

Intractable cryptogenic frontal lobe epilepsy in a patient with MURCS association

Nese Dericioglu¹, Serap Saygi²

¹ Institute of Neurological Sciences and Psychiatry

² Department of Neurology, School of Medicine, Hacettepe University Ankara, Turkey

Received April 18, 2006; Accepted June 9, 2006

ABSTRACT – The MURCS association is a rare, nonrandom association of müllerian duct aplasia, renal aplasia and cervicothoracic somite dysplasia. The etiology is unknown. Although it is usually a sporadic disorder, familial cases with uterovaginal anomalies have been reported. Occasionally, it may be accompanied by abnormalities involving various other organs or systems. Malformations related to the central nervous system are very rare and the presence of seizures has not been reported previously. We present a 26-year-old female with MURCS association who had late onset, drug resistant partial seizures presumably originating in the frontal lobe.

Key words: MURCS association, epilepsy, ictal SPECT, frontal lobe seizures, MRKH syndrome

The realization that müllerian aplasia/hypoplasia sometimes occurs in association with a specific constellation of other congenital abnormalities, has led to the description of the MURCS association (müllerian duct aplasia, renal aplasia and cervicothoracic somite dysplasia), which is a rare developmental disorder of unknown etiology. It may also be accompanied by various other malformations in different organs or systems. Involvement of the central nervous system (CNS) is very rare and the presence of epilepsy has not been reported so far. Here we present a young female patient with MURCS association who had cryptogenic partial epilepsy and drug resistant seizures, presumably originating in the frontal lobe.

Case report

A 26-year-old female patient was admitted to the Neurology clinic because of drug-resistant seizures that had started 3 years earlier. She was born at term with no perinatal problems and there was no history of consanguinity. Her physical and cognitive developmental milestones were reported to be normal. She denied having any risk factors for seizures including head trauma, infection or febrile convulsions. Physical examination revealed a short stature (150 cm), short neck and low posterior hairline. Neurological examination was unremarkable with normal IQ (she was a university graduate). Personal history revealed primary amenorrhea for

Correspondence:

N. Dericioglu,
Institute of Neurological Sciences and
Psychiatry,
Hacettepe University,
Sihhiye 06100,
Ankara,
Turkey
<ndericio@hacettepe.edu.tr>

which she had been examined before. She was reported to have aplasia of the uterus and hypoplastic ovaries. Her karyotype was 46 XX.

Her family history was unremarkable except for febrile convulsions in her brother. Initially her seizures were diurnal and preceded by indescribable feelings. When they occurred in sleep, she usually woke up with a feeling of fear accompanied by palpitations. The seizures were brief and occurred frequently, almost every day. Sometimes the seizures could generalize, with her head and body turning to the left. After the initiation of antiepileptic drug therapy with carbamazepine, her seizures became nocturnal and she no longer had aura.

The patient underwent video-EEG monitoring while she was on a carbamazepine (800 mg/day) and phenobarbital (100 mg/day) combination. Twenty-three seizures were captured in two days. Her seizures occurred soon after she fell asleep (during the day or at night) and lasted for 20-40 seconds. She was awakened by the seizures during which she moved her body and extremities, especially her legs, violently in bed. Interictal EEG disclosed a slow background rhythm with 7-8 Hz waves. Ictal EEG changes were masked by movement artifacts; however, slow waves with a slight predominance on the right side were evident during some of the seizures. High resolution (3T) cranial MRI was unable to demonstrate any lesions except several, non-specific gliotic changes in the white matter (figure 1). An ictal single-photon emission computed tomography (SPECT) was performed successfully (she was

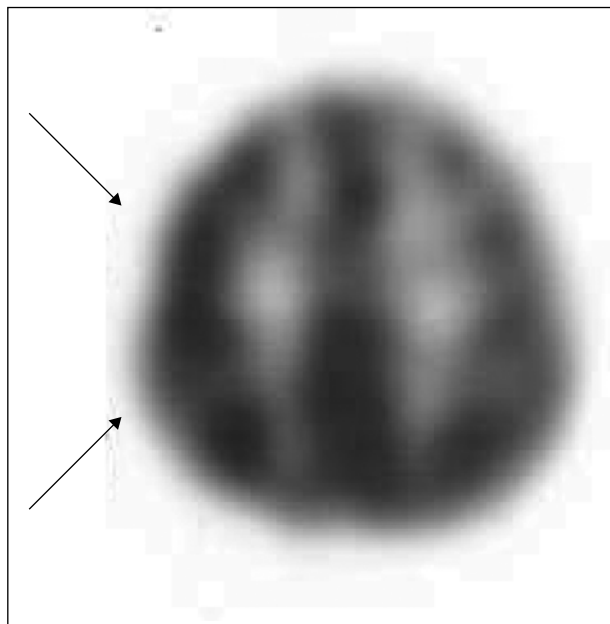


Figure 2. Ictal SPECT demonstrates hyperperfusion in the right fronto-parietal area.

injected within 14 seconds during a 26-second seizure) with ^{99m}Tc -ECD, and was consistent with hyperperfusion in the right fronto-parietal area (figure 2). She was also evaluated for physical findings. An X-ray of the neck revealed vertebral fusion and was diagnostic for the Klippel-Feil anomaly (figure 3). Abdomino-pelvic ultrasonography was repeated and displayed absence of the

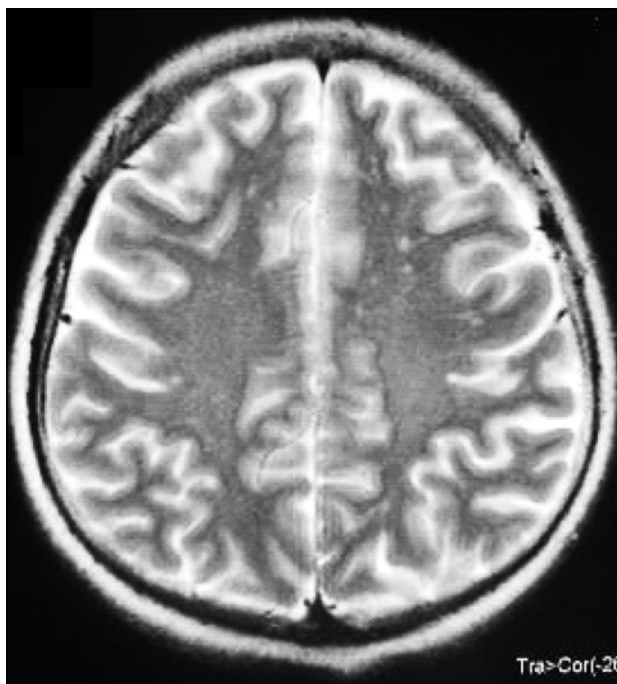


Figure 1. Axial T2-weighted cranial MRI image indicating multiple, non-specific, hyperintense white matter lesions.



Figure 3. Lateral cervical X-ray indicates vertebral fusion, which is consistent with the Klippel-Feil anomaly.

uterus, ovaries and right kidney. Her left kidney was hypertrophic.

The patient was discharged from hospital after the addition of levetiracetam to her existing medications and is currently waiting for a phase III evaluation.

Discussion

The Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome, characterized by congenital absence of the vagina and rudimentary uterus (due to lack of müllerian development), with normal uterine tubes, ovaries and secondary female sex characteristics, may occur in association with urinary tract anomalies (approximately 1/3 of cases) and skeletal anomalies (10-20% of cases) (Willemssen 1982a, 1982b). In 1979, in a review of 30 patients, Duncan *et al.* proposed the designation of an entity, the MURCS association, consisting of anomalies in all three systems (Duncan *et al.* 1979). The four most common malformations that they found in this association were uterine aplasia/hypoplasia (96% of cases); renal agenesis or ectopy (88%); vertebral anomalies between C5 and T1 (80%) and adult stature of less than 152 cm (60%). The clinical characteristics of our patient, *i.e.* short stature, aplasia of the uterus and ovaries, unilateral renal aplasia and cervical vertebral fusion (Klippel-Feil anomaly), were consistent with the MURCS association. This is a rare anomaly of unknown etiology and is usually a sporadic disorder in an otherwise normal family. It is believed to be a non-random association because of the developmental characteristics of the embryo. At the end of the fourth week of fetal life, the blastemas of the lower cervical-upper thoracic somites, arm buds and pronephric ducts are in close proximity to one another. The MURCS association could be produced at that time by a teratogenic event, which would affect the relationship between these blastemas. Support for this concept is provided by the case of a patient who was exposed to thalidomide at the fetal age of 27-29 days (Hoffman *et al.* 1976). The presence of MRKH syndrome in only one of monozygotic twins (Heidenreich *et al.* 1977), also suggests an environmental origin for the defect. On the other hand, although most cases appear to be sporadic, there are reports of families in which siblings displayed uterovaginal agenesis with other malformations of the MURCS association (Winter *et al.* 1968, Rodriguez *et al.* 1977). Thus in some cases, it is believed that the MURCS association may be a genetically determined pleiotropic condition in which affected relatives show a spectrum of anomalies. Recently, it has been reported that the MRKH syndrome, when described in familial aggregates, seems to be transmitted as an autosomal dominant trait with an incomplete degree of penetrance and variable expressivity (Opitz 1987, Pavanello *et al.* 1988). This suggests the involvement of either mutations in a major developmental gene or a limited chromo-

somal deletion. Expression and/or function defects in HOX genes, that are shown to play key roles in body patterning and organogenesis (in particular during genital tract development) are believed to have a possible role in this syndrome. HOX genes encode a highly conserved family of transcription factors and have fundamental roles in morphogenesis throughout the animal kingdom (Krumlauf 1994). Vertebrate HOX genes are known to play an important part in development of the CNS, axial skeleton, gastrointestinal and urogenital tracts, external genitalia and limbs (Mark *et al.* 1997).

Various accompanying malformations (upper limb defects, rib abnormalities, deafness, external ear defects, facial asymmetry, cleft lip and palate, micrognathia and gastrointestinal abnormalities, cardiac defects, abnormalities of the venous and pulmonary systems) have been reported in this association. There are also data indicating the involvement of the CNS. Extreme hydrocephalus due to aqueduct stenosis (Orstavik *et al.* 1992), cerebellar cyst and heterotopia of Purkinje and granule cells in the cerebellar cortex in the vicinity of the cyst (Greene *et al.* 1986) and occipital encephalocele (Suri *et al.* 2000, Lin *et al.* 1996) have been reported. In an autopsy study of a stillborn female infant of 41 weeks gestation, Lin and colleagues reported the presence of polymicrogyral formation in both hemispheres; small midbrain, pons and cerebellum besides an occipital encephalocele (Lin *et al.* 1996). Microscopic investigation revealed nests of primary neurons in central frontal white matter.

To the best of our knowledge, none of the cases reported in the literature so far, had epilepsy. Our patient had late onset, drug resistant epilepsy. Semiological characteristics were consistent with frontal lobe seizures. Ictal SPECT findings were in favor of the right fronto-parietal area and ictal EEG recordings in some seizures pointed to the right hemisphere.

Although we could not detect any lesions in cranial MRI that might be responsible for the seizures, the possibility of a subtle malformation of cortical development cannot be ruled out. On the other hand, slow background activity in EEG may indicate the presence of a more widespread abnormality that does not alter cognitive functions. Certainly the possibility of a mere coincidence of epileptic seizures in this case with MURCS association can not be excluded. Nevertheless, given the rare occurrence of this malformation, any accompanying abnormalities deserve attention. The existing literature points to the involvement of the CNS in some patients and the case reported by Lin *et al.* (1996) clearly demonstrates malformation of cortical development, a pathological substrate known to be associated with seizures. In fact, the CNS might be more frequently affected than is appreciated since some patients may be asymptomatic, as is evident in the autopsy case reported by Greene *et al.* (1986).

At present, the etiology and pathogenesis of this rare malformation are not known. Either an environmental

insult or a genetically determined condition might play a role. As more information related to associated malformations is gathered, it might be easier to unravel the underlying pathophysiology. This information, on the other hand, might shed light not only on brain development but also on the mechanisms leading to seizures in cryptogenic partial epilepsy. □

References

- Duncan PA, Shapiro LR, Stangel JJ, *et al.* The MURCS association: Mullerian duct aplasia, renal aplasia and cervicothoracic somite dysplasia. *J Pediatr* 1979; 95: 399-402.
- Greene RA, Bloch MJ, Huff DS, *et al.* MURCS association with additional congenital anomalies. *Hum Pathol* 1986; 17: 88-91.
- Heidenreich W, Pfeiffer RA, Kumbhani HK, *et al.* Diskordante eineiige Zwillinge mit Mayer-Rokitansky-Kuster Syndrome. *Geburtshilfe Frauenheilkd* 1977; 37: 221.
- Hoffman W, Grospietsch G, Kuhn W. Thalidomide and female genital malformations? *Lancet* 1976; 2: 794.
- Krumlauf R. Hox genes in vertebrate development. *Cell* 1994; 78: 191-201.
- Lin HJ, Cornford ME, Hu B, *et al.* Occipital encephalocele and MURCS association: case report and review of central nervous system anomalies in MURCS patients. *Am J Med Genet* 1996; 61: 59-62.
- Mark M, Rijli FM, Chambon P. Homeobox genes in embryogenesis and pathogenesis. *Pediatr Res* 1997; 42: 421-9.
- Opitz JM. Vaginal atresia (von Mayer-Rokitansky-Kuster or MRK anomaly) in hereditary renal adysplasia (HRA). *Am J Med Genet* 1987; 26: 873-6.
- Orstavik KH, Steen-Johnsen, Foerster A, *et al.* VACTERL or MURCS association in a girl with neurenteric cyst and identical thoracic malformations in the father: a case of gonosomal mosaicism? *Am J Med Genet* 1992; 43: 1035-8.
- Pavanello C, Eigier A, Otto PA. Relationship between Mayer-Rokitansky-Kuster (MRK) anomaly and hereditary renal adysplasia (HRA). *Am J Med Genet* 1988; 29: 845-9.
- Rodriguez-Rodriguez S, Jimenez M, Forsbach G, *et al.* Sindrome de Mayer-Rokitansky-Kuster-Hauser de tipo familiar. *Gac Med Mex* 1977; 113: 447.
- Suri M, Brueton LA, Venkatraman N, *et al.* MURCS association with encephalocele: report of a second case. *Clin Dysmorphol* 2000; 9: 31-3.
- Willemsen WNP. Renal-skeletal-ear-and facial anomalies in combination with the Mayer-Rokitansky-Küster (MRK) syndrome. *Eur J Obstet Gynecol Reprod Biol* 1982; 14: 121.
- Willemsen WNP. Combination of the Mayer-Rokitansky-Kuster and Klippel-Feil syndrome- a case report and literature review. *Eur J Obstet Gynecol Reprod Biol* 1982; 13: 229.
- Winter JS, Kohn G, Mellman WJ, *et al.* A familial syndrome of renal, genital and middle ear anomalies. *J Pediatr* 1968; 72: 88-93.