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Neurogenic diabetes insipidus in children with hypoxic encephalopathy: six new cases and a review of the literature

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Abstract Hypoxic encephalopathy is rarely mentioned as a cause of neurogenic diabetes insipidus (DI) in children. We here report six cases of DI which occurred after severe hypoxic/ischaemic brain damage and include a review of the literature on 28 paediatric cases of neurogenic DI due solely to severe hypoxia/ischaemia. Airway obstruction, haemorrhagic shock and sudden infant death syndrome are the three major causes of hypoxia/ischaemia. The ages (25/28) ranged from 0.03 to 18 years (mean 7.27 years, median 5 years). The intervals between the hypoxic insult and the onset of DI (23/28) ranged from 0.08 days (2 h) to 13 days (mean 4.07days, median 3.5 days). Linear regression analysis revealed no significant correlation between the age and the interval. Nineteen cases (82.6%) developed DI within 6 days after the hypoxic/ischaemic insult. Only two neonates survived with developmental delay. The remaining 26 cases died.

Conclusion Neurogenic DI can be caused by hypoxia/ischaemia and is an ominous sign of severe brain damage in children with hypoxic encephalopathy. It is important to recognize this potential sequel by regularly monitoring intake and output, plasma sodium level, and urine specific gravity.

Key words Hypoxia/ischaemia · Hypoxic encephalopathy · Neurogenic diabetes insipidus · Polyuria

Abbreviations *AVP* vasopressin · *DI* diabetes insipidus

Introduction

Neurogenic diabetes insipidus (DI) is caused by a relative or absolute deficiency of vasopressin (AVP) [19]. The deficiency is due to impairment of the supraoptic and paraventricular nuclei. In children, intracranial tumours and defects of the CNS are the most common causes of neurogenic DI [9]. Infrequently neurogenic DI may occur after severe hypoxic/ischaemic brain damage secondary to carbon monoxide poisoning [11], respiratory failure [8], or cardiorespiratory arrest [1, 13] and complicates the management of an already critically ill patient. Up to now there are only a few reports of children with neurogenic DI associated with hypoxic encephalopathy [1, 7, 13, 16]. We report six children who developed neurogenic DI after severe hypoxia. Except for hypoxic episodes, some of the children in these reports (including this one) had other intracranial lesions which might have played some role in the development of DI. In order to know the relationship between neurogenic DI and hypoxia/ischaemia, we also analysed the characteristics of 28 paediatric cases reported to have neurogenic DI occurring solely after episodes of hypoxia/ischaemia.

Material and methods

We reviewed the charts of all children who, from September 1992 to September 1994, developed neurogenic DI after a severe hypoxic insult. The patients who had intracranial tumours, head injury, brain surgery, or DI before their hypoxic episodes were excluded. Crite-

ria for the diagnosis of neurogenic DI in a child included: (1) urine output spontaneously exceeding an amount equal to 1.5 times the calculated maintenance fluid intake for 2 h (consecutive); (2) urine specific gravity not greater than 1.005 (and urine osmolality not more than 300 mOsm/kg H_2O if measured); (3) a plasma sodium level greater than 150 mmol/l (and serum osmolality greater than 310 mOsm/kg H_2O if measured); (4) a concurrent low AVP level or observed response to exogenous AVP or desmopressin treatment; (5) no diuretics in use over the preceding 12 h, and (6) normal renal function and levels of potassium and calcium [3, 7, 16].

Plasma sodium levels were measured by the ion-selective electrode method. Serum and urine osmolalities were measured by the freezing point depression method. Urine specific gravity was measured by a refractometer. The blood for AVP measurement was collected in an EDTA tube, its plasma was separated immediately and kept below –70° C for analysis with the Vasopressin ^{125}I RIA Kit of INCSTAR, Minnesota, USA.

All available literature on DI associated with hypoxic encephalopathy in paediatric patients (age ≤ 18 years) was reviewed. The children whose causes of DI could be clearly identified as solely due to hypoxia/ischaemia were included. Those patients who had intracranial lesions or insults which could affect the brain before the onset of DI were excluded. Those lesions or insults consisted of brain surgery, head trauma, intracranial haemorrhage, meningitis, encephalitis, malfunction of ventriculoperitoneal shunt, Reye syndrome, and poisoning.

Results

Six children fulfilled the criteria of DI associated with hypoxia/ischaemia. Their demographic data and causes of hypoxia are listed in Table 1. After the hypoxic episode, these children were immediately placed on the ventilator and received cardiorespiratory support until they died of cardiac decompensation (cases 4 and 5) or the termination of ventilatory support by their families (cases 1, 2, 3, and 6). Neurological examination of these patients persistently showed a score of $E_1M_1V_1$ according to the modified Glasgow coma scale. Their neurogenic DI was treated with intravenous fluid, intranasal insufflation of desmopressin, or continuous infusion of AVP (Table 2). We did our best to keep hydration and electrolytes within normal limits until their death.

From the literature and this study, there are 28 cases whose DI solely resulted from hypoxia/ischaemia (includes cases 1 and 6 of this study) (The interested reader can contact the authors to obtain all details and full list of references on these 28 cases). Airway obstruction, haemorrhagic shock and sudden infant death syndrome are the three major causes. Twenty-five children had their ages available for analysis. The ages ranged from 0.03 to 18 years (mean 7.27 years, median 5 years). Twenty-three children had their intervals between the hypoxic insult and the onset of DI specified. The intervals ranged from 0.08 days (2 h) to 13 days (mean 4.07 days, median 3.5 days). Linear regression analysis revealed no significant correlation between the age and the interval. Nineteen patients (82.6%) developed DI within 6 days after the hypoxic/ischaemic insult (Fig. 1). Only two neonates survived with developmental delay. The remaining 26 patients died.

Table 1 Age, sex, weight and cause of hypoxia

Case	Age (years)	Sex	Weight (kg)	Interval[a] (h)	Cause of hypoxia
1	0.3	M	8.1	120	Sudden infant death syndrome
2	1	F	8.5	184	Pneumococcal meningitis, cyanosis and convulsion
3	1.5	M	14.5	56	Pneumococcal sepsis with meningitis, convulsion and cyanosis
4	5	M	15.5	169	Coxsackievirus B_1 encephalitis, convulsion, cardiorespiratory arrest
5	8	F	29.2	83	Encephalopathy, convulsion, cyanosis and shock
6	13	F	34.0	12	Smoke-inhalation injury and burn, dead on arrival

[a] Interval from the hypoxic insult to the onset of neurogenic DI

Table 2 Biochemistries[a] and management (*DDAVP* desmopressin, *IVF* intravenous fluid)

Case	Plasma Na (mmol/l)	Serum osmolality (mOsm/kg)	Urine osmolality (mOsm/kg)	Urine Sp Gr before [c]	Urine flow (ml/kg/h)	AVP (ng/l)	Urine Sp Gr after [d]	Therapy
1	155	–	–	1.005	6.7	–	1.036	DDAVP
2	165	–	–	1.004	6.4	–	1.021	DDAVP
3	155	322	71	1.003	10	0.65	1.031	AVP
4	178	386	–	1.005	7.3	< 0.5	–	IVF only
5	154	–	–	1.006 [b]	10.0	0.58	1.041	AVP
6	171	343	93	1.003	23	–	1.035	DDAVP

[a] Serum urea nitrogen, creatinine, K, and Ca were within normal limits in all the 6 patients
[b] Serum glucose level = 488 mg/dl, urine sugar = 2+
[c] Urine Sp Gr before: urine specific gravity at the diagnosis of DI
[d] Urine Sp Gr after: maximal urine specific gravity after therapy with DDAVP or AVP

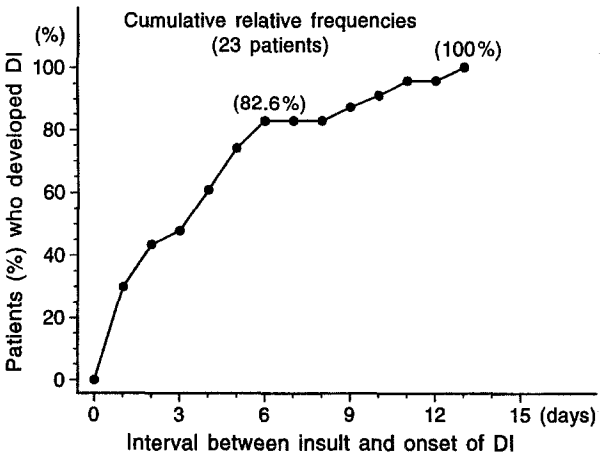

Fig. 1 Cumulative percentage of the patients who developed neurogenic DI after the hypoxic/ischaemic insult

Discussion

Although neurogenic DI occurring after a hypoxic/ischaemic episode has been reported in paediatric patients since 1975 [15], this is still not specifically mentioned in large series reports [9, 17] and several textbooks [4, 5, 18, 19]. Hopefully, this report, with a collective review of 28 paediatric patients, will draw public attention to this disease entity.

In general, hypoxic injuries are global and affect all neurons without specificity to region or vascular blood supply. However, the supraoptic and paraventricular nuclei are markedly resistant to arrest of the cerebral circulation and to lack of oxygen because the neurohypophyseal system has many neurosecretory cells and an intricate bilateral blood supply [10]. Of the neurosecretory cells 90% has to be destroyed before DI becomes evident [12]. Thus it is likely that the appearance of neurogenic DI following a severe hypoxic episode denotes wide-spread neurological damage.

During hypoxia/ischaemia the very low P_aO_2 will cause disruption of cerebral intracellular oxidative metabolism with cellular disintegration and loss of integrity of cellular membranes, an influx of sodium leading to severe cerebral oedema, and subsequent compression necrosis of brain tissue [2]. Machiedo et al. [15] reported postmortem examinations on two patients with DI after hypoxia/ischaemia. The posterior pituitary showed evidence of haemorrhage, oedema, and acute and chronic inflammatory infiltrates. The cortex showed evidence of widespread anoxic changes and necrosis. The pituitary gland of Halebian et al. [11] patient, however, showed autolysis without a cellular infiltrate despite the brain revealing severe anoxic change. Fiser et al. [7] reported autopsy findings on brain-dead children with neurogenic DI. The pituitary glands in their series had varying degrees of oedema, congestion, haemorrhage, and coagulative necrosis. These suggest that a spectrum of destruction of the hypothalamic-pituitary area is possible and accounts for the variability in the time of onset of neurogenic DI after the insult.

Head trauma, brain surgery, meningitis and encephalitis can cause neurogenic DI [9]. It is possible that meningitis or encephalitis in addition to hypoxia played some role in the development of neurogenic DI in three (cases 2, 3 and 4) of our six patients . Case 5 had symptoms and signs of encephalopathy. Extensive search including CSF examination and culture and antibody titres failed to isolate an aetiology. In reviewing the literature we excluded those children who might have had one of these insults and selected those solely due to hypoxia/ischaemia for this review. Twenty-eight cases were suitable for analysis. Following a hypoxic/ischaemic insult the child could develop DI in just 2 h or as late as 13 days. Most (82.6%) showed evidence of DI in 6 days. The interval between the hypoxic insult and the onset of DI was not related to the age of the patients. This wide range suggests hypoxic injuries to the brain are different in severity and the tolerance to hypoxia is different in every child. Neonates appeared to show better prognosis though they could not be free of complications.

Polyuria is reportedly present in 76% of children with brain death [7]; however, DI is only present in about 40% of them [7, 20]. Polyuria could be mistaken for DI. Polyuria in patients without DI has been attributed to non-oliguric acute tubular necrosis [6], glucosuria, or the administration of furosemide, mannitol, or contrast media [7, 14]. Both conditions can lead to hyperosmolar states which could be detrimental to the already injured brain and should be handled properly to maintain fairly normal parameters [21]. Neurogenic DI should be considered in the differential diagnosis of polyuria and dehydration occurring in critically ill patients who have suffered hypoxic encephalopathy.

Some patients with hypoxic/ischaemic encephalopathy are potential organ donors. The supply of paediatric donor organs remains critically short, despite an apparent social acceptance of this concept [22]. Since organ viability can be preserved after short episodes of asystole, every effort must be made to salvage potentially useful organs from brain-dead children [14]. An accurate assessment of fluid, electrolyte and renal function is mandatory to maintain a physiological state until the organs are harvested.

Our findings suggest that neurogenic DI might occur in children with hypoxic encephalopathy and is an ominous sign of severe brain damage. The patients who develop neurogenic DI solely due to a hypoxic/ischaemic insult will likely die despite vigorous resuscitative efforts. Neonates appear to have a better chance of surviving, but will likely have developmental delay. It is important to recognize this potential sequela by regularly monitoring intake and output, plasma sodium level, and urine specific gravity.

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