

Cerebral Aneurysm and Aortic Coarctation in a 46, XY Female. Is it Causal or Coincidental?

Sun-Min Ju, M.D., Hyeong-Joong Yi, M.D., Yong Ko, M.D., Kwang-Myung Kim, M.D.

Department of Neurosurgery, Hanyang University Medical Center, Seoul, Korea

Most vascular disorders tend to affect both the brain and heart, and among them, a clinical syndrome constituting cerebral aneurysm and aortic coarctation (AC) has been well recognized. Persistent hypertensive impact to the cerebral vasculature with developmental anomaly of the neural crest, precursor of ectomenchymal, would be closely associated with development of the cerebral aneurysm in AC. Gonadal steroid hormone, a guardian of the cardiovascular system, has been known for its protective effects on the vascular wall. Gonadal steroid hormone (androgen) insensitivity such as 46,XY female syndrome may increase the risk of hypertension and subsequent vascular anomalies. The authors report on a 46-year-old 46,XY female patient with AC who underwent surgical clipping of the ruptured cerebral aneurysm. Clinical implications and proposed pathogenetic mechanisms of aneurysm in this intersex syndrome are presented and discussed.

KEY WORDS : Aneurysm · Cerebral · Aortic coarctation · Hypertension · Steroid hormone · Gonadal · Intersex syndrome.

Introduction

Cerebral aneurysm in a patient with AC is highly connected with secondary hypertension induced by AC, in the similar way the polycystic kidney disease gave rise to the cerebral aneurysm¹⁶⁾. Risks of development of the intracranial aneurysm and cervicocephalic arterial dissection were reported to be high in patients with congenital heart disorders, and these conditions were sufficiently explained by the embryological defect of the cranial neural crest which is responsible for sprouting of carotid arteries, aortic arches and ductus arteriosus^{5,7)}.

A syndrome of 46,XY female is an infrequent clinical and psychosexual complex, characterized by expression of female phenotype, while by expression of male karyotype¹³⁾. This disorder also can be called "androgen insensitivity syndrome (AIS)" or "testicular feminization syndrome (TFS)", because of its peripheral defect of sex hormone activity. Since gonadal steroid hormone is a strong protector of the cardiovascular system, its dysfunction could result in various patterns of hypertensive cardiac and non-cardiac vascular lesions^{3,19)}.

- Received : May 27, 2004 • Accepted : October 5, 2004
- Address for reprints : Hyeong-Joong Yi, M.D., Department of Neurosurgery, Hanyang University Medical Center, #17 Haengdang-dong, Seongdong-gu, Seoul 133-792, Korea
Tel : 02) 2290-8499, Fax : 02) 2281-0954
E-mail : hji8499@hanyang.ac.kr

We report a case of cerebral aneurysm in a 46,XY female patient with the AC. To our knowledge, association of cerebral aneurysm and AC in a 46,XY female syndrome has not been reported. And therefore, this is the first case report assuming pathophysiology for the unique combined cerebral and cardiac vascular lesions.

Case Report

This 45-year-old left-handed woman presented with repeated spells of syncopal attacks and dysphasia. Gradually progressed speech disturbance and loss of consciousness happened once or twice in a day for 1 week. About one year ago, she had been hospitalized for evaluation of intermittent chest pain and collapse during walking, and intractable high blood pressure. After full work up, she was recommended to operate on the AC, but surgical repair was refused at that time. Neurological examination at admission showed drowsy mentality, left abducens palsy, motor dysphasia, and left hemiparesis (grade 3). On physical examination, she showed disfiguring complexion, including hypertelorism, lengthy philtrum, small earlobes and prognathism. She was measured 162cm in height, 55kg in weight, and showed no pubic or axillary hair. The blood pressure of each arm was measured different. The femoral pulse on both sides was feeble and delayed. Echocardiography showed moderate left ventricular hypertrophy, decreased apical wall motion, and almost total blockage of

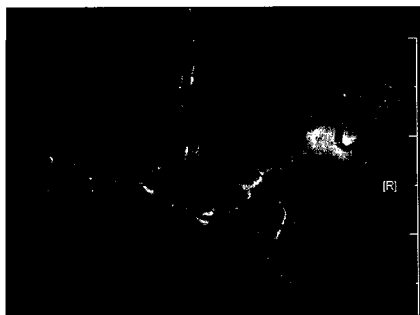


Fig. 1. Preoperative computed tomographic angiography shows a large aneurysm at the right middle cerebral artery bifurcation (18×13mm) and slightly vasospastic M1 segment.

ography revealed a large aneurysm (18×13mm) at the bifurcation of the right middle cerebral artery(MCA) (Fig. 1).

She underwent microsurgical obliteration of the aneurysm via a right transsylvian approach under a normotensive general anesthesia. Aneurysmal neck was not easily separated from the encircling M2 segments, but it was isolated from the cerebral circulation by 5 clips. Postoperatively, hypervolemic hemodilution therapy was ensued. She showed mild dysphasia and moderate degree of motor weakness on the left extremities (grade 2/3). Angiography, on the 3rd postoperative week, showed successful clipping of the aneurysm, and aortography also displayed AC and concurrent abundant collateral vascular channels around the subclavian arteries (Fig. 2).

Meanwhile, peripheral blood was sent to the laboratory to uncover possible genetic abnormality to find karyotype of 46,XY (Fig. 3). TFS¹⁶ was strongly suggested, and then, gynecological consultation was inquired. Her breast development was normal and inguinal hernia was not observed. Since her suspicious menarche at 18 years old, she had not experienced any further menstrual bleeding, consequently, she has been suffering infertility despite 14 years of marriage. Pelvic sonogram discovered shallow vagina (4.5cm), indistinguishable cervix and uterine body, and atrophied uterus (2.7×1.5cm) of blind pouch, as well as no residual ovaries. Tiny remnant testes were also suspected. Circulating plasma level of gonadal steroid hormones was estimated. Testosterone (3.46ng/ml) was elevated and further escalated (8.15ng/ml) after injection of human chorionic gonadotrophin, whereas estrogen remained low level. Peripheral blood was also sent to detect the androgen receptor (AR) mutation. And, the mutant allele was identified by polymerase chain reaction(PCR) amplification of the short tandem repeat (CAG)_n, highly polymorphic in the population, present in the first exon of the AR gene (Xq11.2-12).

the descending aorta. Magnetic resonance imaging of head disclosed an oval signal void lesion as well as subarachnoid hemorrhage of subacute stage at the right deep sylvian fissure. Computed tomographic angi-

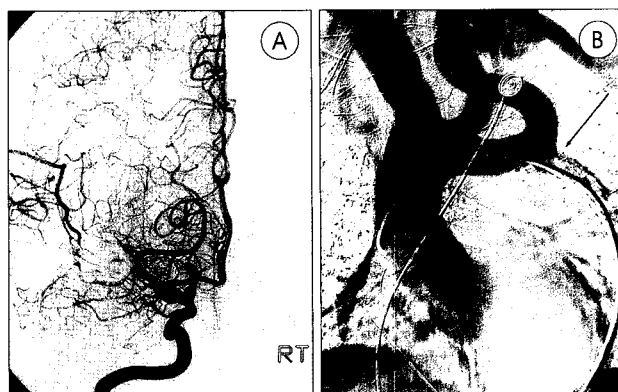


Fig. 2. A : Postoperative right carotid angiogram, anteroposterior view, shows complete obliteration of the aneurysmal sac while no residual vascular malformations. B : Aortography exhibits almost total blockage of the descending aorta just distal to the ductal entry and abundant collateral vascular channels around the subclavian arteries.

Complete TFS was confirmed, and exploratory laparoscopic biopsy of inguinal testes was scheduled to detect and remove potential malignant degeneration of gonads.

However, she denied any further invasive procedure with writing down "informed refusal" about this. After 2 months of rehabilitation, she went back home and has been waiting for surgical repair of the known AC.

Discussion

The incidence of AC with cerebral aneurysm ranged only 0.19% to 1.9%^{2,7)}. Conversely, the incidence of aneurysms in individuals with postductal AC, adult type, is sufficiently high enough (as high as 50%) to render this association a definite clinical syndrome^{8,16)}. Because AC and polycystic kidney disease are the only two congenital abnormalities that usually related to severe secondary hypertension, association with the aneurysm is more plausibly attributed to the presence of hypertension^{4,16)}. The hypertension seems to be the most important single causative factor, when considering relation between cerebral and cardiovascular anomalies, irrespective of their underlying etiologic diseases.

Most vascular diseases appear to have a tendency to affect both the heart and the brain⁷⁾. Neural crests produce both cardiac and non-cardiac structures, and cranial parts of neural crests give rise to ectomesenchyme. They populate the pharyngeal arches III, IV and VI, in which are formed the carotid arteries, the aortic arch, and the ductus arteriosus, respectively^{1,5,7)}. After partial ablation of the cardiac neural crest in the chicken embryo, Rosenquist et al demonstrated

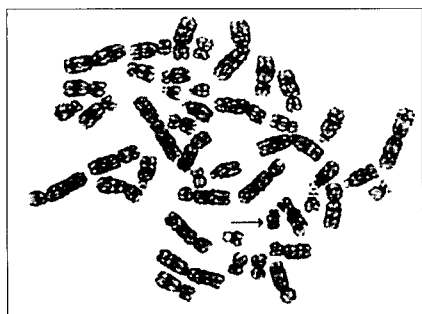


Fig. 3. Karyotyping obtained from phytohemagglutinin stimulated T-lymphocyte culture of metaphase chromosome with Giemsa banding technique, displays 46,XY. Arrow indicates the Y chromosome.

coarsening and disarray of elastin fibers (impairment of elastic matrix in the great vessels)⁹, as well as Type I and III collagen in the arterial wall¹⁰. The phenotype of each heritable connective tissue disorder is determined by the

organ distribution of the affected extracellular matrix protein¹¹, and furthermore, the primary arteriopathies of the central nervous system also may result from a defect in a single component of the extracellular matrix constituting the vascular wall. Schievink et al¹² reported that patients with a variety of congenital heart disorders may be at an increased risk of intracranial aneurysm development and cervicoccephalic arterial dissection. In this aspect, embryological defect of the neural crest seems to be the common pathogenic factor explaining the association of cerebral and cardiovascular abnormalities.

Gonadal steroid hormones are known to play an important role in normal cardiovascular regulation and in the pathogenesis of cardiovascular disease. However, their mode and site of action are not simple or straightforward. Estrogen is thought to exert vascular reactivity on the endothelial nitric oxide function and vascular smooth muscle^{14,19}. However, the effects of testosterone on the regulation of the endothelial and vascular smooth muscle have been far less known, and attenuation of vasopressin-induced vasoconstriction or adrenergic enforcement has only been recognized until now^{6,14}. In recent experiment using testicular feminized mouse, AR deficiency and altered plasma sex hormone showed a marked diminution in endothelial function and impaired vascular calcium channel activity. Therefore, AR deficiency and eventual alteration of circulating androgen hormone (testosterone) may be strong contributory factors in development of hypertension^{3,15}. We are not sure that resistance of the sex hormone *per se*, would be the causative factor of AC and cerebral aneurysm. Instead, persistent hypertensive threat by the AC to the cerebral vascular trees would result in formation of the cerebral aneurysm.

TFS or AIS is an infrequent genetic intersex syndrome characterized by total or partial resistance of end organs to the

peripheral effect of androgens due to the nonfunctional AR. Of these, complete form (CFTS) manifests both male karyotype (46,XY) and female phenotype of the external genitalia, instead of ambiguous phenotype as shown in incomplete form (ITFS). The female genitalia are attributable to the complete absence of testosterone effect in spite of high plasma level of testosterone¹³. Findings compatible with the CFTS in the present case are male karyotype, female phenotype (female external genitalia, whereas infertility and lack of second sex characters), high plasma level of testosterone and presence of AR gene mutation. Facial disfigurement, severe hypertension, late-onset AC and cerebral aneurysm, however, are unusual features compared to the typical CFTS. The clinical and prognostic implications of the CFTS, on the other hand, had been mainly directed to the psychosexual aspects (frustrated sexual function, confused gender identity, fear of infertility), instead of physical aspect. Accordingly, those affected by CFTS should be raised as female^{17,18}. The incidence of malignant transformation of gonads is not negligible (20%) and may approach 33% at the age of 50, therefore, laparoscopy and gonadal biopsy is mandatory to prevent and detect this malignancy. For these reasons, management of patients with CFTS should be comprehensive, and one should inform patients about the problems of amenorrhea, infertility, risk of malignancy, and need for gonadectomy¹³. On the contrary to our belief, only one patient exhibited stroke, while almost half of them presented with obesity, osteoporosis, and hypertension among 14 subjects with CFTS, according to the clinical series of Wisniewski et al¹⁸. So, this case report added the second rare occasion of stroke in these patients.

Conclusion

To the present, experimental and clinical evidence of CFTS accompanying cerebral and cardiovascular anomalies has not been widely confirmed. Therefore, assuming their association according to this single case report would be highly speculative. However, severe secondary hypertension can exert the cerebral circulation especially in defective androgen hormone milieu, which can lead to development of cerebral aneurysm, it is important to recognize the possibility of cerebral aneurysm in such patients.

References

1. Bergwerff M, Verberne ME, DeRuiter MC, Poelmann RE, Gittenberger-de Groot AC : Neural crest cell contribution to the developing circulatory system. Implications for vascular morphology? *Circ Res* **82** : 221-231,

Aneurysm and Aortic Coarctation

- 1998
- Fukuda H, Sako K, Yonemasu Y : Coarctation of the descending aorta with aneurysm of the anterior communicating artery. **Surg Neurol** **23** : 380-382, 1985
 - Jones RD, Pugh PJ, Hall J, Channer KS, Jones TH : Altered circulating hormone levels, endothelial function and vascular reactivity in the testicular feminised mouse. **Eur J Endocrinol** **148** : 111-120, 2003
 - Kang MS, Park IS, Lee CH, Hwang SH, Jung JM, Han JW : Aneurysms of the Proximal Segment of the Middle Cerebral Artery. **J Korean Neurosurg Soc** **35** : 70-74, 2004
 - Kappetein AP, Gittenberger-de Groot AC, Zerman AH, Rohmer J, Poelmann RE, Huysmans HA : The neural crest as a possible pathogenetic factor in coarctation of the aorta and bicuspid aortic valve. **J Thorac Cardiovasc Surg** **102** : 830-836, 1991
 - McConnaughey MM, Iams SG : Sex hormones change adrenoceptors in blood vessels of the spontaneously hypertensive rat. **Clin Exp Hypertens** **15** : 153-170, 1993
 - Mercado R, Lopez S, Cant C, Sanchez A, Revuelta R, Gmez-Llata S, et al : Intracranial aneurysms associated with unsuspected aortic coarctation. **J Neurosurg** **97** : 1221-1225, 2002
 - Park SC, Neches WH : The neurologic complications of congenital heart disease. **Neurol Clin** **11** : 441-462, 1993
 - Rosenquist TH, Beall AC, Mdis L, Fishman R : Impaired elastic matrix development in the great arteries after ablation of the cardiac neural crest. **Anat Rec** **226** : 347-359, 1990
 - Rosenquist TH, Mdis L : Spatial disorder of collagens in the great vessels, associated with congenital heart defects. **Anat Rec** **229** : 116-124, 1991
 - Schievink WI, Michels VV, Piepgras DG : Neurovascular manifestations of heritable connective tissue disorders : A review. **Stroke** **25** : 889-903, 1994
 - Schievink WI, Mokri B, Piepgras DG, Gittenberger-de Groot AC : Intracranial aneurysms and cervicocephalic arterial dissections associated with congenital heart disease. **Neurosurgery** **39** : 685-690, 1996
 - Shah R, Woolley MM, Costin G : Testicular feminization syndrome : the androgen insensitivity syndrome. **J Pediatr Surg** **27** : 757-760, 1992
 - Stallone JN : Sex differences in nitric oxide-mediated attenuation of vascular reactivity to vasopressin are abolished by gonadectomy. **Eur J Pharmacol** **259** : 273-283, 1994
 - Stallone JN, Salisbury RL, Fulton CT : Androgen-receptor defect abolishes sex differences in nitric oxide and reactivity to vasopressin in rat aorta. **J Appl Physiol** **91** : 2602-2610, 2001
 - Stehbens WE : Etiology of intracranial berry aneurysms. **J Neurosurg** **70** : 823-831, 1989
 - Wisniewski AB, Migeon CJ : Long-term perspectives for 46,XY patients affected by complete androgen insensitivity syndrome or congenital micropenis. **Semin Reprod Med** **20** : 297-304, 2002
 - Wisniewski AB, Migeon CJ, Meyer-Bahlburg HF, Gearhart JP, Berkovitz GD, Brown TR, et al : Complete androgen insensitivity syndrome : long-term medical, surgical, and psychosexual outcome. **J Clin Endocrinol Metab** **85** : 2664-2669, 2000
 - Zhang A, Altura BT, Altura BM : Sexual dimorphism of vascular smooth muscle responsiveness is dependent on anions and estrogen. **Steroids** **56** : 524-526, 1991