MALIGNANT HYPERTENSION IN CHILDHOOD

BY

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Essential hypertension remains one of the most important problems in clinical medicine. Until the cause is discovered both nomenclature and classification must of necessity be provisional and incomplete. Nevertheless in recent years, increasing attention has been given to this subject and certain definite advances made. This applies particularly to the so-called malignant type of primary or essential hypertension. Malignant hypertension may be defined as a progressive, generalized, vascular disorder associated with gross hypertension, in which renal dysfunction is a secondary and late manifestation. The condition is predominantly one of middle life and in consequence its occurrence in childhood has received little notice. For this reason the following case has been presented in some detail. A careful study of the literature of the last twelve years has revealed only eleven cases below the age of fourteen which fulfil the clinical criteria and of these only four were confirmed at autopsy.

In this article it is proposed to indicate the essential features of the condition in childhood as far as this is revealed by the eleven cases previously mentioned, and to describe in detail a case under my own care.

The main features are shown as follows:

<table>
<thead>
<tr>
<th>Total Cases</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age</td>
<td>10 years</td>
</tr>
<tr>
<td>Sex—</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
</tr>
<tr>
<td>Clinical Features—</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
</tr>
<tr>
<td>Papilloedema</td>
<td>12</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>8</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>7</td>
</tr>
<tr>
<td>Convulsions</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
</tr>
<tr>
<td>Exertion dyspnoea</td>
<td>1</td>
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</tbody>
</table>

These symptoms and signs are associated with a severe and progressive hypertension for which no cause can be found. In the above cases the average highest systolic pressure recorded was 230 mm. of mercury and the diastolic...
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160 mm. The course of the disease is rapid and relentless. The average duration in this series was two years. The longest period of survival after the onset of symptoms was five years and the shortest six months.

Haemorrhage may take the form of haematuria, melaena or epistaxis. In five cases intermittent but severe haematuria was an outstanding feature. Renal failure is a terminal event and the blood urea rarely rises to high levels. Papilloedema is always present. The striking features are the severity of the hypertension, the rapid tempo of the course and the fatal ending. Death occurs from cardiac, cerebral or renal defect or from intercurrent infection.

The adult picture has been clearly described by Wagener and Keith (1939) in America and by Ellis (1938) in this country. The adult and childhood pictures are similar. There are, however, certain differences. The haemorrhagic features, notably haematuria, so striking in some of the children, are less marked in adults; but nervousness, lack of energy, dyspnœa on exertion and nocturnal frequency of micturition, infrequent in childhood, are prominent adult symptoms. In both, the onset may be sudden or insidious; in both, a rapid course leads inevitably to a fatal termination.

Pathology. It must be stressed that this is a generalized disease of the arterial system. In consequence, the characteristic lesions are found not only in the kidney but also in the bowel, brain, pancreas, adrenals, testes and elsewhere. In America, biopsy of the vessels of the pectoral muscles is part of the routine examination in suspected cases.

MORBID ANATOMY. The predominant changes are found in the heart and kidneys. There is marked left ventricular hypertrophy. The kidneys as a rule are only slightly reduced in size, though in certain cases one has been smaller than the other. The histology of each kidney in such cases was similar, and there was nothing to suggest congenital abnormality. The surface shows diffuse, flat granular elevations of varying size, standing out above slightly depressed red areas. Petechial haemorrhages may or may not be present. The granularity referred to is not marked and the capsule strips fairly easily. On section the cortex and medulla are sharply demarcated for the most part, though the cortical markings may be obscured by greyish flecks and streaks. The renal pelvis frequently shows dark red haemorrhagic areas and the renal artery may be thickened.

HISTOLOGY. The lesions are more distinctive and two well-defined processes are evident. The smaller arteries show a cellular proliferation of the intima often leading to occlusion of the lumen. This is called by Ellis 'endarteritis fibrosa' and is clearly distinguished from the arterial thickening associated with the increase in elastic tissue present in all cases of hypertension. The arteriolar lesions are more severe in character. The walls of the arterioles are swollen by the presence of a homogeneous material which appears purplish in colour when stained with haematoxylin and eosin. This change has been termed 'acute fibrinoid' necrosis. It may be followed by occlusion of the lumen, infiltration of the vessel wall with blood, or local aneurysm formation.

In the kidney itself these lesions are well developed. Fibrinoid necrosis of the individual capillary loops or of the whole glomerulus may be seen. This
may lead to adhesion of capsule and tuft. Proliferative capsulitis is sometimes present, but true crescent formation is rare. The interlobular arteries show endarteritis fibrosa and the smaller arterioles, particularly the afferent arterioles to the glomeruli, show fibrinoid necrosis. In the arcuate and larger arteries elastic lamination may be present. The tubules may show hyaline droplet degeneration and there is some increase in the stroma with round-celled infiltration. Nevertheless, in spite of the widespread vascular damage, one of the striking features is the relative normality of the nephrons. In fact the majority of the glomeruli appear normal, in marked contrast to the picture of chronic glomerulo-nephritis.

The vascular changes described in detail for the kidney, are found in other organs, notably in the pancreas, adrenals, bowel, brain and retina. The whole picture is in fact one of diffuse arterial and arteriolar disease.

Case report

J. O. D., female aged ten years was admitted to the Westminster Hospital on August 7, 1938. The child had complained of vague headaches for three to four years. Two years before admission these became severe, frontal in position and associated with vomiting. For the preceding six months she had experienced intermittent gross haematuria and failing vision.

Measles and chicken pox had occurred in early childhood but there was no history of acute nephritis or recurrent tonsillitis.

Examination. This revealed a thin sallow child with no obvious oedema. The tonsils appeared healthy though the tonsillar glands were palpable.

Cardio-vascular system. Obvious cardiac enlargement was present, associated with the classical signs of patent ductus arteriosus.

The blood pressure was 240/145 mm. Hg in the upper limbs and 270/160 mm. Hg in the lower.

Eyes. Both retinae showed extensive changes, with papilloedema, exudate and haemorrhages. Vision: right, 6/60; left: patient was just able to count fingers at three feet.

Urine. At first macroscopic haematuria was present but this soon cleared. In the interval there was only a trace of albumin, a few red cells and no casts. The urine was sterile.

Blood urea (8.8.38) 43 mgm. per cent. Urea clearance 40 per cent. of normal.

Blood picture (8.8.38): Red blood cells 4,600,000. Haemoglobin 82 per cent. (23.8.38) Red blood cells 3,600,000. Haemoglobin 56 per cent.

Progress. For ten days haematuria continued and there was a sharp bout of epistaxis. After this, her general condition improved and she gained 4 lb. in weight. In view of the political situation she was removed to a provincial hospital on September 9, 1938.

On October 17, 1938 she was re-admitted to the Westminster Hospital. The blood pressure in the arms was now 250/150 mm. Hg, and retinopathy more extensive. A further severe attack of haematuria occurred soon after admission. The blood urea was now 61 mgm. per cent. A lumbar puncture revealed an increase in pressure to 275 mm. of cerebro-spinal fluid, but an otherwise normal fluid. The child's condition now began to deteriorate rapidly. Haematuria continued until November 9, 1938. Skiagraphs of the renal tract revealed no abnormality. For the ten days before death, the child became drowsy and presented severe abdominal pain with melaena. Pulmonary
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Drowsiness and oedema became evident and the blood pressure began to fall. At this stage drowsiness and high temperature with multiple arthritis, suggested a terminal septicæmia. Death occurred on November 14, 1938, two-and-a-half years from the onset of definite symptoms.

Autopsy. The body was wasted.

CARDIO-VASCULAR SYSTEM. The ductus arteriosus was patent and there was gross hypertrophy of the left ventricle. The smaller vessels throughout the body appeared firmer and more prominent than normal.

KIDNEYS. The right was normal in size and weighed 75 grammes. The left one was a little smaller. The capsule showed a reddish-yellow motting with certain shallow depressions but no granularity. The cortico-medullary ratio was slightly diminished and the pattern a little distorted. There were numerous red blotches in both renal pelves and, on the right side, a haemorrhagic mass the size of a walnut projected into the lumen. The histology of this revealed endarteritis fibrosa and arteriolar necrosis of the pelvic vessels.

INTESTINES. There was a peritoneal exudate covering the last six feet of ileum. The bowel was purplish red in colour and incision revealed extensive haemorrhagic ulceration of the whole of the ileum and a large part of the jejunum. Apart from a few small angiomata in the liver, other organs appeared healthy.

Histology. The characteristic vascular findings, namely endarteritis fibrosa and acute arteriolar necrosis, were present in the kidney, renal pelvis, bowel, spleen, pancreas and adrenals. These are well illustrated in the accompanying plates (fig. 1 to 6).

It will be seen that this child presented the criteria of malignant hypertension, viz. headaches, vomiting, papilloedema, haemorrhage and a progressive hypertension with terminal renal dysfunction. There is one disappointing feature: the child was seen at a provincial hospital in 1935 as a case of congenital morbus cordis, but no record of the blood pressure at the time is available, When first seen by me she was entering the phase of renal failure. Nevertheless, in spite of severe hypertension and extensive bilateral retinopathy, the blood urea was only just above the upper limit of normal and subsequent renal histology revealed no evidence of a previous inflammatory lesion. A similar haemorrhagic enteritis has been recorded in one of the four children in whom autopsy was carried out (Klemperer and Otani, 1931).

Differential diagnosis. In a condition in which the ultimate etiology is still uncertain, differential diagnosis is clearly an important issue. The question arises as to whether this condition is a distinct entity or a clinical and pathological syndrome common to several disease processes. In answer to this, three conditions merit attention. The first of these is glomerular nephritis. No one will deny that in the terminal stages of this disease, vascular failure may rapidly occur, hypertension and retinopathy become intense and the picture resemble the terminal stage of malignant hypertension. In fact, when renal failure has supervened, a clinical differentiation may be impossible. A clear history of acute or sub-acute nephritis would, of course, suggest the answer. Histological examination would, however, be more conclusive. In chronic glomerular nephritis, although endarteritis fibrosa and arteriolar necrosis may be present in certain areas, their presence in organs other than the kidney is rare, whereas glomerular fibrosis, minimal in hypertension, would be everywhere visible.

The second condition, chronic pyelo-nephritis, has only recently received the attention it deserves. Weiss and Parker (1939) believe that this accounts
Fig. 1.—Renal parenchyma, showing almost normal architecture.

Fig. 2.—Kidney: vessels showing typical changes.

Fig. 3.—Glomerulus, showing areas of acute fibrinoid necrosis.

Fig. 4.—Mass in renal pelvis with vessel showing well-marked endarteritis fibrosa.

Fig. 5.—Vessels show aneurysm formation and rupture: small intestine.

Fig. 6.—Endarteritis fibrosa in suprarenal vessels.
for 20 per cent. of all cases labelled malignant hypertension. They consider that pyelitis of early childhood can no longer be considered a benign and innocent infection of the renal pelvis. In a series of such cases followed for long periods, they found that some enter a latent or chronic phase and were later related to certain types of pregnancy toxaemia, subsequent attacks of pyuria and to arterial hypertension of progressive severity. They found vascular changes of the type seen in malignant hypertension in a baby of six months and a girl of twelve years, both of whom had had previous acute pyelo-nephritis.

Without describing healed or chronic pyelo-nephritis in detail, it is sufficient to say that, according to Weiss and Parker (1939), the full clinical picture of malignant hypertension may result. Nevertheless the histological features show unmistakable differences: here again arteriolar necrosis may be present in the kidney, but in addition the tubules in certain areas are lined with flattened atrophic epithelium and filled with colloid casts: the glomeruli show pericapsular fibrosis: there is marked infiltration of the interstitial tissue with inflammatory cells: the renal pelvis shows chronic inflammatory thickening together with thickening and infiltration of the renal capsule. Vascular changes in other organs are minimal or absent.

The third group is less well defined. It includes cases with the title of 'renal dysbiotrophy.' The causal factor here is presumed to be an underlying tissue inferiority. The kidneys are said to be small, pale and fibrosed and one may be much smaller than the other. Many of the glomeruli are atrophied or fibrosed, while others show varying degrees of chronic inflammatory reaction. Other developmental anomalies are not uncommon. The presence of a patent ductus arteriosus, in the case under consideration, and the difference in size of the two kidneys, might at first sight suggest that it belongs to this group, but the histology of both kidneys was identical and in no way comparable with that described above.

In addition to renal dysbiotrophy, this group includes cases of renal agenesis and renal hypoplasia, associated with hypertension. The picture is by no means clear: some may be undoubted cases of imperfect renal development but others previously included in this category are more probably examples of latent or chronic pyelo-nephritis.

It is clear from these facts that the clinical picture of malignant hypertension may be produced by more familiar disease processes. At the same time, a study of the histology suggests that there is a group of cases fulfilling all the essential criteria described in the earlier part of this paper. Whether this is in fact a disease entity, or is capable of further subdivision, remains to be seen.

In diagnosing any suspected case of malignant hypertension during life there are therefore four conditions to be considered—a developmental renal anomaly, the terminal phases of chronic glomerular nephritis, chronic pyelo-nephritis, and primary malignant hypertension. The final diagnosis must await full histological investigation. Some idea of the relative distribution of these causes is given by Weiss and Parker (1939) in their assessment of fifty-five patients with 'contracted kidneys': twenty-seven were due to nephrosclerosis of the benign or malignant types, eighteen to pyelo-nephritis and ten to glomerulo-nephritis.
Prognosis and treatment. The condition is invariably fatal. The maximum duration both for children and adults was five years and the minimum six months. The most important prognostic feature is the state of renal function. Once this begins to fail and especially when the blood urea rises, the end is not far distant. In such circumstances, treatment is essentially palliative. Surgical measures have certainly passed beyond the experimental stage, but at present their satisfactory application is confined to the more benign grades of hypertension. Wagener and Keith (1939) state that malignant hypertension does not respond satisfactorily to surgical treatment. The palliatives available are well known and need not be considered in detail. They include a daily regime with rather more rest than usual; sedatives, of which, in children, chloral hydrate in small repeated doses is probably the best; and measures for dealing with hypertensive attacks such as hypertonic salines per rectum or by the intravenous route: venesection and lumbar puncture. Venesection would of course depend on the blood picture, but a severe degree of anaemia in this condition is rare.

The mechanism. The ultimate cause or causes of this type of hypertension await discovery. Promising investigation is still in progress and Wagener and Keith (1939) have recently reviewed with great clarity the march of events from the pioneer work of Gull and Sutton to the present day. This leaves the conception of malignant hypertension as a primary spastic, and initially reversible, vascular obstruction, leading ultimately to an organic and irreversible obstruction. In other words the vascular lesions which have been accepted as the criteria of the condition, are secondary and in the nature of a reaction to strain. Whether the disease runs a truly malignant course or takes a less rapid one, would seem to depend on the extent and persistence of the angiospasms and, to a certain extent, on the adaptability of the individual vascular system concerned. The main problem at the moment is the source and nature of the initial spastic agent. Upon this point finality has not yet been reached but the work of Pickering (1938), Goldblatt (1938), Wilson and Byrom (1939) and others, point strongly to a humoral rather than a nervous mechanism.

Summary

(1) The clinical and pathological picture of malignant hypertension in childhood, as described in recorded cases, is reviewed.

(2) A full description is given of the condition occurring in a child of ten years.

(3) Present views concerning pathogenesis are considered.

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