CASE REPORT

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Pheochromocytoma and Sudden Death as a Result of Cerebral Infarction in Turner's Syndrome: Report of a Case

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ABSTRACT: Various etiologies for hypertension in Turner's syndrome, a common feature of the disorder, are well recognized. Pheochromocytoma is not among them. A young woman with Turner's syndrome, recently diagnosed with hypertension, died suddenly and unexpectedly. A hemorrhagic cerebral infarct and an adrenal gland pheochromocytoma were found at necropsy. This is the first reported case of pheochromocytoma associated with Turner's syndrome.

KEYWORDS: pathology and biology, pheochromocytoma, Turner's syndrome, hypertension, death, cerebral infarction

Developmental abnormalities in Turner's syndrome frequently include coarctation of the aorta and urinary tract malformations. Both these conditions are associated with hypertension. In addition, idiopathic hypertension is common in Turner's syndrome. A case of severe hypertension and sudden unexpected death in Turner's syndrome is presented. Hypertension proved at necropsy to have been due to an adrenal gland pheochromocytoma. Death was the result of a cerebral infarct, a recognized but uncommon complication of pheochromocytoma. We review the mechanisms of cerebral infarction in pheochromocytoma and the evidence that Turner's syndrome may predispose to neurogenic tumors such as pheochromocytoma.

Case Report

A 27-year-old white woman was found dead in her apartment on a Sunday by her father, who had repeatedly failed to reach her by telephone over the preceding 2 days. On Friday

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morning she had called the office where she worked to report that she felt ill and would not come in.

Evaluation for primary amenorrhea and short stature at 14 years of age had identified Turner's syndrome, with a karyotype of 45,X0. Her blood pressure at that time was recorded as normal. A course of exogenous hormone therapy, since discontinued, had induced secondary sexual characteristics. She was not known to smoke tobacco or to use oral contraceptive agents. While her general health had been good, a physician whom she had consulted for upper respiratory illness 3 1/2 months antemortem had identified hypertension (208/124 torr, right arm) in blood pressure measurements performed on both the upper and the lower extremities. Propranolol and enalapril were prescribed, with partial relief (blood pressure 132/102 torr, right arm, 2 1/2 weeks antemortem). Levels of catecholamines or their catabolic products in serum or urine had not been determined.

External examination found a habitus typical of Turner's syndrome; the body was short (measured length, 146 cm), the nuchal hairline was low and the neck was slightly webbed, the nipples were wide-set with minimal breast development, cubitus valgus was present and the fourth metacarpal bones were short, and the distal arms and legs appeared disproportionately bulky by comparison with the torso. Pigmented nevi were not seen. Changes of early decomposition, with slight mummification of the fingers, were apparent.

Internal examination found the heart to be structurally normal and to weigh 291 g, with a left ventricular wall thickness of 14 mm at the base. There was no evidence of recent or remote myonecrosis or of endocardial or valvular thrombosis. The aorta was normal in caliber throughout its length. The female internal genitalia were infantile, and ovaries could not be identified grossly. The lower poles of the kidneys were fused ("horeshoe kidney") ventral to the great vessels. Both ureters were duplicated throughout their lengths and followed courses ventral to the kidney. The single renal arteries were widely patent, and the renal parenchyma appeared normal. The left adrenal gland weighed 6 g and was unremarkable; the right weighed 48 g and measured 7.5 by 7 by 4.5 cm in greatest dimensions (Figs. 1 and 2). The other endocrine organs were grossly normal.

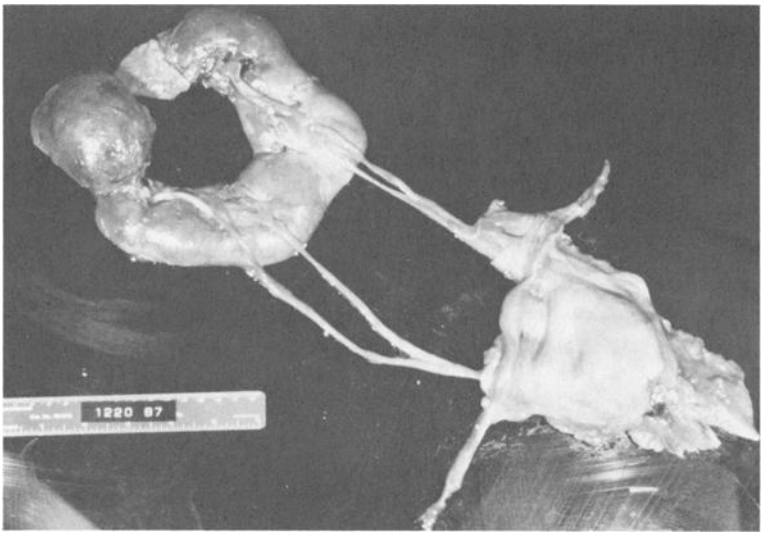

FIG. 1—*Adrenal glands, "horseshoe" kidney, duplicated ureters, bladder, and internal genital organs, dissected* en bloc. *The right adrenal gland is markedly enlarged. Grossly identifiable ovaries are absent, and the uterus and tubes are small.*

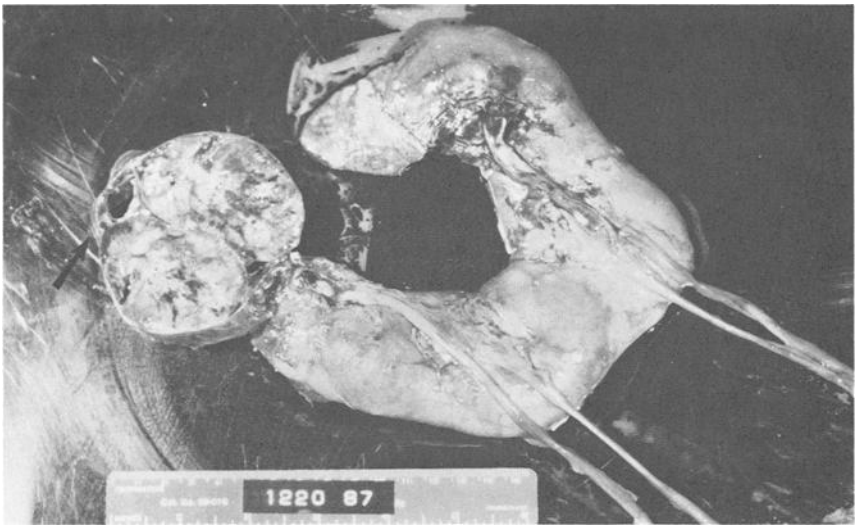

FIG. 2—*The right adrenal gland has been hemisected. Residual cortical tissue* (arrow) *can still be identified, but the majority of the gland consists of focally hemorrhagic tumor.*

On microscopy, the adrenal mass proved to be a pheochromocytoma. Sections of the tissues at the usual sites of the ovaries showed scanty fibrous stroma without germ cells. Sections of the left adrenal gland and the other endocrine organs were unremarkable. There was no evidence of renal disease. Many sections of the heart were examined; there was mild to moderate myocytic hypertrophy, but contraction bands, myocyte necrosis, and inflammation were not seen. Sections of retroperitoneal adipose tissue included prominent foci of brown fat and several small arteries that exhibited slight medial hypertrophy. Owing to the presumed length of the postmortem interval, determinations of levels of catecholamines or their catabolic products in serum or urine were not attempted. The concentrations of urea nitrogen and creatinine in vitreous humor were 102 and 1.9 mg/dL, respectively, and ionic strengths of sodium, potassium, and chloride in vitreous humor were respectively 158, 22, and 136 mEq/L. These data were interpreted as consistent with terminal dehydration.

The brain weighed 1411 g and was externally remarkable for softening of the left parasylvian cortex and white matter. The vessels at the base of the brain were intact and widely patent. Coronal sections of the brain following formalin fixation showed a hemorrhagic infarct in the distribution of the left middle cerebral artery, involving the frontal and parietal lobes, insula, and superior and middle temporal gyri (Fig. 3). The underlying white matter was demarcated and softened. The caudate nucleus also was infarcted. No hemorrhages or focal lesions were present in the remainder of the brain. On microscopy, no embolic material could be identified in any of multiple sections.

Discussion

Turner's syndrome is thought to result most frequently from loss of a paternal X chromosome from a fertilized egg, producing an embryo with a karyotype of 45,X0 [*1*]. The mortality rate of such embryos and fetuses is high [*2*], but some grow and develop normally with unrecognized Turner's syndrome until, as in this case, primary amenorrhea prompts investigation [*3*]. The constellation of associated findings and disorders frequently includes hypertension. Coarctation of the aorta has been reported in 15% of cases in children or adults [*4*],

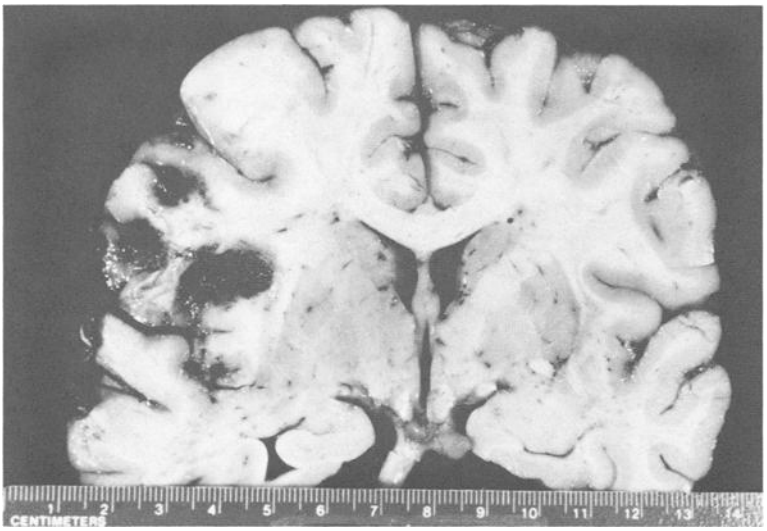

FIG. 3—*A coronal section of the cerebral hemispheres at the level of the optic chiasm shows a hemorrhagic infarct of left parasylvian gray matter. The adjacent white matter appears abnormal.*

and malformations of the urinary tract are said to be present in as many as 90% of cases [5]. Upper body hypertension is a well-known sequela of coarctation of the aorta, and urinary tract malformations may predispose to renal disease that leads to systemic hypertension. For reasons that are not clear, idiopathic systemic hypertension also is common in Turner's syndrome (30% of cases in children or adults) [4].

Pigmented nevi are frequent in Turner's syndrome (36% of cases in children or adults) [4], and instances of ganglioneuroma [6], neuroblastoma [7,8], pancreatic islet-cell tumor [9], cecal and appendiceal carcinoid tumor [10], and choroidal melanoma [11] associated with Turner's syndrome have been reported. These associations are consistent with Bolande's paradigm of neurocristopathy [12], and it has been suggested that Turner's syndrome predisposes to neurogenic tumors [10]. The literature appears to contain no instance of pheochromocytoma associated with Turner's syndrome.

Pheochromocytoma, a tumor of the sympathetic nerve chain that occurs both sporadically and in kindreds, may secrete catecholamines that produce dramatic elevations in blood pressure. Both cerebral infarction and intracranial hemorrhage are well-recognized complications of pheochromocytoma [13], often occurring in persons in their second and third decades [13,14]. In one series, 17% of autopsied patients with pheochromocytoma had experienced a hemorrhagic cerebrovascular event [15]. Platelets exposed to high concentrations of catecholamines aggregate readily [16], and pheochromocytoma has been associated with nonbacterial thrombotic endocarditis and occlusion of carotid and cerebral vessels at multiple sites [17], as well as with platelet thrombi within small intramyocardial vessels [18]. Angiography also has documented cerebral vasospasm associated with pheochromocytoma [19].

Death in this case was due to hemorrhagic cerebral infarction consistent with thrombotic or thromboembolic occlusion of the left middle cerebral artery. The wall of that vessel was normal. Although no lesions were found within the heart or cerebral vessels, thromboembolism cannot be excluded. We consider vasoocclusion more likely to have resulted from a

combination of cerebral vasospasm and platelet hyperaggregability. Hemorrhage may be presumed to have occurred on reperfusion, following resolution of vasospasm and lysis of an occluding thrombus.

This case illustrates that the possibility of pheochromocytoma should be considered when evaluating hypertension in persons with Turner's syndrome. Pheochromocytoma and other neural-crest lesions may be more frequently associated with Turner's syndrome than is recognized at present. Cerebrovascular accidents associated with pheochromocytoma may be due to vascular rupture, vasospasm, or thromboemboli, compounded by hypercoagulability. Forensic pathologists have an opportunity to contribute substantially to delineation of the natural history of hypertension and neurally derived neoplasia in Turner's syndrome, as well as to the understanding of cerebrovascular events associated with pheochromocytoma.

Note added in proof: An instance of pheochromocytoma associated with multiple cerebral and cerebellar infarcts was described after this report was accepted for publication ("Case Records of the Massachusetts General Hospital. Case 15-1988," *New England Journal of Medicine*, Vol. 318, No. 15, 14 April 1988, pp. 970-981).

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