edema occurs because of the persistence (not the formation) of elevated levels of brain inositol and amino acids. In hyponatremia, organic osmolyte levels begin to decrease in the brain within 24 hours,[45] and by 2 days, the brain content of inositol, glutamine, and taurine have decreased by 60% to 80% (from normal values of approximately 50 mmol/L).[44,46] Rapid correction of chronic hyponatremia causes brain dehydration because cells adapted to hypoosmolality are unable to reaccumulate osmolytes fast enough to keep pace with the increasing serum sodium concentration.[44,46]

Thus, organic osmolytes play an important role in the brain's adaptation to osmotic stress. Changes in the concentration of these solutes occur relatively slowly (in several hours to days). In contrast, the "idiogenic osmole" hypothesis proposes a response in unmeasured cell solute content that is extremely rapid, accumulating in some cases faster than water can diffuse into the brain.

To further explore the role of organic osmolytes in dialysis disequilibrium, Silver recently conducted studies measuring known organic osmolytes by high-performance liquid chromatography (HPLC) in the brains of acutely uremic rats that had undergone rapid hemodialysis.[10] Results in this group were compared with those in acutely uremic and nonuremic controls. None of the measured brain organic osmolytes increased after dialysis. As in Silver's previous study, retention of urea after dialysis was sufficient to explain the degree of cerebral edema observed. The findings were in agreement with a preliminary report by Zhou et al[22] that found no change in postdialysis brain organic osmolytes as mea-

sured by HPLC and ^1H magnetic resonance spectroscopy in a rat model of hemodialysis similar to that developed by Silver et al.[9,10]

It is, however, plausible that organic osmolytes would contribute to cerebral edema after dialysis. One study of acutely uremic rats found increased levels of brain osmolytes, possibly acting as "protective" solutes in response to toxic levels of urea.[24] When plasma osmolality is reduced rapidly by dialysis, retention of these osmolytes (along with urea) could potentially contribute to cerebral swelling, analogous to the brain swelling that occurs after rapid correction of hypernatremia. However, this proposed mechanism is distinctly different from the "idiogenic osmole" hypothesis, which proposes that new solute forms during dialysis.

Although most of the major brain organic osmolytes appear to have been identified, one cannot entirely account for brain osmolal content (plasma osmolality × brain water) with measured electrolytes and organic osmolytes. Thus, unidentified osmolytes may play a role in the brain's response to osmotic stress. Furthermore, results of studies done in experimental animals are not necessarily applicable to humans. In this regard, studies of brain organic osmolytes in uremic patients before and after dialysis through nuclear magnetic resonance spectroscopy would be of great interest.[47]

DIALYSIS DISEQUILIBRIUM SYNDROME: ADDITIONAL MECHANISMS

The "reverse urea effect" appears to be a significant factor in the pathogenesis of brain swelling after dialysis. However, other mechanisms may contribute to brain edema or neuronal excitability after rapid dialysis. A seemingly small decrease in osmolality (10 mOsm/kg) increases neuronal excitability in hippocampal brain slice preparations.[48] This effect cannot be reproduced by ineffective osmoles, and can be reversed by an increase in osmolality. The cause of this effect is unknown, but it may be secondary to cell swelling. As a result of cell swelling, the extracellular space decreases, a process with two effects that could potentially increase the susceptibility to seizure activity: (1) increased extracellular resistance to current, which increases the voltage generated by discharging neurons (voltage = current × resistance); and (2) increased extracellular potassium concentrations.[48] Cell swelling may also lead to local ischemia and release of neuroexcitatory transmitters such as glutamate and aspartate.[49] These transmitters may predispose to seizure activity and to further brain swelling by stimulating ion-coupled receptors, which trigger influx of Na and Cl.

CONCLUSION

Several studies have shown that the reverse urea effect is an adequate explanation for brain swelling after rapid hemodialysis. This mechanism is supported by experimental evidence demonstrating that urea moves slower than water across the blood-brain barrier. The idiogenic osmole hypothesis relies on measurements of total tissue osmolality that are of uncertain validity. An accumulation of cellular organic osmolytes would not be the expected response to a decrease in plasma osmolality as occurs with rapid dialysis. It is thus not surprising that experimental studies have found no evidence for an increase in organic osmolytes after hemodialysis. Although a role for brain organic osmolytes in the dialysis disequilibrium syndrome has not been completely excluded, the old "reverse urea effect" should remain a tenable hypothesis to describe events in this setting.

What relevance does this controversy have for clinicians? The concept of a "reverse urea effect" confirms what nephrologists almost instinctively believe: that in the setting of hemodialysis, the plasma urea concentration matters. When the plasma urea level is high, retention of brain urea increases the risk of disequilibrium after acute or chronic dialysis; the nephrologist must therefore take care to avoid this potential complication. Dialysis disequilibrium can be avoided by decreased rates of solute removal, addition of mannitol, use of a higher sodium bath, or a combination of these maneuvers.

APPENDIX

The calculations presented in Tables 3 and 4 are based on three assumptions: (1) brain and plasma osmolalities are equal before and after dialysis (measured brain osmolality is therefore ignored); (2) brain solute and water contents in uremic controls are equal to predialysis brain solute and water contents in dialyzed groups; (3) changes in brain urea and electrolyte content are the only changes in brain solute that occur during dialysis.

Because brain and plasma osmolalities are taken to be equal, the predialysis brain solute content equals the

product of the plasma osmolality and measured brain water content of uremic controls:

Predialysis brain solute

= Predialysis plasma osmolality × Predialysis brain water

The postdialysis brain solute content equals the predialysis brain solute content adjusted for the observed differences (Δ) in brain urea and electrolyte contents between dialyzed and nondialyzed uremic animals:

Postdialysis brain solute = Predialysis brain solute

− (Δ brain urea + Δ brain electrolytes)

The predicted postdialysis water content in each of the dialyzed groups equals that group's postdialysis brain solute content divided by that group's postdialysis plasma osmolality:

Predicted brain water

= Postdialysis brain solute/Postdialysis plasma osmolality

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Brief Report

Nephrology Dialysis Transplantation

Molecular basis for the dialysis disequilibrium syndrome: altered aquaporin and urea transporter expression in the brain

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Abstract

Background. Cerebral disorders caused by brain oedema characterize the dialysis disequilibrium syndrome, a complication of rapid haemodialysis. Brain oedema is presumably caused by the 'reverse urea effect', i.e. the significant urea gradient between blood and brain after dialysis, with, as a result, an inflow of water into the brain. To assess the molecular basis of this effect, we examined the expression of urea transporter UT-B1 and aquaporin (AQP) 4 and AQP9 in the brain of uraemic rats.

Methods. Brain, kidneys and one testis were collected from four sham-operated (control) and four uraemic rats, 10 weeks after 5/6 nephrectomy (Nx). Protein abundance was measured by semi-quantitave immunoblotting using affinity-purified rabbit anti-rat antibodies applied on tissue crude homogenates.

Results. The results are expressed as means ± SE of band density (arbitrary units). In Nx compared with control rats, the brain expression of UT-B1 was reduced by half (32 ± 3 *vs* 62 ± 8, $P < 0.01$) whereas that of AQ4 was doubled (251 ± 13 *vs* 135 ± 5, $P < 0.001$), and that of AQP9 increased by 65% (253 ± 22 *vs* 154 ± 10, $P < 0.01$). UT-B1 expression was also lowered by Nx in kidney medulla (45 ± 21 *vs* 141 ± 4, $P < 0.01$) but was unchanged in testis.

Conclusions. The conjunction of a reduced expression of UT-B and an increased expression of AQPs in brain cells may bring a new clue to understanding the DDS mechanism. Because of low UT-B abundance, urea exit from astrocytes is most probably delayed during rapid removal of extracellular urea through fast dialysis. This creates an osmotic driving force that promotes water entry into the cells (favoured by abundant AQPs) and subsequent brain swelling.

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Keywords: chronic renal failure; kidney; oedema; rat; subtotal nephrectomy; UT-B1

Introduction

Dialysis disequilibrium syndrome (DDS), a complication of haemodialysis, is characterized by neurological symptoms including headache, disorientation, nausea, seizures and coma. This syndrome is assumed to result from brain swelling occurring as a consequence of a rapid haemodialysis process. Johnson *et al.* observed that DDS was prevented by the use of dialysate fluid containing urea at a concentration similar to that of the patient's blood [1]. This observation suggests that brain swelling was due to a significant brain to blood urea gradient after dialysis and led to the concept of the 'reverse urea effect' [2]. The involvement of urea in the DDS was supported further by animal experiments which allowed direct measurements of brain water and urea content [2–4]. In binephrectomized rats, haemodialysis reduced urea concentration in the brain far less than in plasma and markedly increased brain water content. This increase was prevented by addition of urea to the dialysate [3,4], thus confirming the mechanism by which the same procedure protected patients from DDS [1].

It is now well established that water and urea movements across plasma membranes are greatly 'facilitated' by specific water channels (aquaporins; AQP) and urea transporters (UTs), respectively, which allow fast transmembrane equilibration. In the absence of such proteins, water and urea diffusion through cell membranes is quite slow and equilibration between the cells and their surrounding interstitium is therefore delayed.

Among the AQPs and UTs cloned so far, AQP1, AQP4, AQP9 and UT-B1 are expressed in the brain. AQP1 was detected in epithelial cells of choroid plexus [5], whereas AQP4, AQP9 and UT-B1 have been localized in perivascular astrocyte end feet,

in ependymal cells lining cerebral ventricles and in endothelial cells [6–8]. AQP4, AQP9 and UT-B1 presumably facilitate rapid equilibration of water and urea throughout brain parenchyma. Inasmuch as urea permeability of the blood–brain barrier is increased by a specific transporter (UT-B1), the early finding of Kleeman *et al.* that urea moves much more slowly into rabbit brain than into other tissues such as muscle is somewhat puzzling [9].

The involvement of AQP4 in brain oedema has been stressed by the findings that AQP4 mRNA is upregulated in rats with focal cerebral ischaemia [10] and that mice lacking AQP4 are partially protected from brain oedema in water intoxication and ischaemic models of brain injury [11]. We previously have reported decreased UT-B1 mRNA abundance in the brain of uraemic rats [12]. In contrast, UT-B1 protein expression increases in brain of aged rats [13].

Because DDS involves abnormal equilibration of water and urea between blood and brain tissue, we evaluated the expression of AQP4, AQP9 and UT-B1 proteins in the brain of rats with chronic renal failure. Immunoblotting was used for semi-quantitative analysis of these proteins in the brain of uraemic rats studied 10 weeks after 5/6 renal ablation. Our study reveals opposite changes in the abundance of the UT and the water channels (fall in UT-B1 and rise in AQPs). Such disturbances may explain urea retention and water accumulation in the brain when haemodialysis of uraemic patients results in a rapid fall in blood urea level.

Methods

Animals and induction of chronic renal failure

Four male 7-week-old Sprague–Dawley rats (Charles River, France) weighing ~220 g were subjected to subtotal nephrectomy (Nx) achieved by surgical ablation of 5/6 of the renal mass in two steps. Under pentobarbital anaesthesia (Sanofi Santé Animale, France), the right kidney was decapsulated to preserve the adrenal gland, and its two poles (about two-thirds of kidney mass) were excised. Bleeding was minimized by application of collagen powder (Pangen, Fournier, France) on the cut surfaces and by mild pressure for 2–3 min. One week later, the left kidney was decapsulated and removed after ligature of the renal pedicle. Four control rats underwent laparotomy and kidney decapsulation, but both kidneys were left intact. Rats had free access to tap water and standard rat chow during the whole experiment (M25, Extralabo, France).

Ten weeks after subtotal nephrectomy, rats were anaesthetized with pentobarbital, and a blood sample was drawn from the jugular vein. Kidneys were removed and weighed. The kidney medulla, encompassing the inner stripe of outer medulla and the inner medulla, was excised from coronal kidney slices. The whole right cerebral hemisphere of each rat was collected as well as one testis. Chronic renal failure was confirmed by measuring blood urea concentration, using a commercial kit (Urea-Kit, BioMérieux, Marcy-L'Etoile, France).

Western blot analysis

Affinity-purified rabbit polyclonal antibodies were used as primary antibodies to reveal AQP4, AQP9, and UT-B1 proteins selectively. Glial fibrillary acidic protein (GFAP) was also studied as a marker of astrocytes. For AQP4 and AQP9, commercial polyclonal antibodies raised against the 19 amino acid C-terminal peptide sequences of rat AQP4 or rat AQP9 were used (Alpha Diagnostic International, San Antonio, TX). For UT-B1, the antibody used here was raised against a 20 amino acid peptide corresponding to the C-terminal sequence of rat UT-B1, as characterized elsewhere [8]. GFAP was revealed with a protein A-purified rabbit polyclonal antibody (Promega, Madison, WI).

Tissues were finely minced with a razor blade and then thoroughly homogenized in ice-cold lysis buffer (250 mmol/l sucrose, 10 mmol/l triethanolamine, pH 7.6) containing protease inhibitors (Complete Mini EDTA-free protease inhibitor cocktail tablets, Roche Diagnostics, Meylan, France). Protein concentration was determined by the Bradford method (Biorad, Hercules, CA). Samples were then solubilized in Laemmli buffer, and heated at 65°C for 10 min before loading. Proteins (15 µg) of each tissue for each rat were separated by SDS–PAGE (10%) and transferred to PVDF membranes. Blots were blocked for 45 min at room temperature with phosphate-buffered saline containing 5% non-fat dry milk, followed by incubation with one of the specific primary antibodies (0.25 µg/ml) for 2 h at room temperature. The membranes were then thoroughly washed and incubated for 60 min with the secondary antibody, a goat peroxidase-conjugated anti-rabbit IgG polyclonal antibody (0.2 µg/ml) (Promega, Madison, WI).

Bands were visualized on Hyperfilm-ECL (Amersham) by chemiluminescence (ECL+, NEN, Boston, MA). Apparent molecular weights were determined using pre-stained protein markers, broad range (New England Biolabs, Beverly, MA). Equal protein loading was ascertained by Coomassie blue staining of the PVDF membranes at the end of the experiment. After scanning, the density of the bands on the films was quantified using NIH image software. The abundance of the corresponding water channels and UT was expressed in arbitrary units of density. The abundance of each protein in each tissue includes both unglycosylated and glycosylated forms.

Statistics

Data are expressed as means ± SE. Differences were analysed by Student's *t*-test. They were considered significant for $P < 0.05$.

Results

About 85% of total kidney mass was removed during the 5/6 Nx procedure. Ten weeks later, the remnant kidney was markedly hypertrophied, reaching about half of the total kidney mass of control rats (1643 ± 208 *vs* 3170 ± 196 mg). Plasma urea concentration was increased >4-fold, from 4.9 ± 1.3 to 22.8 ± 2.6 mmol/l ($P < 0.001$).

In the brain, AQP4 is expressed as a monomeric and a dimeric form of mol. wt 32 and 62 kDa,

respectively. AQP9 is expressed as a faint unglycosylated form of 31 kDa and two major glycosylated forms at ~48 kDa [14]. UT-B1 is expressed as an unglycosylated form of 29 kDa, and glycosylated forms of 33 kDa (Figure 1). Experimentally induced chronic renal failure altered the expression of UT and AQPs in the brain. In uraemic rats, the 62 kDa band of AQP4 was much more intense than in control rats, whereas the faint 32 kDa band was reduced. Altogether, these changes resulted in a doubling of total AQP4 protein (251 ± 13 *vs* 135 ± 5 arbitrary units, $P < 0.001$) (Figure 1). Glycosylated forms of AQP9 were significantly enhanced in the brain of uraemic rats, resulting in a 1.6-fold increase in the abundance of total AQP9 protein (253 ± 22 *vs* 154 ± 10, $P < 0.01$) (Figure 1). Both forms of UT-B1 were reduced by half, from 62 ± 8 to 32 ± 3, $P < 0.01$ (Figure 1). GFAP, the marker of glial cells, is revealed as a doublet, the protein of lower molecular weight being a degraded form [15]. In uraemic rats, the 1.4-fold increase in GFAP abundance was not statistically significant (from 30 ± 2 to 42 ± 5, $P < 0.10$) (Figure 1).

In the kidney, UT-B1 is revealed as an unglycosylated form of 29 kDa, as in the brain, and as glycosylated forms identified as a broad band at ~47.5 kDa. The abundance of UT-B1 was markedly reduced in the kidney medulla of three out of four Nx rats, resulting in a mean abundance of 45 ± 21 and 141 ± 4 for Nx and control rats, respectively (Figure 2). The inter-individual differences in UT-B1 abundance were not correlated with the level of uraemia. In the testis, UT-B1 is expressed solely as a non-glycosylated protein of 48 kDa that is presumably a new longer form of UT-B, not yet cloned [8]. It is noteworthy that testis UT-B was unchanged by chronic renal failure (Figure 2).

Discussion

The present study reveals that major changes occur in the expression of AQPs and UT in the brain of rats with chronic renal failure. Ten weeks after severe reduction of kidney mass, the brain exhibits a large fall in the expression of UT-B1 and a marked increase in the expression of AQP4 and AQP9.

If the level of expression of AQPs and UT-B1 represents the limiting factor for rapid osmotic and urea equilibration, the changes seen in uraemic rats should affect the kinetics of water and urea movements between blood and brain. The reduction in UT-B1 abundance should slow down urea egress from the brain, while the increase in AQPs should facilitate osmotically driven water influx in the brain. These changes probably do not matter much in a chronic state because the composition of extracellular fluids does not change very rapidly, and simple diffusion allows equilibration with surrounding tissues, even if more slowly. However, if similar changes occur in the brain of patients with end-stage renal failure, it may be assumed that, during rapid removal of urea from blood and extracellular fluids by haemodialysis,

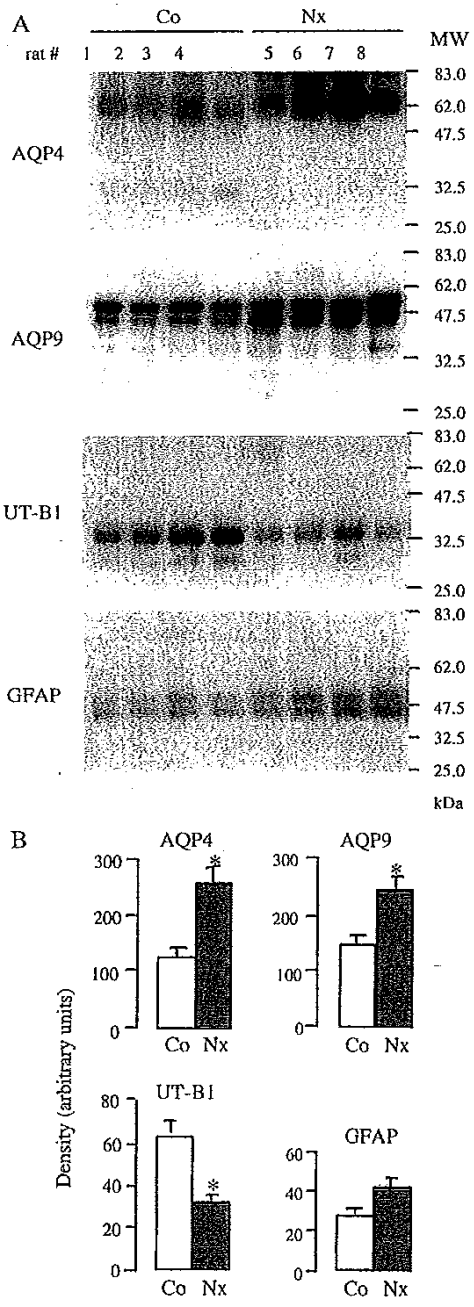

Fig. 1. Semi-quantitative immunoblotting analysis of protein abundance of AQP4, AQP9, UT-B1 and GFAP in the brain of control (Co) and 5/6 nephrectomized (Nx) rats. (A) Each lane, corresponding to a single rat, was loaded with 15 μg of protein. MW = molecular weight markers. (B) Quantification of band densities (means ± SEM of four rats). $*P < 0.05$ *vs* the control group. The abundance of AQP4 and AQP9 was significantly higher, and that of UT-B1 significantly lower in rats with subtotal nephrectomy than in control rats. GFAP, used as an astrocyte marker, showed a modest, non-significant increase.

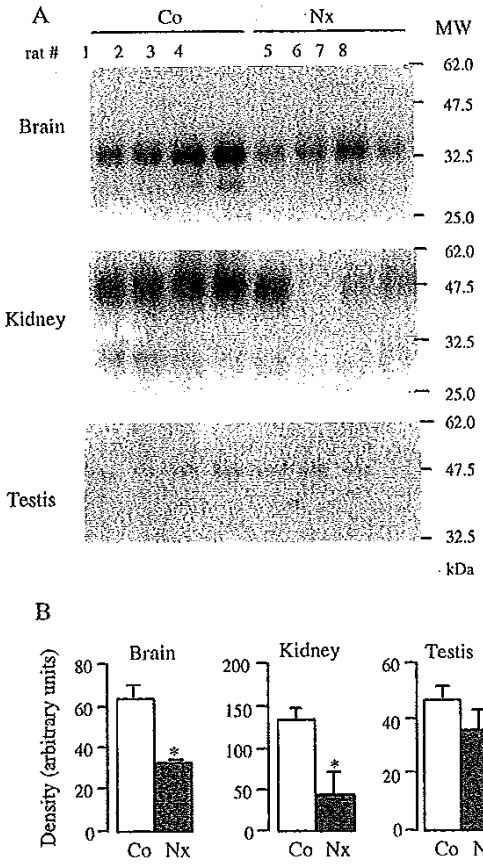

Fig. 2. Semi-quantitative immunoblotting analysis of protein abundance of UT-B1 in brain, kidney medulla and testis of control (Co) and 5/6 nephrectomized (Nx) rats (the blot for brain UT-B1 is the same as that in Figure 1, but is shown again here for comparison with the other two organs). (A) Each lane, corresponding to a single rat, was loaded with 15 μg of protein. MW = molecular weight markers. (B) Quantification of band densities (means ± SEM of four rats). $^*P < 0.05$ *vs* the control group. The abundance of UT-B1 was significantly lower in brain and kidney of rats with subtotal nephrectomy than in control rats. In contrast, UT-B1 abundance in the testis was not affected by advanced renal failure.

urea exit from brain tissue is delayed. The resulting brain to blood urea gradient will easily retain and/or drive water into brain cells, resulting in brain swelling. Thus, the present findings provide a molecular basis for the DDS and give strong support to the 'reverse urea effect' hypothesis [2].

In clinical practice, DDS can be prevented by a gentle start of initial haemodialysis in order to obtain a gradual reduction of blood urea nitrogen (BUN). Once chronic haemodialysis is established, DDS is either absent or much less clinically expressed, in spite of substantial intradialytic BUN reduction (>70%), reflecting the development of some compensatory adaptations.

The mechanism responsible for the marked reduction in UT-B1 expression in brain and kidney during chronic renal failure in rats is unclear. The high urea concentration in plasma and body fluids might be involved, but this is certainly insufficient because no fall in UT-B1 expression occurred in the testis. Tissue-specific factors might be implicated. Moreover, the testis-specific UT-B form, longer than that in the kidney and brain [8], might be regulated differently.

Increased expression of brain AQPs (AQP4 and AQP9) has been reported in various aetiological conditions of brain oedema such as brain tumours, head trauma, stroke and liver failure [10,16,17]. The present study reveals that renal failure is an additional aetiology leading to increased AQP expression in the brain. This increase surpasses that of GFAP, the marker of astroglial cells in which AQP4 and AQP9 are expressed, thereby probably reflecting an over-expression of AQPs in perivascular astrocytic end feet. In contrast to their brain counterparts, kidney AQPs (AQP1, 2 and 3) are reduced in rats with chronic renal failure induced by similar surgical reduction of the renal mass [18]. Therefore, the changes in the expression of cell membrane water channels in uraemic rats appear to be organ specific.

AQPs and UT-B1 are predominantly expressed as glycosylated forms, but the functional consequence of their glycosylation is not clear. For AQP4 and AQP9, no study has examined this question yet, to our knowledge. As concerns UT-B1, its membrane targeting and urea transport functions do not seem to be altered by mutation of the *N*-glycosylation consensus site [19].

The signal and the mechanism(s) involved in the overexpression of AQPs in the brain of uraemic rats are still unknown. This overexpression might be ascribed to the elevated vasopressin plasma level associated with severe chronic renal failure [20]. Indeed, it has been reported that vasopressin, through V1a receptors, induced an increased water flux through the astrocytic syncytium [21]. Such an increased water flux may rely on upregulation of AQP abundance as observed here. Elevated AQP levels may pertain to P38-mitogen activated protein kinase that upregulates AQP4 and AQP9 in rat astrocytes cultured under mannitol-induced hyperosmotic conditions [22]. The possibility that an elevated serum sodium concentration might play a role in the changes observed in the abundance of AQPs and UT of uraemic rats is unlikely because the serum concentration of sodium was shown to be unaltered in rats with uraemia achieved with identical surgical Nx and studied at a similar stage of chronic renal failure [23].

In conclusion, the findings reported herein reveal that chronic renal failure results in dramatic changes in the expression of water channels and UT in the brain. A marked decline in UT-B1 is associated with a doubling of AQP4 and AQP9 abundance in the brain of uraemic rats. These results provide new clues for the understanding DDS and, more generally, call for more studies addressing the detailed alterations in

UTs and water channels in brain and other tissues during chronic renal failure.

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Conflict of interest statement. None declared.

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Dialysis Disequilibrium Syndrome: A Narrative Review

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ABSTRACT

Dialysis Disequilibrium Syndrome (DDS) is characterized by neurological symptoms caused by rapid removal of urea during hemodialysis. It develops primarily from an osmotic gradient that develops between the brain and the plasma as a result of rapid hemodialysis. This results in brain edema that manifests as neurological symptoms such as headache, nausea, vomiting, muscle cramps, tremors, disturbed consciousness, and convulsions. In severe cases, patients can die from advanced cerebral edema. Recent advancements in cell biology implicate the role of urea disequilibrium (with a smaller contribution from organic osmolytes) as the pathophysiological mechanism responsible for this syndrome. In this review, we discuss the pathogenesis, clinical features and prevention of DDS.

Case

A 54-year-old male with a past medial history of lupus nephritis, hypertension, and hypercholesterolemia presented to the emergency department with anorexia and generalized malaise. On physical examination, the patient had bilateral lower extremity edema and blood chemistries showed elevated concentrations of potassium (6.3 mEq/l), blood urea nitrogen (BUN) (131 mg/dl), and creatinine (13.3 mg/dl). A diagnosis of acute on chronic renal failure due to progressive lupus nephritis was made. Hyperkalemia failed to correct with medical management and emergent hemodialysis was initiated via a right internal jugular dialysis catheter. The treatment was carried out for 4 hours with the following dialysate composition: potassium 2 mEq/l, calcium 2.5 mEq/l, bicarbonate 35 mEq/l, and sodium 140 mEq/l. The dialysate flow rate was 500 ml/min and the blood flow rate was 250–300 ml/minute. Postdialysis laboratory results showed lower levels of serum potassium (3.2 mEq/l), BUN (71 mg/dl), and creatinine (8.9 mg/dl). About an hour after the completion of the dialysis treatment, the patient developed a generalized tonic–clonic seizure and was treated with intravenous lorazepam. Repeat laboratory evaluation demonstrated no electrolyte or divalent ion abnormalities. Computed tomography (CT) scan and magnetic resonance imaging (MRI) of the brain were both unremarkable. Electroencephalogram showed changes suggestive of diffuse metabolic encephalopathy. Dialysis disequilibrium syndrome (DDS) was considered as a possible cause of the seizure. Subsequently, the patient was dialyzed with low blood flow rates and shorter time periods with a gradual increase in dialysis clearance. No further seizures developed.

Introduction

Dialysis Disequilibrium Syndrome, defined initially in 1962 (1), is an acute neurological complication of hemodialysis characterized by signs and symptoms that can include fatigue, mild headache, nausea, vomiting, blurred vision, muscle cramps, tremors, disturbed consciousness, convulsions, and coma. It can lead to death due to cerebral edema (2,3). The neurological symptoms are more common toward the end of a dialysis treatment that is characterized by rapid urea clearance in which accentuates the plasma cerebrospinal fluid (CSF) urea concentration gradient. The term disequilibrium is employed because the syndrome typically occurs when the blood biochemistry parameters are improving (3,4).

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Pathogenesis

Animal studies have established that DDS is caused by cerebral edema that develops as a consequence of rapid hemodialysis and the creation of an osmotic gradient between the brain and plasma (5–7). The gradient is created by a difference in the urea concentration of the two compartments. Head CT scans in CKD patients undergoing either initial or intermittent hemodialysis (8,9) have demonstrated decreased brain parenchymal density reflecting increased brain water content (8,9). Recently, the presence of interstitial edema of the cerebral cortex has been shown by diffusion-weighted MRI in nephrectomized animals and humans after an initial hemodialysis treatment (10,11). Currently, three causal mechanisms have been postulated for the cerebral edema seen in DDS.

Reverse Urea Effect

The reverse urea effect occurs when there is slow removal of urea from the brain compared with a large decrease in plasma urea concentration. This ultimately causes a concentration gradient between the brain and plasma which promotes an osmotically induced increase in brain water content and brain edema (12). Uremic rats that underwent rapid hemodialysis had a 53% reduction in the plasma urea content but only a 13% reduction in brain urea content resulting in significant blood–brain urea and osmotic gradients (7,12,13). This increase in osmotic gradient was due primarily to differences in urea concentration and not those of other organic osmolytes such as glutamine, glutamate, taurine, and myoinositol (13). The gradient was also not due to differences in sodium and potassium concentrations (12).

In the steady state, brain urea concentration is similar to the plasma urea concentration (5,7). The reflection coefficient, a measure of the relative permeability of a particular membrane to a particular solute, provides information about urea movement between the brain and plasma. A reflection coefficient of 1 denotes solute impermeability and 0 denotes complete solute permeability. The reflection coefficient of urea is approximately 0.44 (14), which implies that urea has some restrictions in its ability to rapidly cross the blood–brain barrier. As a result, a sudden drop in the plasma urea concentration will promote a lag in the equilibrium between brain and plasma urea concentrations; this generates an osmotic gradient and net water movement into the brain (12,15).

A recently proposed molecular basis for DDS supports the reverse urea effect hypothesis. Water and urea cross plasma membranes through water channels (aquaporins [AQP]) and via urea transporters (UTs), respectively. When present, these pathways allow rapid transmembrane equilibration to occur while their absence delays water and urea diffusion through cell membranes. Aquaporins (AQP4 and AQP9) and UT-B1 are mainly expressed in the brain and presumably facilitate rapid equilibration of water and urea throughout the brain parenchyma. In uremic rats, a marked reduction in UT-B1 and an increase in AQP4 and AQP9 are noted in brain parenchyma (16–19). It is conceivable that these disturbances result in urea and water accumulation in brain tissue of uremic patients undergoing hemodialysis when a rapid fall in the blood urea concentration occurs (19) (Figs. 1–3).

Organic Osmolytes (Idiogenic Osmoles)

Hemodialysis in uremic animals produces a mean urea gradient of 12 mmol/kg of H_2O between the cerebral cortex and plasma, which is in part responsible for the resulting brain edema (7). However, at least 35–45 mOsm/kg of H_2O gradient is required for the significant change in brain water content (20,21). Therefore, a small change in the urea gradient cannot fully account for the brain edema that is noted in these laboratory animal models. It has been proposed that other osmotically active substances (organic osmolytes) are present in the brain at the end of dialysis and are responsible for the observed brain swelling (5).

Similar brain-urea concentrations and brain-plasma urea gradients were observed after slow and rapid hemodialysis in uremic dogs (20). Despite this, the osmolarity of the brain was significantly higher at the end of rapid hemodialysis (332 ± 7 mOsm/kg H_2O) compared with slow hemodialysis (306 ± 8 mOsm/kg H_2O). A difference in the concentration of Na^+, K^+, Cl^-, and urea (8 mmol) in the brain could not explain for this higher osmolarity after rapid hemodialysis. Because of these findings, it was postulated that during rapid hemodialysis with a standard dialysate, new osmotically active solutes (organic osmolytes) generated in the brain are in part responsible for the otherwise unexplained larger than expected osmotic gradient difference (5). However, there is some evidence against a major role for these osmolytes in generating the gradient. These include studies demonstrating that concentrations of specific brain organic osmolytes (glutamine, glutamate, taurine, and myoinositol) do not significantly rise after rapid hemodialysis (13,15). Therefore, organic osmolytes are unlikely to be a major contributor to the pathogenesis of DDS. The conflicting evidence available suggests that urea disequilibrium and perhaps (to a minor degree) organic osmolytes contribute to cerebral edema.

Cerebrospinal Fluid pH and Brain Intracellular pH

The clinical setting in which DDS occurs is often characterized by an accompanying metabolic acidosis. The correction of this acidosis by dialysis may contribute to the development of DDS. It is known that brain intracellular pH and CSF pH remain normal in the setting of CKD and metabolic acidosis (22–24). However, a paradoxical acidemia (fall in pH) of the CSF occurs when systemic metabolic acidosis is rapidly corrected with dialysis or with the administration of exogenous alkali (24,25). This rapid correction leads to a rapid elevation of arterial pH and bicarbonate which itself leads to

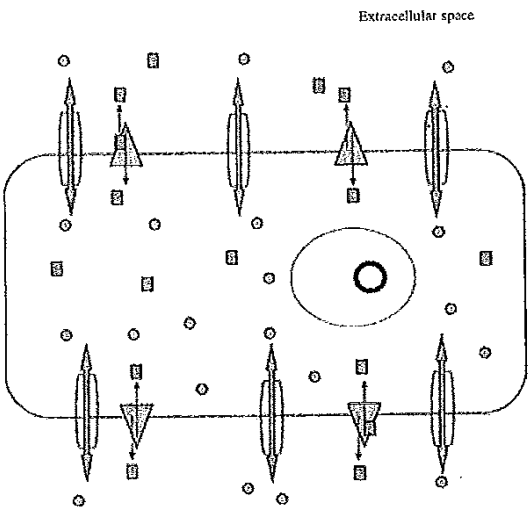

FIG. 1. Normal brain cell. Water molecules (circles) and urea molecules (small squares) transport across the brain plasma membrane through aquaporin water channels (elongated squares) and urea transporters (triangles). These transporters help maintain equilibrium. In the absence of these transporter proteins, diffusion of these molecules becomes slow and delayed.

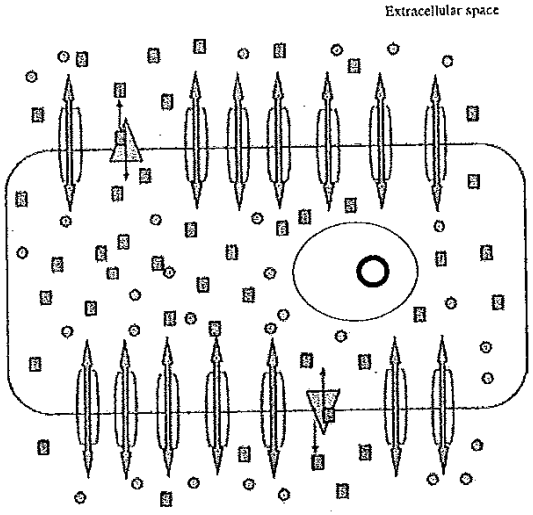

FIG. 2. Brain cell of the uremic rat. In response to a chronic uremic state, adaptation of brain cells occurs by decreasing the number of urea transporters (note the number drops from 4 to 2) and increasing the number of aquaporin channels (note the number increases from 6 to 14) in brain cells of uremic rats.

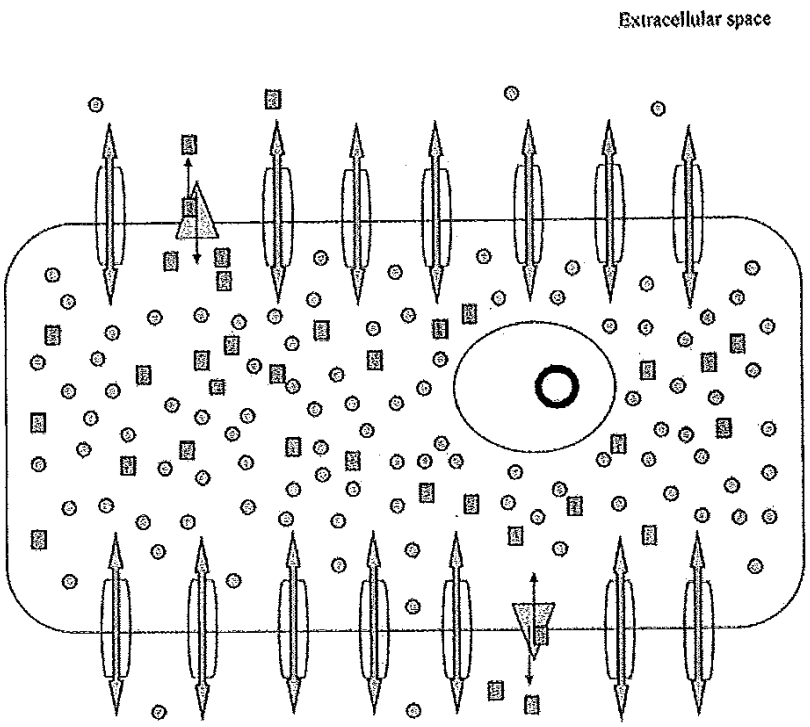

FIG. 3. Brain cell of a uremic rat undergoing hemodialysis. During hemodialysis there is a decrease in the extracellular urea concentration (note small square number drops from 15 to 4). As cellular adaptation occurs in the chronic uremic state by decreasing urea transporters, there is less efflux of urea from the intracellular to the extracellular space. Also, there is an increased number of aquaporin channels in relation to the urea transporters which results in a net influx of water inside the cells resulting in brain cell edema (note size of the cell increased compared with that in Fig. 2).

TABLE 1. Clinical manifestations of dialysis disequilibrium syndrome

Symptoms	Benna et al. (3)	Al-Hilali et al. (29)	Sadowski et al. (30)	Agraharkar et al. (31)
Nausea/vomiting	76	–	23	3.3
Muscle cramps	86	22.5	38	4.2
Headache	60	37.5	20	–
Altered sensorium	13.6	–	–	–
Convulsion/ myoclonus/tremor	6	–	–	–
Psychomotor agitation	29	–	–	–
Hypotension/shock	85	72.5	46	12.5
Cardiac arrhythmias	16	–	–	–
Dizziness	–	55	42	–

Values are expressed in percentage.

secondary hypoventilation and a rise in plasma CO_2. The high levels of plasma CO_2 rapidly diffuse into the CSF elevating CSF PCO_2. This, together with the failure of the higher plasma bicarbonate to enter the CSF due to its slow transport across the blood–brain barrier (22–25), results in a fall in the CSF pH. This so-called paradoxical CSF acidosis is also associated with an increased brain H^+ ion production due to increased organic acid production in the brain. This increase in brain osmole content leads to a 12% increase in the brain water content which is a hallmark of DDS (5,22). Exactly how this acid–base derangement leads to brain edema in DDS is unknown. Definitive evidence to support this hypothesis is currently lacking.

Clinical Manifestations

Dialysis Disequilibrium Syndrome is characterized mainly by neurological symptoms such as fatigue, mild headache, nausea, vomiting, disturbed consciousness, convulsions, and coma. These symptoms are usually mild, transient, and self-limited though, rarely, DDS can be fatal. Symptoms are most often seen in patients with very high plasma urea concentrations, in patients with CKD (versus acute kidney injury), and with aggressive urea removal with the initial hemodialysis treatment (1). It is more common in children, in patients with a history of head injury, subdural hematoma, stroke and malignant hypertension, and in patients with conditions such as hyponatremia that predispose to cerebral edema (2,26–28). As shown in Table 1, the frequency of each symptom is highly variable (3,29–31). In rare cases DDS can present as either demyelination of the pontine and extrapontine areas (32,33) or as subcortical white matter lesions in parietal and occipital lobes of brain. The latter lesion is quite similar to the reversible posterior leukoencephalopathy syndrome (34).

Diagnosis

Dialysis Disequilibrium Syndrome is a clinical diagnosis, occurring in a patient at risk of undergoing hemodialysis. There is no laboratory test or biological marker available to diagnose DDS and it remains largely a diagnosis of exclusion. The clinician needs to consider processes that cause similar manifestations such as uremia, hyponatremia, hypoglycemia, stroke and subdural hematoma (2). Electroencephalography has been examined as a test to improve the diagnosis of DDS, but is of limited clinical value (35,36). Although no radiological study is available to make a diagnosis, certain imaging techniques such as diffusion-weighted MRI may be helpful in supporting the diagnosis (10,11).

Management

Management of DDS is based primarily on preventative measures to reduce the development of cerebral edema. As (i) these measures have little risk and (ii) there are no guidelines indicating which patients receiving their first dialysis are "not" at risk, interventions to minimize DDS have become common practice for a patient's initial dialysis. While certain modalities such as peritoneal dialysis and hemofiltration/hemodiafiltration are not associated with DDS, they are not practical or available for all patients initiating dialysis. Interventions that are available during hemodialysis to prevent DDS include: (i) slow, gentle initial hemodialysis, (ii) increasing dialysate sodium levels, and (iii) administration of osmotically active substances.

Slow, Gentle Initial Hemodialysis

In a CKD patient with a high urea concentration who is begun on hemodialysis, a low clearance treatment can be performed by decreasing the dialysis time (2 hours), decreasing the blood flow rate (200 ml/minute), and by using a less efficient (small) dialyzer or a combination of these techniques. A goal urea reduction ratio of about 0.4–0.45 or a diffusive Kt/V of 0.6–0.7 are probably reasonable goals. As convective/ultrafiltrative urea removal does not contribute to the blood CSF osmotic gradient, this element of overall Kt/V can theoretically be ignored. If the patient can tolerate this dialysis treatment, then the efficacy of dialysis can gradually be increased in subsequent dialysis treatments until conventional treatments are performed (37–43).

An impractical but probably effective technique to avoid DDS is the use of a urea-enriched dialysate to avoid a large rapid decline in the serum osmolarity during hemodialysis. One reported approach is to start urea and osmotic gradients with a dialysate urea concentration approximately 10% lower than serum urea concentration. Over a series of dialysis treatments, the patient's blood urea concentration is gradually reduced, thereby avoiding DDS (37,38,42,43).

High Sodium Dialysate/Sodium Profiling

Another intervention to reduce DDS is the use of a high dialysate sodium concentration (fixed or profiled) to minimize osmotic disequilibrium. An increase in serum sodium of 2 mEq/l yields an osmotic force

equivalent to about that of 11 mg/dl of BUN. Sodium profiling employs the same concept except that it targets the osmotic effects of early urea removal and lowers the dialysate sodium concentration later in the treatment (39). The impact of a declining dialysate sodium later in treatment on the risk for DDS is uncertain. What is certain is that any benefit from sodium profiling over a fixed dialysate sodium (with the same time-averaged sodium concentration) is completely unexplored. Use of a fixed dialysate sodium of 143–146 mEq/l for the initial treatment is reasonable in an at-risk patient.

Administration of Osmotically Active Substances

The decrease in the serum osmolarity that occurs during hemodialysis can be reduced by using a high-glucose-concentration dialysate (not readily available in most centers) or by using intravenous mannitol during dialysis. Hemodialysis with high-glucose dialysate (717 mg/dl) can reduce osmolarity fluctuation, although a beneficial, prophylactic effect on DDS can be seen with dialysate glucose concentration as low as 200 mg/dl. With mannitol, a 1 g/kg/dialysis of intravenous infusion may be used to prevent DDS during hemodialysis. A further benefit has been reported by combining high-glucose dialysate (717 mg/dl) with intravenous infusion of mannitol (44–46). It is worth noting that the osmotic effect of any rise in serum glucose will dissipate soon after treatment ends (along with any posttreatment benefit), while the effect (and potential benefit) of mannitol will persist longer.

Summary

Dialysis Disequilibrium Syndrome develops in patients with chronic uremia who undergo hemodialysis with rapid lowering of the BUN concentration. Neurologic symptoms and other complications occur primarily due to cerebral edema. Patients who are at high risk of developing DDS should undergo initial slow, gentle hemodialysis. Unless patients are intolerant of this treatment (unlikely), an incremental increase in hemodialysis clearance can be undertaken. If more aggressive hemodialysis treatment is mandatory or additional caution is warranted, a high dialysate sodium during the treatment and the addition of mannitol will probably decrease the risk for DDS.

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