Agenesis of the Corpus Callosum in Turner's Syndrome: Report of a Case and Review of the Literature

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Abstract- Turner's syndrome (TS) is a genetic disorder caused by loss of entire or a substantial part of the X-chromosome, but association with central nervous system (CNS) abnormalities is rarely reported. A 32-year-old female with TS was found to have agenesis of the corpus callosum (ACC) and various clinical features including coarctation of aorta, hypertelorism, small jaw, short and webbed neck, cubitus valgus, and absence of the uterus. Karyotype analysis revealed X monosomy cell line (45, X). There have been only three other cases of TS associated with ACC. High prenatal lethality of TS fetuses with congenital CNS malformations may decrease the incidence of this association. Neuropsychological studies showed a normal intelligence neither prominent learning disability nor discrepancy between verbal and non-verbal items.

Key Words: Agenesis of the corpus callosum, Chromosomal study, CNS abnormality, Turner's syndrome

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INTRODUCTION

Turner's syndrome (TS) is a female genetic disorder, in which all or a substantial part of the X-chromosome is deleted. The clinical characteristic features include short stature, webbed neck, and gonadal dysgenesis. Some patients have cardiovascular, renal, and skeletal anomalies[1]. Mental retardation is not a prominent feature, but malformations in the central nervous system (CNS) have been reported in patients with TS[2-6]. There have been only 3 TS patients who have agenesis of the corpus callosum (ACC)[2,3,6]. The mechanisms of the association between TS and ACC remain unclear, although it may be coincident. This report describes a 32-year-old female patient who incidentally was found to have both TS and ACC.

CASE REPORT

The patient, a 32-year-old dextrous woman, was the second child of non-consanguineous parents. The patient was delivered smoothly at 39 weeks with a birth weight of 3 kg but without perinatal distress. There was no history of abuse of drugs, alcohol, or cigarettes by her mother during the pregnancy. However, low body weight and short stature were noted at 4 months.

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Delayed developmental milestones including walking and speaking were not present until one year later. The patient's family had no history of seizures, and other neurological disorders. She has never had a menstrual period and absence of the uterus was found at teenage.

At examination, her body height was 144 cm, and body weight was 38.5 kg. Physical examination showed that she had a short and webbed neck, hypertelorism, low-set hairline, small jaw, cubitus valgus, multiple pigmented nevi, and short stature. There was no finger or nail anomalies, single palmar crease, nor abnormal muscle tone.

She was found to have hypertension, but did not pay much attention until 3-4 years ago. She started to take anti-hypertensive medications. In March 2007, she visited a cardiologist for young onset hypertension. Computed tomography angiography showed coarctation of the aortic arch. One episode of loss of consciousness with a generalized tonic-clonic convulsion occurred soon after a subcutaneous injection of lidocaine, before cardiac catheterization. Ictal symptoms lasted for 1 minute, and she regained consciousness several minutes later. Brain computed tomography showed complete agenesis of the corpus callosum. Neurological examinations identified dyscalculia only with four errors out of five serial subtractions of 7 from 100. Electroencephalography (EEG) revealed no epileptic activities nor background abnormalities. There were no classic split-brain symptoms including visual alexia for stimuli from to the left visual field or tactile anomia and dyspraxia of the left hand.

Blood tests showed normal levels of blood cell counts, C-reactive protein, glucose, electrolytes, creatinine, thyroid function, and homocysteine. Conversely, there were a slight elevation of hepatic enzymes: aspartate aminotransferase = 44 U/l (normal range, 0-34 U/I), and alanine aminotransferase = 41 U/l (normal range, 0-36 U/I), and an elevated anti-thyroid peroxidase antibody level 500.8 IU/ml (normal range, <12 IU/ml). Sex hormonal tests identified normal levels of prolactin and luteinizing hormones with an elevated level of follicular stimulating hormone 91.8 mIU/ml (normal range, 3.6-13.7 mIU/ml), and a diminished estrogen level 13.3 pg/ml (normal range, 37-200 pg/ml). Karyotype analysis confirmed the presence of X monosomy cell line (45, X). Pelvic ultrasound demonstrated two normal-sized ovaries but an absent uterus.

Brain magnetic resonance images (MRI) was further performed and revealed virtually total agenesis of the corpus callosum with sparing of a tiny genu. A slightly enlarged, high riding third ventricle interposed between the lateral ventricles that displaced laterally. Marked dilatation of the occipital horns appeared with small, parallel, widely separated frontal horns (Fig.).

The neuropsychological examinations disclosed no discrepancy between verbal and non-verbal items on the

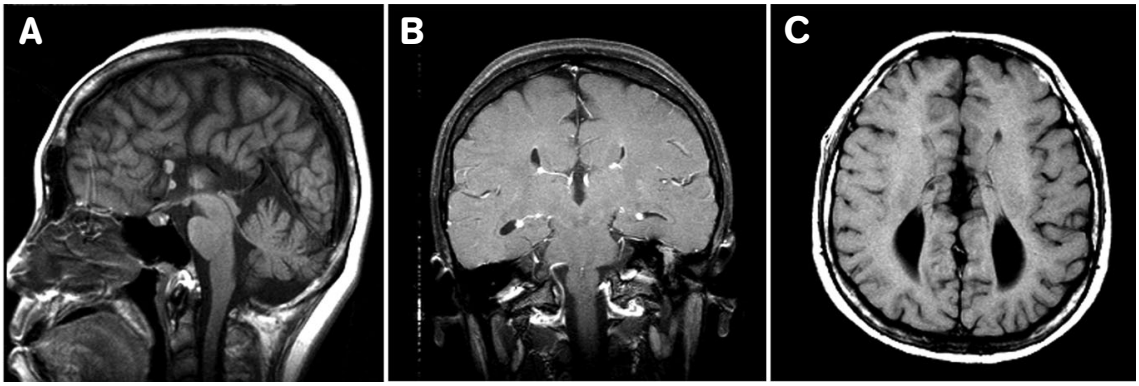

Figure. Brain MRI scans in the present patient showing absence of the corpus callosum and abnormal pattern of gyri radiation (sagittal plane, A), abnormally high-riding third ventricle interposed between the lateral ventricles, making them laterally displaced (coronal plane, B), and dilatation of the occipital horns with small, parallel, widely separated frontal horns (axial plane, C).

WAIS-III. In verbal subsets, the scores were 9 in similarities, 4 in arithmetic, and 9 in digit span, while in performance subsets, the scores were 10 in picture completion, 3 in digit symbol-coding, 7 in block design, 12 in matrix reasoning, and 7 in picture arrangement. Her full intelligence quotient (IQ) was 83, with a verbal IQ score 85 and a performance IQ score 84.

DISCUSSION

The patient had demonstrated TS and virtually complete ACC, with hypertelorism, small jaw, short and webbed neck, cubitus valgus, absence of the uterus, and coarctation of aorta. In females, TS is the most common sex abnormality, and several studies including neuropsychological tests, EEG, MRI, and neuropathology postulated an important role for X-chromosome genes in the development and specialization of brain structures and function[5,7-10]. Little has been reported to date regarding the association between TS and CNS malformations, probably due to a high incidence of chromosomal abnormalities with spontaneous abortions from 50 to 80% of all pregnancy losses and a relatively little chance for fetuses with CNS malformations to survive[11,12]. Radiological and pathological abnormalities in TS included cerebral and cerebellar atrophy, heterotopic gray matter, pachygyria and microgyria of the cortex, reduction of parietal lobe volume, bilateral perisylvian atrophy, and altered callosal and posterior fossa structures[5,10,13,14].

Table. *Clinical features of 4 patients with Turner's syndrome and absence of the corpus callosum*

	Araki et al.[2] 1987	Kimura et al.[3] 1990	Abd et al.[6] 1997	Lee et al. 2008
Genotype	45,X	45,X	45,X/46,X,r(X) mosaic	45,X
Short stature	+	+	+	+
Motor developmental delay	+	+	+	+
Renal anomaly	+	+	-	-
Hashimoto's thyroiditis	+	-	-	-
Coarctation of aorta	-	-	-	+
Facial features				
Hypertelorism	-	+	+	+
Low-set ears	-	+	-	-
Highly arched palate	-	+	-	-
Wide mouth	-	-	+	-
Other dysmorphic features				
Short fingers	-	+	-	-
Single palmar crease	-	-	+	-
Cubitus valgus	-	+	+	+
Low hairline	+	-	-	+
Webbed neck	-	-	-	+
Multiple pigmented navi	+	+	-	+
Neurological features				
Optic nerve hypoplasia	-	+	-	-
Hypotonia	-	+	-	-
Generalized joint laxity	-	-	+	-
Electroencephalography	NA	Background asymmetry	NA	Normal
Seizure	-	-	-	+
Learning disability	Normal	Profound	Mild	Normal

NA: not available; +: present; -: absent.

Review of the literature revealed that there have been only three patients with both TS and ACC (Table)[2,3,6]. All of four patients had short stature, ACC, and motor developmental delay. This patient and the patient of Araki had no significant neurological findings or mental retardation, but the other two had learning disability. Neuropsychological symptoms in patients with TS include learning disability, poor performance IQ but better verbal IQ, impaired visual-spatial processing and visual-perceptual abilities[15]. In our patient, visual alexia with stimuli from the left visual field was not found. In addition, tactile anomia and dyspraxia were not detected from the left hand. The clinical features in our patient is different from patients with acquired disconnection syndromes. Whether the residual genu of the corpus callosum of our patient may help maintain interhemispheric connection is an interesting question. Corpus callosum function in humans has been investigated in "split-brain" patients, whose callosum and other cerebral commissure including the anterior commisure were damaged surgically for the treatment of epilepsy, i.e. surgical commissurotomies[16]. Individuals with commissurotomy manifest a 'disconnection syndrome' that included an absence of callosal transfer of sensory information, and a disturbance of bimanually coordinated motor activity[17]. Overall, patients with ACC had a better, interhemispheric integration than patients with commissurotomy on many forms of visual and tactile information[18]. Different from typical cerebral commissurotomy, anterior commissure is not surgically damaged in patients with callosotomy. In addition, the relative importance of age at onset of defect in the corpus callosum for interhemispheric transfer (IHT) has been illustrated[19]. The patients with early callosotomy and children with ACC showed little evidence of a disconnection syndrome in IHT tests with simple tactile information, whereas those with callosotomy in late adolescence and adulthood showed marked transfer deficits[19]. This suggest that remarkable neural plasticity and compensatory mechanisms of alternative neural pathways may play an important role. Further investigation of more sensitive measures including visuo-motor interhemispheric transfer, arithematic tests and functional imaging may be helpful in our patient.

On the other hand, higher incidence of cardiovascular diseases, such as congenital cardiac anomalies (around 30% of patients), hypertension, ischemic heart diseases, and aortic dissection were found in previous studies[1]. Our patient had young onset hypertension, and coarctation of aorta that were not mentioned in the other 3 reports.

ACC is a rare brain malformation. The corpus callosum is the major pathway of association fibers between the two cerebral hemispheres. Its development occurs between approximately 8 and 17 weeks gestation, sequentially forming lamina terminalis, lamina reunions of His, sulcus medianus telencephali medii, massa commissuralis, and finally, the definite corpus callosum[20]. Disturbed embryogenesis during this period can lead to its absence or other abnormalities. The precise incidence of agenesis of the corpus callosum is unknown, with the literature providing wide estimates depending on the population studied[21]. A study by Swayze et al.[22], reported 5 cases out of 7000 brain MRI scans (about 0.07%) have partial or complete agenesis of the corpus callosum in a United States radiology centre for varying non-emergency clinical reasons. However, postmortem perinatal death studies gave incidences ranging from 0.004% to 0.0075%[23]. Anomalies of the corpus callosum often present as a part of chromosomal syndromes (trisomy 8,13,18, or 21) as well as a number of X-linked syndromes, associated with Chiari malformation, encephalocele, and anomalies of neuronal migration such as schizencephaly, lessencephaly, pachygyria, and heterotopias[24,25]. ACC was also reported to be associated with other cerebral or extra-CNS malformations, with extremely variable clinical features, ranging from asymptomatic to severe mental retardation. But there is a general agreement that isolated ACC is per se asymptomatic, with the symptomatology mainly determined by the associated cerebral malformations[26-30].

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