Neurological complications of arterial hypertension

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SUMMARY   During a 10-year period 45 children were identified as having had neurological complications associated with severe arterial hypertension. Convulsions were the most common complication, occurring in 42 (92%) children. Two (4%) children each presented with a facial palsy and 2 (4%) with alterations in the level of consciousness. Nineteen (42%) presented with epileptic seizures as the first sign of arterial hypertension. The prognosis for children having had a single episode of hypertensive encephalopathy was good. Long-term follow-up showed no permanent neurological deficit on physical examination, and no focal abnormality on brain scan by computerised tomography. Psychometric analysis similarly failed to show any significant difference in cognitive assessment between children having had an episode of hypertensive encephalopathy and a control group with chronic renal disease, although reading skills were generally behind for chronological age and the average IQ was about 90 in both groups.

Previous reviews have paid little attention to central nervous system involvement in hypertension, although studies from centres quote an incidence of complications occurring in 8 to 11% of hypertensive children.[1 2] More recently there have been several comprehensive case reports documenting complications encountered after the treatment of severe hypertension both in adults and children.[3–5] Cuneo and Caronna[6] proposed that the neurological complications of hypertension could be classified into three syndromes which differ clinically but share the same underlying pathological process. The characteristic effect of hypertension on the brain is involvement of the small arteries. The pathological process in these arteries may be acute as in hypertensive encephalopathy (HE), or chronic as in lacunar infarction or cerebral haemorrhage. Traditionally HE is believed to leave no residual deficits if the blood pressure is promptly reduced. The purpose of this review is to characterise the nature and frequency of neurological complications as encountered in hypertensive children during a 10-year period, and to determine the prognosis.

Methods

Case records of 45 children, 25 boys and 20 girls, with severe arterial hypertension referred to the paediatric nephrology unit at Guy's Hospital between 1971 and 1980 were reviewed. All children had developed neurological complications as the presenting sign or as a consequence of the hypertension.

Thirty patients were available to follow-up and were seen at a mean interval of 2·7 years (one month to 10·6 years) after the episode of HE.

A complete neurological examination, including an assessment of visual acuity (Snellen), was undertaken by one investigator (R S T) in each case. All children were given a general cognitive assessment and a reading test. The Wechsler scale of intelligence (revised) was used in all cases except in 2 where the McCarthy scales of children's abilities was used. The reading tests were Neale's analysis of reading ability and the Schonell graded word reading test. All children were asked about their interests and friendship patterns, and wherever possible parents were also asked about friendship patterns and social contacts. There were no disagreements in the cases where this was undertaken. A control group of 10 age-related children with varying degrees of chronic renal insufficiency and well-controlled hypertension was drawn from sequential attenders to outpatients.

The statistical tests used were the χ^2 test, or Student's *t* test.

Brain scans by computerised tomography (CT) were undertaken whenever possible in children who did not require sedation. Interpretation of the scans was carried out by a neuroradiologist (R D H) who had been told about the nature of the study but did not have the individual clinical details concerning

the children. Electroencephalogram recordings were not routinely undertaken as it had previously been shown that hypertension and HE did not produce specific changes.[2] [7]

Results

The mean age at presentation of the neurological complication was 9·9 (range 0·25–16) years. Forty-two (92%) children presented with epileptic seizures and in 19 (42%) a seizure was the presenting sign of the previously undetected hypertension. Descriptions of convulsive episodes available from the case-notes suggest that 6 children had partial motor convulsions and 25 children had generalised motor convulsions with diminished conscious level recorded in each case. Two (4%) children presented with a lower motor neurone paralysis of the face and 2 (4%) with an alteration in the level of consciousness described as drowsiness with normal withdrawal to pain. Of 11 (24%) children who died 5 were known to have hypertensive seizures as a complication of the preterminal illness, generally renal failure. No child was febrile at the time of the convulsive episode.

The cause of the hypertension in the majority of children was primary renal disease (Table 1). Chronic glomerulonephritis and reflux nephropathy accounted for nearly 60% of parenchymal renal disease. In 2 patients HE followed renal transplants for dysplastic kidneys at 4 days and 5 months postoperatively, both children having had their own kidneys removed. In the 3 patients with haemolytic uraemic syndrome, and the one with systemic lupus erythematosis, haematological and immunological investigations showed that the disease was 'in remission' at the time of the convulsion and therefore that renal involvement was implicated as the cause for the hypertension.

In 2 patients no primary diagnosis was made but hyper-reninaemic hypertension was confirmed. One patient had a major coarctation of the abdominal aorta affecting both renal arteries thus causing hypertension. The patient with minimal change nephrotic syndrome developed hypertension secondary to steroid therapy, and acute renal failure in another patient with juvenile rheumatoid arthritis was a consequence of septicaemia.

In 35 patients, of whom 20 were aged between 2 and 10 years, the blood pressure had been recorded after the acute neurological episode. Mean values for systolic and diastolic pressure in this series were in excess of the mean plus 2 standard deviations for children of different ages.[1] In order to examine the possibility of a metabolic factor contributing to the pathogenesis of the convulsive episode, data available for systolic blood pressure were analysed, for the degree of correlation, with values for levels of plasma creatinine, urea, sodium, calcium, and albumin (Table 2). There was a tendency for children to have seizures at lower levels of systolic blood pressure with only varying plasma sodium levels. However, in view of the wide range of values for plasma sodium it was not possible to predict a precise level at which seizures were thought to occur more often. Data on arterial carbon dioxide tension at the time of presentation were not generally available for meaningful analysis. Five children however, suffered HE characterised by convulsive episode within 24 hours of haemodialysis (3 in the immediate postrenal transplantation period), and contributory factors—such as fluid and electrolyte disequilibration after dialysis—could therefore not be discounted.

At presentation 16 (35%) children had evidence of hypertensive retinopathy, either papilloedema alone or in association with retinal haemorrhages. In 7 (16%) children there was a previous history of a convulsive episode. In 4 these were diagnosed as simple febrile convulsions sustained during the first 3 years of life, one of whom was receiving anticonvulsant therapy. The others were diagnosed as having idiopathic epilepsy and all were receiving the appropriate anticonvulsant therapy. Seven (16%) had had more than one hypertensive fit after the initial episode and one child in this group had died. Three children in this group were also receiving anticonvulsant therapy.

Neurological examination in 30 children showed no evidence of motor or sensory deficit not noticed before the episode of HE. One patient was known to have had a left hemiplegia since infancy (HE at 7·2 years), and another an ocular-motor apraxia diagnosed at 4 years (HE at 9·3 years). There was no evidence of lower motor neurone facial paralysis in the 2 children who had presented with this lesion 4 years and 1 year before this study.

Twenty-nine CT brain scans were undertaken in 25 children. In 15 (60%) children, these were

Table 1 *Cause of renal disease responsible for arterial hypertension in the 45 children*

Diagnosis	Number of children	Died
Reflux nephropathy	13	2
Chronic glomerulonephritis	13	3
Haemolytic-uraemic syndrome	3	—
Cystinosis	3	2
Renal dysplasia	3	1
'Hyper-reninaemic'? aetiology	2	—
Acute poststreptococcal nephritis	2	—
Juvenile nephronophthisis	1	—
Renovascular disease	1	—
Obstructive uropathy	1	1
Systemic lupus erythematosis	1	1
Minimal change nephrotic syndrome	1	—
Acute anuric renal failure	1	1

Table 2 *Analysis of biochemical findings at the time of hypertensive encephalopathy*

	Number of children	Plasma levels		Systolic blood pressure (mmHg)		r	P
		Mean ± SE	Range	Mean	Range		
Creatinine (µmol/l)	26	310 ± 58	27–1025	178	120–230	0·28	NS
Urea (mmol/l)	29	18 ± 2·7	5–48	175	130–230	0·11	NS
Sodium (mmol/l)	27	135 ± 0·9	124–142	175	120–230	0·39	<0·05
Calcium (mmol/l)	27	2·3 ± 0·4	1·0–3·4	178	120–230	0·17	NS
Albumin (g/l)	29	35 ± 9	10–49	178	120–230	0·09	NS

Conversion: SI to traditional units—creatinine: 1 µmol/l ≈ 0·0113 mg/100 ml; urea: 1 mmol/l ≈ 6·02 mg/100 ml; calcium: 1 mmol/l ≈ 4·0 mg/100 ml.

interpreted as normal. The mean interval from the episode of HE to scan was 1·9 years (range 1 month–10·6 years). Cerebral atrophy was the only finding in 8 children based on enlargement of Sylvian fissures, inter hemispheric fissures, cerebral sulci, and ventricular size. Seven of these children had been receiving prolonged corticosteroid therapy (15–30 mg/m^2 on alternate days) for periods of time ranging from 1 to 5·4 years as part of the immunosuppression treatment after renal transplants. One other child with cerebral atrophy had recovered from acute haemolytic uraemic syndrome but remained in chronic renal failure. Three children with renal transplants and normal CT scans had also been receiving corticosteroids for periods of time ranging from 1·2 to 2·7 years. Left cerebral hemiatrophy was observed in one patient known to have mild educational subnormality and to have epilepsy; right lateral ventricular dilatation was found in another child with epilepsy, mild subnormality, and a left hemiplegia. Both these children were diagnosed as having hyper-reninaemic hypertension of uncertain aetiology. In the third child with epilepsy, a CT scan had been undertaken before the episode of HE, and postrenal transplantation on two occasions had revealed changes only of cerebral atrophy.

Results of the cognitive assessment show no significant differences between the HE group (full-scale score mean 89; range 59–126) and controls (full-scale score mean 92; range 46–124). No precise comments can be made on the side effects of antihypertensive drugs as a cause of intellectual impairment in the two groups, there being a similarly wide range of values for cognitive assessment in both. There is some indication that in terms of verbal scores the HE group functioned worse than controls but this did not reach significant levels. Analysis of data from those children who had received renal transplants and had therefore been subjected to long periods of time spent in hospital showed a slightly better verbal scale score compared with children who had spent a far shorter time in hospital. The HE group however, did show significant differences in reading problems, defined as a reading age of at least 2 years behind chronological age ($\chi^2 = 5·84$, P<0·05). This could not be accounted for on the basis of time away from school.

In terms of social relationships, the HE group showed a number of children with no social contact with any child outside his immediate family. Seven of the group could name no other children with whom they were friendly, even among the children they met in hospital. There was no association between social isolation, IQ, or reading skills.

Discussion

Transient cerebral dysfunction caused by hypertension was first described by Oppenheimer and Fishberg in 1928,[8] and called HE. Normally changes in systemic blood pressure do not materially influence cerebral blood flow. If blood pressure is raised cerebral vessels constrict, and if blood pressure is lowered they dilate, so preserving the constancy of blood flow. In normotensive individuals the range of pressures over which such 'autoregulation' occurs is wide, between a mean pressure of about 60 and 120 mmHg, compared with a normal mean resting pressure of 90 mmHg.[9] When blood pressure is lowered below the autoregulatory range cerebral blood flow falls, while above the range 'breakthrough' of autoregulation occurs with cerebral hyperaemia.[10] This is associated with focal damage to the cerebral arterioles, increased permeability, and oedema.[11] Clinically the picture is one of HE. The upper and lower limits of blood pressure tolerated vary with systemic and cerebral acid-base balance since the pH of the local perivascular space is an important determinant of cerebrovascular resistance. Thus hypercapnoea induces strong cerebral vasodilatation which impairs autoregulation.

There are no specific symptoms of hypertension and any neurological sign should be regarded as a complication. Headache, usually severe and generalised, is the most common complaint. Visual complaints range from blurring of vision to transient blindness.[12] Nausea and vomiting are initial complaints in many patients. Seizures, both focal and generalised, occur more frequently in children.[12 13]

Severe hypertension in childhood is most frequently secondary and nearly always of renal parenchymal origin.[1][12] There are few reports of cerebrovascular complications associated with hypertension secondary to coarctation of the aorta[14][15] and indeed no such child was seen at Guy's Hospital, a referral centre for both paediatric nephrology and cardiology, throughout the period of this study. It would appear that most infants with coarctation of the aorta present predominantly with heart failure before arterial hypertension becomes a problem.

In this study a significant number, 19 (42%), of children had each had an epileptic seizure as the presenting sign of the previously undetected arterial hypertension. Although several reviewers have concluded that blood pressure screening for essential hypertension in children is laborious and not cost effective,[16][17] there is a clear case for careful monitoring of blood pressure in all children with diagnosed renal disease. In individual patients with renal disease an acute rise in blood pressure may not be the only contributory factor causing a convulsive episode. Factors such as disequilibrium syndrome,[18] and the use of high dosage corticosteroids may be additional provoking factors. Previous history of seizure disorder as encountered in 7 (16%) of the children in this series may illustrate the predisposition of any child to have a convulsion given the correct provoking stimulus. The finding of an excess of children with previous febrile (4 or 9%) and non-febrile (3 or 7%) seizures with only one 1st-degree relative having been recorded with non-febrile seizures is interesting. Although it raises the possibility that hypertension and fever as provoking agents for seizures may have a genetic overlap, the study design does not allow any clear conclusion. Prospective family history data and detailed allowance for the effect of the shift to lower intelligence in this group would be needed to investigate this further.

Management of the acute clinical situation was initially directed at arresting seizure activity, generally with diazepam. To ensure optimum control of blood pressure, antihypertensive agents were used in conjunction with frequent monitoring until the normotensive state had been established. Prophylactic anticonvulsants were not routinely used after satisfactory control of blood pressure because they did not seem to be necessary and because of concern about drug interaction in transplanted patients. Parental education about the emergency management of seizures would however seem reasonable in a child with chronic renal disease.

Long-term follow-up in the survivors of this group of children who have had episodes of HE is undoubtedly encouraging. There appear to be no sequelae on neurological examination in this group of patients whose epilepsy and hypertension were vigorously treated. However, permanent neurological damage is a well recognised problem both in children and adults who have suffered episodes of HE associated both with and without convulsive episodes.[2][3][5] The lack of parenchymal changes in the brain as illustrated by CT scan makes it unlikely that small cortical haemorrhages have occurred which could be related to an episode of HE. Minor degrees of cerebral atrophy were seen almost exclusively in patients receiving corticosteroids, a finding previously observed.[19] The clinical significance of this finding is uncertain although in adults it has been shown that degrees of cerebral atrophy found on CT brain scan do not correlate with psychometric assessment in dementia.[20]

Psychometric assessment failed to demonstrate convincing differences in cognitive functioning between the HE and control groups. There are indications that these children will have educational difficulties in addition to those expected on the basis of absences from school—that is in reading. The precise cause of these reading difficulties is uncertain in this study, although the association between organic brain dysfunction and reading problems is well recognised.[21] The poor social relationships formed by many of the children in the HE group deserves attention and this is one of the factors which may be related to later psychiatric disorder.[22] The evidence, such as it is from the study, would seem to suggest that it is worth assessing educational progress in children who in addition to chronic illness have had neurological complications associated with hypertension, and instituting remedial measures if necessary. Social contacts appear to be difficult for these children and this requires further study. However, it should be possible to alert the parents of such children to the importance of this problem and perhaps encourage them to promote social contact between handicapped and able-bodied children. Although not wishing to add to the considerable concern of parents whose children suffer from chronic ill health, education and social issues are of paramount importance to the future welfare of every child.

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