Plasma and cerebrospinal fluid arginine vasopressin in patients with and without fever

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Abstract

Hyponatraemia has been described in association with a number of acute infectious diseases, mainly bacterial and tuberculous meningitis and pneumonia, and has been attributed to inappropriate secretion of arginine vasopressin (AVP). The mechanism of inappropriate AVP production is uncertain, but there is experimental evidence to suggest that fever may stimulate secretion of AVP into plasma and cerebrospinal fluid. In this study, AVP concentrations in plasma and cerebrospinal fluid from 37 febrile children with infections have been compared with those from 27 afebrile control subjects. Ten of the febrile children had meningitis (eight bacterial, two viral) and the remainder a variety of other infectious diseases. Seventy four per cent of febrile infected children were hyponatraemic (serum sodium <135 mmol/l) compared with only 8% of the afebrile controls. Plasma AVP concentrations were significantly higher in the febrile patients (median 2.92 pmol/l, range 1.0–23.25, n=28) than in controls (median 1.67 pmol/l, range 0.57–6.0, n=14) but there was no significant difference in cerebrospinal fluid AVP concentrations. There was no difference in plasma AVP concentrations between patients with meningitis and those with infections not involving the central nervous system. Careful attention should be paid to fluid and electrolyte balance in all children with acute infections.

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Hyponatraemia and water retention have been reported in children with bacterial and tuberculous meningitis,^{1–4} viral encephalitis⁵ and pneumonia.^{4 6 7} These findings have been attributed to inappropriate secretion of arginine vasopressin (AVP) and in a few studies plasma or cerebrospinal fluid AVP concentrations have been measured and shown to be increased.^{1 6 8} The mechanism of the inappropriate AVP production in these situations remains uncertain,⁸ although it has been suggested that increased AVP concentrations in pneumonia may be the result of intrathoracic pathology interfering with the normal modulation of AVP release via stretch and baroreceptors in the left atrium and carotid sinus.⁹

Experimental studies have indicated that in a variety of animal species, AVP production, hyponatraemia, and hypo-osmolality can be produced by inducing pyrexia.^{10–12} These observations have led to suggestions that AVP may have a role as an endogenous antipyretic.^{13 14}

This hypothesis might explain the findings of Gonzalez *et al* who noted an association between hyponatraemia and a variety of acute infections.¹⁵ However, there is little published information concerning plasma or cerebrospinal fluid AVP concentrations in acute infections other than those of the central nervous or respiratory systems.

The aim of this study was to determine the concentrations of AVP in samples of plasma and cerebrospinal fluid obtained from febrile children with a variety of infectious diseases and compare these with the concentrations found in a group of afebrile control children.

Patients and methods

The study population comprised 37 febrile children with a variety of acute infectious illnesses (table 1). Ten children had meningitis (eight bacterial, two viral). The median age of the study population was 2.5 years, range 2 weeks–14 years; 20 (54%) were boys. All the children were hospital inpatients. Samples were obtained shortly after admission at a time when venepuncture or lumbar puncture was being performed for a clinical indication. The body temperature was recorded immediately before

Table 1 Details of the febrile children

Patient No	Age (years)	Sex	Diagnosis
1	10	F	Pneumonia
2	2.5	F	Upper respiratory tract infection
3	1.5	M	Salmonella enteritis
4	11	M	Pyrexia of unknown origin
5	1.33	M	Viral illness
6	12	M	Urinary tract infection
7	14	F	Urinary tract infection
8	5	M	Viral illness
9	0.75	M	Viral illness
10	1.66	F	Viral illness
11	1.33	F	Tonsillitis
12	1.0	F	Cellulitis
13	3	F	Viral illness
14	9	M	Otitis media
15	1	F	Otitis media
16	1	M	Viral illness
17	0.16	M	Pneumonia
18	0.16	M	Viral illness
19	11	M	Upper respiratory tract infection
20	10	M	Osteomyelitis
21	0.50	F	Otitis media
22	5	F	Viral illness
23	1.5	F	Upper respiratory tract infection
24	0.04	F	Viral illness
25	1.75	M	Cellulitis
26	5	M	Viral illness
27	13	M	Viral illness
28	2.5	F	Bacterial meningitis
29	12	F	Bacterial meningitis
30	7	M	Bacterial meningitis
31	9	F	Bacterial meningitis
32	0.25	M	Bacterial meningitis
33	8	F	Bacterial meningitis
34	1.42	F	Bacterial meningitis
35	1	M	Bacterial meningitis
36	5	M	Viral meningitis
37	7	M	Viral meningitis

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sampling. Plasma samples for AVP determination were obtained from 28 febrile children and cerebrospinal fluid samples from 19. Paired plasma and cerebrospinal fluid samples were obtained in nine of the children. No child was hypotensive or clinically dehydrated at the time of sampling.

The afebrile control population consisted of two groups, totalling 27 children: 15 children who were seen as outpatients for a variety of conditions (table 2), and from whom plasma samples were obtained, and 12 inpatients who underwent lumbar puncture for various clinical indications (table 3) and who provided cerebrospinal fluid samples. The median age of the control population was 7.0 years, range 1 month–15 years; 13 (48%) were boys. There was no significant difference between the age structure of the study and control groups (Mann-Whitney U test, $p=0.13$).

Blood (0.5–1.0 ml) was taken onto ice, centrifuged immediately, and the plasma separated and stored at -20°C until assay. Cerebrospinal fluid (0.5 ml) was also taken onto ice and stored at -20°C . Immediately before AVP assay, the plasma sample was extracted through octadecasilyl silica cartridges (Sep-pak C18, Waters Associates). The AVP concentration in plasma and cerebrospinal fluid was measured by radioimmunoassay, as described previously.¹⁶ The intra-assay coefficient of variation was 5% and the interassay coefficient of variation 15%. The limit of detection of the assay was 0.30 pmol/l. In the data analysis, a non-detectable concentration of AVP was assigned a value of 0.00 pmol/l.⁸

The study was approved by the local ethical committee.

Table 2 Details of the afebrile children who provided plasma samples

Patient No	Age (years)	Sex	Diagnosis
1	4	M	Asthma
2	0.25	F	Skeletal dysplasia
3	0.83	M	Constipation
4	0.04	M	Feeding difficulties
5	10	F	Bell's palsy
6	5	F	Asthma
7	2	M	Failure to thrive
8	1	M	?Breath holding attacks ?Fits
9	8	F	Acute leukaemia
10	14	M	Constitutional short stature
11	12	F	Friedreich's ataxia
12	13	M	Constitutional short stature
13	0.75	F	Failure to thrive
14	15	M	Constitutional short stature
15	12	F	Diabetes mellitus

Table 3 Details of the afebrile children who provided cerebrospinal fluid samples

Patient No	Age (years)	Sex	Diagnosis
1	0.02	F	?Seizure
2	0.58	M	Seizures
3	14	M	Headache ?meningitis
4	13	F	Staging for acute leukaemia
5	10	F	Staging for acute leukaemia
6	11	M	Neck stiffness ?meningitis
7	11	M	Guillain-Barré syndrome
8	5	M	Epilepsy
9	9	F	Headache ?meningitis
10	4	F	Staging for acute leukaemia
11	7	F	Staging for non-Hodgkin's lymphoma
12	15	F	Staging for acute leukaemia

Results

Figure 1 shows the plasma AVP results obtained in febrile and afebrile patients. The plasma AVP concentrations obtained from the febrile children (median 2.92 pmol/l, range 1.00–23.25) were significantly higher than those obtained from the afebrile controls (median 1.67 pmol/l, 0.57–6.0) (Mann-Whitney U test, $p=0.003$). The difference between febrile and afebrile subjects persisted if children with meningitis were excluded from the analysis (median plasma AVP concentration among febrile, non-meningitic patients 2.49 pmol/l, range 1.0–23.25) (Mann-Whitney U test, $p=0.036$). Plasma AVP concentrations in the meningitic children (median 4.14 pmol/l, range 1.16–15.25, $n=6$) were not in fact significantly different from those observed in the other febrile children (Mann-Whitney U test, $p=0.10$). There was no difference in plasma AVP concentrations according to sex, either when all the patients were considered together (Mann-Whitney U test, $p=0.10$) or in the febrile and afebrile subgroups. There was also no correlation between plasma AVP concentration and age ($r=-0.06$, $p=0.70$).

There was no significant difference between the cerebrospinal fluid AVP concentrations obtained from the febrile study children (median

Figure 1 Plasma AVP concentrations (pmol/l) in febrile children with acute infections compared with febrile control children. Among the febrile children, the triangular symbols represent those with bacterial or viral meningitis and the circular symbols, those with other acute infections.

Figure 2 Cerebrospinal fluid AVP concentrations (pmol/l) in febrile children with acute infections compared with afebrile control children. Among the febrile children, the triangular symbols represent those with bacterial or viral meningitis and the circular symbols, those with other acute infections.

0.7 pmol/l, range 0–5.57) and those obtained from the afebrile control children (median 1.06 pmol/l, range 0–2.9) (Mann–Whitney U test, $p=0.38$) (fig 2). There was also no significant difference between the AVP cerebrospinal fluid concentrations obtained from children with meningitis (median 0.56 pmol/l, range 0–5.57, $n=8$) and those obtained from other febrile children (median 0.90 pmol/l, range 0–1.98, $n=10$) (Mann–Whitney U test, $p>0.05$). As with the plasma results, no correlation was found between cerebrospinal fluid AVP concentration and age ($r=0.22$, $p=0.10$) and there was also no significant difference in the results obtained from boys and girls (Mann–Whitney U test, $p=0.24$).

Figure 3 illustrates the relationship between body temperature and plasma AVP concentrations in the febrile children. There was no correlation between body temperature and plasma AVP concentration ($r=0.09$, $p>0.05$). There was also no correlation between body temperature and cerebrospinal fluid AVP concentration (fig 4) ($r=0.23$, $p>0.05$). Among the nine children from whom paired plasma and

cerebrospinal fluid samples were obtained, there was no significant correlation between plasma and cerebrospinal fluid AVP concentrations ($r=0.32$, $p=0.40$).

Serum sodium concentrations, obtained concomitantly, were available for 23/37 (62%) febrile study patients and 12/27 (44%) afebrile control children. The serum sodium concentrations observed in febrile children (median 132 mmol/l, range 129–140) were significantly lower than those in the 12 afebrile study children (median 138 mmol/l, range 133–143) (Mann–Whitney U test, $p=0.002$). There were 17/23 (74%) febrile children who were hyponatraemic (serum sodium concentration less than 135 mmol/l),⁴ whereas only one afebrile control child was hyponatraemic. Six (35%) of the hyponatraemic febrile children had meningitis but the remaining 11 had other acute infections. There was no significant difference between the serum sodium results obtained from the children with meningitis (median 132 mmol/l, range 131–139, $n=7$) and those obtained from the other febrile children (median 133 mmol/l, range 129–140, $n=16$) (Mann–Whitney U test, $p=0.33$). There was no correlation between serum sodium concentration and plasma AVP concentration in the febrile children ($r=0.04$, $p>0.50$) nor between serum sodium and cerebrospinal fluid AVP concentration ($r=0.46$, $p=0.18$).

Discussion

The results of this study demonstrate that increased plasma concentrations of AVP occur not only in children with bacterial meningitis, viral encephalitis and pneumonia, as previously reported, but also in association with a wide range of other acute infections. The occurrence of detectable plasma concentrations of AVP in children with low serum sodium results (<135 mmol/l) confirms the inappropriate nature of the AVP secretion. Hyponatraemia has been previously described in acutely febrile children,¹⁵ and there have been a number of isolated case reports reporting inappropriate AVP secretion in tetanus,¹⁷ viral meningitis,¹⁸ and Rocky Mountain spotted fever.¹⁹ However, no previous study has demonstrated increased AVP production in such a variety of acute infections.

None of the children in this study were on treatment recognised to be associated with increased AVP production, such as vincristine, chlorpropramide, tricyclic antidepressants, or phenothiazines.⁹ Increased AVP production may occur in response to pain or anxiety,^{9 20 21} and increased concentrations in unanaesthetised children might in part reflect the stress associated with venepuncture or lumbar puncture in this age group. However, there seems no reason to suppose that this effect would be confined to the study children, particularly as the age structure of the study and control groups was similar.

In this study, there was a significant difference between plasma AVP concentrations from febrile and afebrile patients, but no significant difference in the cerebrospinal fluid AVP concentrations between study and control groups. It is

Figure 3 Relationship between body temperature and plasma AVP concentration (pmol/l) for the 28 febrile children from whom plasma samples were obtained. The triangular symbols represent children with bacterial or viral meningitis and the circular symbols represent children with other acute infections.

Figure 4 Relationship between body temperature and cerebrospinal fluid AVP concentration (pmol/l) for the 19 febrile children from whom cerebrospinal fluid samples were obtained. The triangular symbols represent children with bacterial or viral meningitis and the circular symbols represent children with other acute infections. The shaded area indicates the lower limit of detection of the assay.

possible that this may reflect the difficulty of establishing 'control' cerebrospinal fluid values in a paediatric population. There were 5/12 (42%) afebrile control children who underwent lumbar puncture because of an actual or suspected abnormality of the central nervous system (table 3) and increased cerebrospinal fluid AVP concentrations have been described in association with a variety of non-infectious central nervous system pathologies.^{16 22-25} Another methodological consideration is the fact that it was not possible to standardise the time of day at which the samples were obtained; discrepancies in the sampling times might therefore have obscured differences between groups in the cerebrospinal fluid AVP concentrations.²⁶ However, no diurnal rhythm of AVP cerebrospinal fluid concentration has been demonstrated in humans.²⁷ Moreover, it is recognised that under physiological conditions, AVP concentrations in cerebrospinal fluid and blood are differentially regulated²⁶ and that various stimuli which increase plasma AVP concentrations may produce little alteration in cerebrospinal fluid levels.²⁸ Even when stimulatory effects are found, AVP release into cerebrospinal fluid has a greater threshold than release into blood.²⁶ In the nine cases in this study, in whom paired blood and cerebrospinal fluid samples were available, there was no correlation between plasma and cerebrospinal fluid AVP concentrations. Indeed, it has been suggested that the increased AVP concentrations in cerebrospinal fluid described in meningitic children are the result of leakage from the circulation across a damaged blood-brain barrier, rather than the result of increased intracerebral production,⁸ and this hypothesis would be in keeping with our observations.

The results of this study do not give any indication of the pathogenetic mechanism responsible for the increased plasma concentrations of AVP. The lack of correlation between body temperature and plasma and cerebrospinal fluid AVP concentrations is in contrast to the results of some experimental studies, in which a relationship between pyrexia and AVP production has been demonstrated,^{12 14} but in agreement with the results of others, in which a direct correlation was not found.^{10 12} It may be that, in some species, fever has an 'all or nothing' effect on AVP production or that a single temperature measurement does not reflect accurately the degree of stimulus to AVP secretion. Alternatively, the mechanism of the increased AVP production in children with acute infections may be unrelated to the occurrence of fever; certainly, there is experimental evidence to suggest that the role of AVP as an antipyretic may vary between species.^{29 30} Increased plasma concentrations of AVP have been described in burned children³¹ and in postoperative paediatric surgical patients,³² and it has been suggested that the increased concentrations probably represent part of the body's stress response.^{9 32} Increased AVP production in acute infections may occur for the same reason.³³

The finding that inappropriate AVP production and hyponatraemia is not an uncommon

phenomenon in febrile children with a variety of acute infections indicates that the serum sodium concentration should always be determined before administering intravenous fluid in such patients. The significance of the inappropriate AVP production, in terms of implications for outcome, is uncertain and was not explored in this study. Among children with bacterial meningitis, both the degree of hyponatraemia on admission and its duration seem to correlate with long term outcome³⁴ and this has been attributed to the effect of AVP on brain water permeability and cerebral oedema.³⁵ Although this may seem at first to have little relevance to children with infections not involving the central nervous system, it has been suggested that AVP has a role in the pathogenesis of febrile convulsions through its effect on brain water permeability.³⁶ In this study, eight children (median age 1.6 years, range 1.0-5) underwent lumbar puncture after a presumed febrile convulsion; there was no significant difference in the plasma or cerebrospinal fluid AVP concentrations obtained from these children and those obtained from febrile children in the age group at risk from febrile convulsions (6 months-6 years³⁷) who did not have convulsions (Mann-Whitney U test: $p=0.10$ for plasma; $p=0.08$ for cerebrospinal fluid). However, in view of the small numbers, further studies would be necessary to explore this issue and to investigate the relationship between AVP production and hyponatraemia and eventual outcome in febrile infected children.

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Maternal chickenpox

Maternal chickenpox in early pregnancy has been associated with abnormalities in the fetus including microphthalmia, cataracts, Horner's syndrome, microcephaly, and growth defects of limbs, fingers, and muscles. Congenital varicella syndrome was found in three of 61 patients (5%) in three previously reported studies. Now another 40 mothers with first trimester chickenpox have been reported from Connecticut (James Balducci and colleagues, *Obstetrics and Gynecology* 1992;79:5-6). One mother elected for termination of pregnancy and three had spontaneous abortions. There is no comment about abnormality in these fetuses. One fetus was shown by ultrasound examination to have a large omphalocele and the pregnancy was terminated. None of the pregnancies was complicated by congenital varicella syndrome as previously described.

Maternal chickenpox is not common because most mothers have had the disease in childhood. These authors quote an incidence of 0.7 per thousand pregnancies but it is not clear whether that figure is for chickenpox at any stage in pregnancy or just the first trimester. In any event congenital varicella syndrome is rare but it should disappear altogether with chickenpox immunisation (see Archivist 1991:1212).

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