Case Report

Intracranial Congenital Berry’s Aneurysm, Recurrent Subarachnoid Hemorrhages, and Congenital Adrenal Hyperplasia: Any Association?

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Abstract
We report the case of a 30-year-old hypertensive phenotypically female that was brought to our Acute and Emergency department obtunded with a Glasgow Coma Scale of 4/15. She developed acute subarachnoid rebleed, 43 days after the first one because of left posterior communicating artery non-traumatic saccular aneurysmal rupture. She had primary amenorrhea, poor secondary sexual characteristics, hypertension, and long-standing unexplained hypokalemia. Her work-up uncovered the presence of 46-XX karyotyping and 17-hydroxylase deficiency. The pertinent medical literature does not mention an association between intracranial Berry aneurysmal formation and congenital adrenal hyperplasia due to 17-hydroxylase deficiency. To the best of our knowledge, this is the first-ever reported case.

INTRODUCTION
Acute non-traumatic subarachnoid hemorrhage harbors high morbidity and mortality figures in addition to several challenging complications. Early aneurysmal obliteration, whether neurosurgical or endovascular, remains the best measure to prevent aneurysmal re-rupture and rebreeding, which doubles the mortality rate [1-3]. The formation of intracerebral saccular Berry’s aneurysms has been seen in patients with pseudoxanthoma elasticum, Ehler-Danlos syndrome type IV, adult polycystic kidney disease, and fibromuscular dysplasia but the pertinent medical literature does not mention an association with endocrinopathies [4-6].

CASE PRESENTATION
A 23-year-old “phenotypically female” was brought to our Acute and Emergency department by her family after collapsing at home, before one hour. She was obtunded with a Glasgow Coma Scale of 4/15 and had a blood pressure of 190/110 mmHg, a regular pulse rate of 120 beats per minute, and a respiratory rate of 21 cycles per minute. She was afebrile but had neck stiffness (and negative Kernig’s sign). She had longstanding hypertension, which was diagnosed at the age of 15 years; since then, she had been taking oral losartan (10 mg twice a day), metoprolol (50 mg twice a day), and spironolactone (50 mg twice a day). Her weight at the time of admission was 123 Kg and her height was 155 cm. The family denied a history of head trauma and illicit drug abuse. Her older sister (33 years old) had primary amenorrhea, poor secondary sexual characteristics, and hypertension, as well. The patient’s CT brain is shown is figure 1.

The patient was admitted to the intensive care unit, intubated, and mechanically ventilated. After one day, she died.

Her hypertension was diagnosed incidentally by a gynecologist, who was investigating her primary amenorrhea and poor secondary sexual characteristics; her external genitalia are of a phenotypic female. Because she was single, no vaginal examination was done but her abdominal/pelvic ultrasound revealed bilateral small polycystic ovaries and a small uterus. Karyotyping was ordered and it turned out to be 46 XX. Therefore, she was given a diagnosis of polycystic ovaries and the family had been told that her hypertension was part of her hormonal disturbances. We were unable to get her previous serum hormonal tests and their results.

A battery of tests (which was ordered by her gynecologist and general practitioner) including complete blood count and erythrocyte sedimentation rate, bleeding time, prothrombin and activated thromboplastin times, blood urea and electrolyte, liver function, serum TSH, and general urine examination did not reveal any abnormality apart from serum potassium of 2.7 mEq/L.
and serum sodium of 154 mEq/L. Aortic and renal arteries CT angiographies were unremarkable, as was her transthoracic echocardiography. Her serum potassium had been always within the range of 2.4 to 2.9 mEq/L since then, in spite of the use of spironolactone and lisinopril therapies. Her blood pressure had been always on the high side, as the patient’s mother had stated.

Before 43 days, she was admitted to our hospital because of sudden and severe panencephalic headache, drowsiness, and vomiting which turned out to be due to acute subarachnoid hemorrhage into the left Sylvian fissure (figure 2). At that time, she was drowsy and her blood pressure was 160/95 mmHg. She was hospitalized and received medical treatment.

Her longstanding hypokalemia and hypertension prompted us to investigate further, during her first hospitalization. Her serum progesterone, ACTH, FSH, and LH were elevated while serum estradiol, cortisol, dehydroepiandrosterone, and testosterone were very low. Serum 11-deoxycorticosterone and corticosterone were markedly elevated. CT angiography of the cervical and cerebral vasculature revealed a saccular aneurysm at the left posterior communicating artery of 7x3.5 mm in maximum diameter (figure 3). We informed the family about the lack of expertise in conventional 4-vessel cerebral angiography and neurosurgical/endovascular interventions in our city. Therefore, they planned to take her to Iran for further management. The patient was discharged home after 3 weeks. Her CT brain scan was unremarkable and her blood pressure was 140/75 mmHg. Her medications were candesartan 16 mg twice daily, spironolactone 50 mg twice daily, amlodipine 10 mg once daily, and dexamethasone 0.5 mg two times a day. During the past 3 weeks, prior to her second presentation, her blood pressure had been always below 140 mmHg (systolic) and 90 mmHg (diastolic). The night before the patient was supposed to travel to Iran, she got her second aneurysmal rupture.

DISCUSSION

Approximately, 20% of all strokes are hemorrhagic and subarachnoid hemorrhage (SAH) constitutes about half of these hemorrhages [7]. The majority of subarachnoid hemorrhages result from rupture of an intracranial congenital Berry’s aneurysm; trauma, ruptured arteriovenous malformations, coagulopathies and bleeding tendencies, vasculitides, illicit drug abuse, intracranial arterial dissections, and congophilic angiopathy are responsible for the rest of these subarachnoid bleeds [1].

The incidence of incidental intracranial saccular aneurysms by radiographic and autopsy series is approximately 5% of the general population and about 20-30% of them harbor 2 or more aneurysms. Non-traumatic aneurysmal SAH has a prevalence of 3-25 per 100 000 population and its mean age at onset is 55 years. Therefore most aneurysms don’t rupture. Most ruptures occur between the ages of 40-60 years; however, children and elderly people are not exempted. The incidence is slightly higher in women, which may be related to hormonal factors (and especially, estrogen deficiency) [8-10].
Longstanding systemic hypertension is a strong risk factor for aneurysmal rupture and SAH. According to Feigin and colleagues, hypertension was significantly associated with SAH risk in both the longitudinal (RR 2.5, 95% CI 2.0-3.1) and case-control studies (OR 2.6, 95% CI 2.0-3.1) [11]. Estrogen deficiency has long been suggested to be a risk factor for SAH and according to Sarti and coworkers, [12] there is a slight female preponderance of 54-61%. However, Alqra and colleagues [13] found that female hormone levels might influence the risk of SAH, but the pathophysiology of this effect and its influence on the difference in incidence of SAH between both genders remains unclear.

Mhurchu and coworkers [15] examined the relationship between menstrual and reproductive factors and the risk of subarachnoid hemorrhage, using a case-control study. They found that increased SAH risk was associated with earlier age at menarche and nulligravidity. No significant association of SAH risk was found with regularity of menstrual cycle, age at pregnancy, age at first birth, and number of births. The greatest risk, however, was for the combined effect of nulligravidity and earlier menarche (<13 years) (adjusted OR=6.37; 95% CI, 1.12 to 36.2). Ding and colleagues [16] concluded that an earlier age at menopause is associated with the presence of a cerebral aneurysm. This suggests that loss of estrogen earlier in a woman’s life may contribute to the pathogenesis of cerebral aneurysm. Therefore, these data may identify a risk factor for cerebral aneurysm pathogenesis and also a potential target for future therapies. On the other hand, Chin and coworkers [17] found that exposure to exogenous estrogen agents in women is associated with a lower frequency of cerebral aneurysms.

The patient was obese and had primary amenorrhea which prompted her gynecologist to think of polycystic ovarian syndrome. She had been prescribed oral metformin, 500 mg twice a day. No hormonal manipulation was done. However, the markedly elevated serum levels of 11-deoxycorticosterone and corticosterone are the hallmarks of 17-hydroxylase deficiency; the patient had congenital adrenal hyperplasia [18].

Therefore, all steroids requiring the action of the enzyme 17-hydroxylase for their synthesis are found in very low concentrations; 17-hydroxypregnenolone, 17-hydroxyprogesterone; 11-deoxycorticol, cortisol, dehydroepiandrosterone, androstenedione, and testosterone are all decreased or even absent. The urinary metabolites 17-hydroxylase corticosteroid and 17-ketosteroid also are decreased or absent. Because of lack cortisol section, serum ACTH is elevated. Serum gonadotropins (FSH and LH) are elevated secondary to deficient sex steroid production by the gonads. Serum estrogens and urinary estrogens are low while serum pregnenolone and progesterone levels are elevated [19,20].

Serum aldosterone and plasma renin activity are usually low. 11-deoxycorticosterone-mediated mineralocorticoid activity results in sodium retention (and hypokalemia) and plasma volume expansion, with subsequent suppressed renin and aldosterone levels in most untreated patients. Therefore, systemic hypertension ensues [21-23].

Because serum levels of corticosterone are elevated, adrenal insufficiency does not occur. One must emphasize that virilization (and development of ambiguous genitalia) does not occur in 46 XX patients with 17-hydroxylase deficiency and that unless hypertension is discovered, those females may have no complaints or findings until reaching puberty. The gonads are unable to secrete estrogen and/or androgens and the adrenals cannot compensate for this deficiency; therefore, such patients present with primary amenorrhea, delayed puberty, and lack or secondary sexual characteristics. Approximately, 85% of patients are hypertensive at the time of diagnosis and hypokalemia is common (but is rarely symptomatic) [24-26].

Our patient has congenital adrenal hyperplasia due to 17-hydroxylase deficiency; a rare genetic disorder of steroid biosynthesis that results in decreased synthesis of glucocorticoids and sex steroids and increased production of mineralocorticoid precursors. More than 80 different genetic mutations of the CYP17A1 gene (the culprit gene) have been described worldwide in patients with 17-hydroxylase deficiency [27]. We have no facilities for doing genetic testing.

This congenital adrenal hyperplasia was the culprit behind her longstanding hypertension, hypokalemia, lack secondary sexual characteristics, and primary amenorrhea. The presence of her intracranial Berry’s aneurysm might have been a mere coincidence. Otherwise, her longstanding hypertension and estrogen deficiency might well have played a role in the formation of her intracranial aneurysm, rupture, and re-rupture.

CONCLUSION

The patient’s primary amenorrhea, hypertension, and hormonal disturbances were wrongly attributed to polycystic ovarian syndrome. The pertinent medical literature does not mention an association between intracranial Berry’s aneurysmal formation (and rupture) and congenital adrenal hyperplasia due to 17-hydroxylase deficiency. To the best of our knowledge, this is the first-ever reported case.

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REFERENCES


