Olgu sunumu / *Case report*

A possible new syndrome (SINAN Syndrome) with situs inversus totalis, congenital hairy nevus, anxiety disorder and congenital nystagmus

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ABSTRACT

*This case is a clinical table, which is firstly described in the literature. In our case, Cardinal symptoms were (**S**itus), (**I**nversus totalis), (**N**evus), (**A**nxiety), and (**N**ystagmus). As the capital letters of the cardinal symptoms code the name of famous Turkish architect, we would like to name this possible new syndrome as SINAN Syndrome. Regarding cardinal symptoms, we predict that SINAN syndrome carries a combined autosomal recessive and X-linked transmission together.* ***(Anatolian Journal of Psychiatry 2012; 13:306-309)***

Key words: *Anxiety, dextrocardia, situs inversus totalis, nevus, nystagmus*

Yeni bir olası sendrom: SİNAN Sendromu

ÖZET

*Bu olgu literatürde ilk kez tanımı yapılan bir klinik tablodur ve bu tablonun kardinal belirtileri, (**S**itus) (**I**nversus totalis), (**N**evüs), (**A**nksiyete) ve (**N**istagmus)tur. Söz konusu belirtilerin baş harfleri tarihteki bir Türk Mimarı'nı kodladığı için söz konusu tabloyu 'SINAN Sendromu' olarak adlandırmayı uygun bulduk ve olası yeni sendromun otozomal çekinik ve X'e bağlı bir geçişi beraber gösterdiğini düşündük.* ***(Anadolu Psikiyatri Derg 2012; 13:306-309)***

Anahtar sözcükler: *Anksiyete, dekstrokardi, situs inversus totalis, nevüs, nistagmus*

INTRODUCTION

Situs inversus is a condition in which organs of the chest and abdomen are arranged in a perfect mirror image reversal of normal positioning. In about 1/8000-20000 people, organs in the chest and abdomen are arranged in opposite position, i.e. heart is on the right and liver, spleen and three-lobed lung are on the left. This arrangement, called situs inversus, is a perfect mirror and relationship between the organs does not change. Therefore various functional problems occur.

Becker nevus syndrome is a rare disorder characterized by pigmented hairy skin patch associated with skin, muscle or bone defects on the same side of the body with skin lesion.[1] Another rare disorder is CHILD syndrome, which is characterized by congenital hemidysplasia with ichthyosiform nevus and limb defects.[2] Here, we present a case with anxiety disorder and gaze-evoked nystagmus, displaying full characteristics of situs inversus totalis in addition to several features of Becker nevus syndrome and CHILD syndrome.

CASE

Male Turkish patient, 28 years old. He is working as a teacher after graduating from university; he' is not married and is living with his family, including a 10-year older brother.

During previous six months, he had complaints of intense anxiety, restlessness, fear of future, ambiguity, tenseness in whole body, contractions, insomnia, unhappiness, inability to enjoy life, loss of interest in job and in people, amnesia, decrease in desire to talk and intermittent suicidal thoughts. He was hospitalized and treated in psychiatry clinic from March 2010 to May 2010.

Patient was hospitalized with a diagnosis of anxiety disorder and venlafaxine treatment was initiated. In the second week of treatment, generalized abdominal cramps developed and generalized abdominal tenderness, defence and distention were found in examination. Leucocytosis and mild increase in hepatic enzymes were observed in biochemical evaluations and fever was determined as 37°C. Biliary sludge was seen

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in the lumen of gall bladder in abdominal ultrasonography. Diagnostic laparoscopy did not reveal a pathological finding since abdominal pain was thought to be associated with venlafaxine. Treatment was tapered and stopped, followed by disappearance of abdominal cramps.

Patient's history revealed treatment for repetitive 3-4 sinusitis attacks between 12-16 years of age, severe headaches for 1-2 months when he was 18; he was treated for urinary calculus and nephritis at the age of 22 and for bronchitis at the age of 24.

Psychiatric examination: Patient was conscious, cooperative and orientated. Psychomotor activity was diminished; he was speaking slowly in a low tone. Amount of speech was normal. Affect was anxious, mood was depressive. Cognitive functions were normal with no hallucinations or delusions. Suicidal thoughts were present. He had over valued opinions on being unsuccessful as a teacher and occasional thoughts of being spied in crowded environments. Minnesota Multiple Personality Inventory revealed a defensive attitude, conflicts of dependence-independence and anxiety was determined in Rorschach with unconditioned stimuli.

Physical examination: Positive findings in physical examination were as follows: Patient was walking with a slightly backward-bent posture (20 degrees). A hairy nevus (1x1 cm) was present in junction of left shoulder and neck, with a similar nevus in the same location of mother; patient also had a hairy nevus (3,5x5 cm) on external side of left forearm (Image 1). Prominent hyperextension was observed in toes. Bilateral maxillary bones were hypoplastic. An indecisive ridge pattern was present on fingertips. Palmar simian lines were faint. Sternum was found to be 1.5 cm shorter. Bluish sclera and broad tongue were present. External ear was asymmetric. Left ear lobe was slightly lower, as compared to right side. No hypogenitalism was observed.

Neurologic examination: There was no pathology in cranial nerves and no rigidity was observed in neck; pupillary isochoric IR+/+, muscle tone was normal in four extremities, bilateral Babinski were negative, bilateral DTRs were mildly increased and cerebral tests were normal. No sensorial defect was found at any level, sense of position was normal; sense of vibration was 21 sec. in lower extremities and 22 sec. in sternum. Bilateral fundoscopy was normal. No findings related to retinitis pigmentosa were determined in optic fundus examination. Nystagmus evoked by abduction was observed in both eyes (gaze-evoked nystagmus). Same type of nystagmus was also found in a number of family members, related to patient's mother. Extension upon abduction on the right side and mild intension upon abduction on the left side were observed.

Family story: Mother was 60 years old and had diabetes mellitus for 10 years. Her first child deceased when he was 6 months old. Her second child is 10 years older than our patient and he is healthy. She also had 3 abortus. There is no history of psychiatric disease of the mother and the whole family. Gaze-evoked nystagmus was ob served in the mother, aunt and great aunt of mother. Nail dsyplasia was observed also in the mother. Telengiectasia on left leg and left foot was pre sent in the mother. Mother had four abortus experience. On the other hand one of her babies died when she was six months and there were not any medical explanation.

Laboratory tests: Electoencephalography was within normal limits. Cranial computerised tomography was also within normal limits; in cranial magnetic resonance imaging, 3 hyperintense foci with a diameter of 2-3 mm. were observed in frontal lobes, subcortical white matter in T2-Flair series.

Neurocognitive tests revealed mild disturbance in sustained attention along with mild defects in verbal memory. Verbal memory disorder was assessed, as frontal type, which was spontaneous memory phase, was defective while recognition memory phase was normal. Edinburgh Lateralization Test revealed strong left-handedness. In spermogram, abnormal sperm ratio was found as 94%.

Echocardiography findings revealed dextrocardia; ultra-

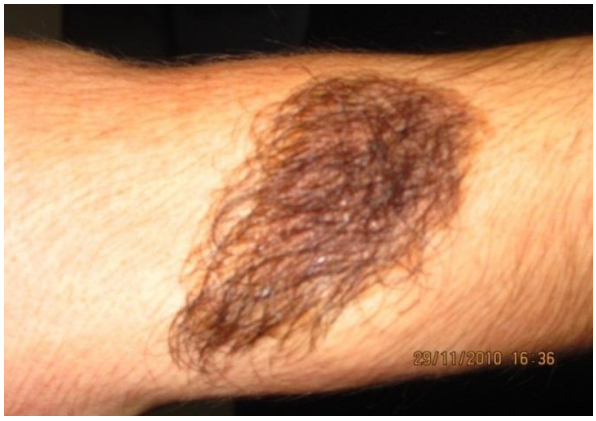

Image 1. Congenital hairy nevus at left arm 1/3 distal area

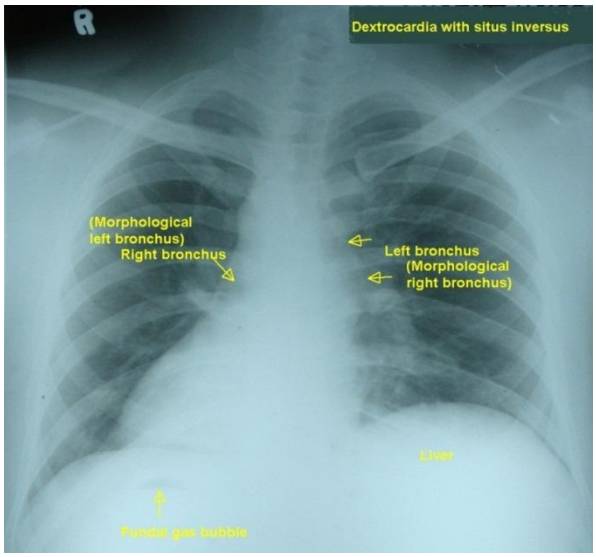

Image 2. PA radiogram of lung

sonographic evaluation of abdomine showed liver and spleen on left side; thorax computerised tomography indicated that three-lobed lung was on the left and two-lobed lung was on the right. Subpleural nodules of milimetric dimensions were observed in right lung. In pulmonary radiograms, alterations indicating bronchiectasia and dextrocardia were determined (Image 2).

Prostate specific antigen: 0.63 ng/ml (range: 0-4), free prostate specific antigen: 0.109 ng/ml (range: 0-1), total testosterone: 3.64 ng/ml (range: 3-10), total cholesterol: 274 mg/dl, HDL-cholesterol: 37 mg/dl, LDL-cholesterol: 213.6 mg/dl, triglycerides: 117 mg/dl, creatinin kynase: 1558 IU/L, GGT: 53 IU/L, AST: 60 IU/L, ALT: 94 IU/L.

Endocrine tests: DHEA-S: 224 pg/ml (range: 160-449), free DHEA: 1140 pg/ml (range: 700-3500), DHT: 39 pg/ml (range: 16-110), cortisole: 83.2 pg/ml (range: 36-137), ACTH: 21.07 pg/ml (range: 0-46), ADH: 1.4 pg/ml (range: 0.8-4.5), aldosterone: 50 pg/ml (range: 50-300), prolactin: 4.09 pg/ml (range: 4.04-15.2), TSH: 0.76 (range: 1.71-4.64), FT3: 2.62 (range: 1.71-3.71), fT4: 1.00 (range: 0.70-1.48)

Echocardiography: Aort: 3.0 cm, left atrium: 3.0 cm, left septum: 1 cm, EF: %70. Diagnosis: dextrocardia. There is no atrial and ventricular septal defect, patent ductus arteriosus. Patient was discharged with amitriptyline 75 mg/day and aripiprazole 10 mg/day.

DISCUSSION

Primary findings of the patient were situs inversus totalis, congenital hairy nevus, congenital nystagmus and anxiety disorder; secondary findings were determined as hypercholesterolemia and hypoplastic skeletal malformations. Among these findings, situs inversus totalis, hypercholesterolemia and hypoplastic skeletal malformations were not present in other family members. A group of signs, e.g. situs inversus totalis and hypoplastic skeletal malformations show an autosomal recessive transmission, as declared by a group of investigators.[3] Findings in our case, namely non-existence of indicated signs in other family members, seem to support recessive transmission. Situs inversus totalis is usually observed rarely in general population. Even though most cases are sporadic, 20-25% show Mendelian inheritance characteristics and incidence is increased in kin marriages. Hypoplastic malformations like lung hypoplasia and diafragmatic defect may be seen in these patients.[4] Based on these facts, we may consider hypoplastic skeletal malformations as secondary findings of situs inversus totalis, rather than a separate morbid entity. Therefore, situs inversus totalis may be considered as the first definite finding of our new syndrome.

On the other hand, hairy nevus is present in our patient's mother. Therefore, it's necessary to accept that this finding has a genetic transmission and assume that this is an X-linked transmission. A number of investigators determined this finding in a group of patients with nevus syndrome. For example, CHILD syndrome (congenital hemidysplasia with ichthyosiform nevus and limb defects) is an X-linked disorder.[2] Another nevus syndrome, Becker Nevus Syndrome that is characterized by a pigmented hairy skin patch associated with skin, muscle or bone defects on the same side of the body as the skin lesion also shows an X-linked transmission. Hypoplastic skeletal malformations and nevus type in our patient shows similarities to clinical features of Becker Nevus Syndrome; therefore in our case, it's necessary to accept that congenital nevus type shows an X-linked transmission. Accordingly, congenital nevus in our patient was also present in his mother.

In addition to findings stated above, congenital and familial type nystagmus was found in our patient. Nystagmus may reflect a failure of early sensorimotor integration. Hackett et al. have found evidence that mutations in the calcium/calmodulin-dependent serine protein kynase gene are frequently associated with X-linked congenital nystagmus.[5] On the other hand, Cabot declared that congenital nystagmus is an X-linked disorder.[6] As a matter of fact, we know that congenital nystagmus in our patient is prevalent in family members related to mother. Hence, we may deduce that nystagmus in our patient also has an X-linked characteristic.

Final primary symptom in our patient was anxiety. It's known that severe anxiety is observed in certain X-linked disorders like fragile X syndrome.[7] Similarly in our patient, anxiety was prevalent among family members related to mother, which leads us to assume that anxiety in our patient also shows an X-linked transmission. Now, we may ask what kind of pathology is indicated in this X-linked transmission. Cabot suggests that Xp11.4-p11.3 is the location of pathology in congenital nystagmus cases.[8] Also in patients with certain pigmentation disorders, a genetic disorder including Xp11 pathology localization is indicated.[8] Therefore, we may more or less suspect for pathology in Xp11 location for nevus in our patient. There are case reports indicating an association between anxiety disorders and Xp11 location.[9] In this case, we need to assume that there is an anomaly in Xp11 location in addition to questionable pathology in chromosome 19.

A secondary finding in our patient was hypercholesterolemia. Observing hypercholesterolemia in such a young patient and especially, presence of this finding together with LDL elevation is an important finding because some cases with elevated LDL may show autosomal recessive transmission.[10] Therefore, we believe that hypercholesterolemia shares the same genetic pathology with situs inversus totalis in chromosome 19.[11]

In addition, a high degree of synistrality was present in our patient; there are trials that indicate to a concordance between cerebral laterality and situs inversus**.** We determined a high degree of synistrality in our patient, using Edinburgh laterality test. This condition suggests that several intracranial structures may be located in reverse position and an 'intracanial situs inversus' may be present in the patient. Certain intracranial structures in individuals with situs inversus totalis may parallel to thoracic and abdominal visceral structures and demonstrate greater prominence on the side opposite to the one, which typically demonstrates greatest prominence in general population. In this case, presence of an 'intracranial situs inversus' in our patient indicates that several soft disorders may be seen in cer-

ebral functions and that this situation may lead to anxiety. In other words, anxiety disorder in our patient may present as part of a general disorder, a syndrome we had described, rather than a sporadic finding.

CONCLUSION

Cardinal findings in our case were S(situs), I(inversus totalis), N(nevus), A(anxiety) and N(nystagmus). As these cardinal symptoms code the name of famous Turkish architect, SINAN who lived 500 years ago, we would like to name this new syndrome after him. SINAN Syndrome has three other cardinal symptoms, in addition to situs inversus totalis, which is seen very rarely; therefore, it should be seen even more rarely than situs inversus totalis, which has a prevalence of 1/8000-20000.

Secondary symptoms of SINAN syndrome are hypoplastic skeletal malformations and hypercholesterolemia. Considering cardinal symptoms and other syndromes that separately present with each of these symptoms, we predict that SINAN syndrome carries a combined autosomal recessive and X-linked transmission. This prediction is based on autosomal recessive transmissions seen in all situs inversus totalis cases. In situs inversus totalis cases, focus is especially on the pathology in 19th chromosomes because in hypercholesterolemia cases and especially in cases with low-density lipoprotein receptor gene, there is pathology in 19th chromosome.[11] Therefore, if an autosomal recessive transmission exists in SINAN syndrome, this may be pathology in 19th chromosome. Considering reports suggesting an X-linked transmission in several situs inversus cases, we may also suggest that SINAN syndrome shows a full X-linked transmission. At least, there is an undeniable X-linked transmission but perhaps, we should also suspect for an autosomal recessive transmission.

It is true that probability of witnessing a second case with this very rarely seen syndrome is extremely low. Therefore our aim was to report this as a one-case syndrome and we expect that number of cases will be increased in future when other research groups recognize the syndrome.

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