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A Case of Brachmann-de Lange Syndrome Associated with Epileptic Apnea

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We describe a case of Brachmann-de Lange syndrome in an infant who had repeated life-threatening episodes of epileptic apnea, and we report a polygraphic recording made while monitoring changes in oxygen saturation. Focal ictal paroxysmal theta-wave activity in the left frontal pole region preceded the apnea. Partial seizures should be included in the differential diagnosis of apnea, and the only way to make a conclusive diagnosis is by polygraphic ictal EEG recording during an apneas spell.

Introduction

Apnea is a life-threatening symptom[1)]. There are many underlying diseases in apnea of infants and children[1)2)]. Epileptic apnea is known to be one of the most common symptoms of atypical neonatal seizures, but rare after 1 month of age[3)4)]. Such seizures themselves, however, are very rare and sometimes intractable. We describe a case of Brachmann-de Lange syndrome in an infant, who had repeated life-threatening episodes of epileptic apnea and who underwent polygraphic recording while changes in oxygen saturation were measured by pulse oximeter.

Case Report

The girl was born following a normal 36-week gestation and uncomplicated delivery, with a birth weight of 3,475 g. There was no relevant family history of mental or neuromuscular disease, although her mother was examined by intravenous pyelography at an early stage of pregnancy. The newborn had microbrachycephaly, hypertrichosis, and characteristic facial appearance with synophrys, bushy eyebrows, depressed nasal bridge, long philtrum, thin upper lip, and crescent-shaped mouth but no limb anomalies. She showed a feeble cry and poor sucking in the neonatal period. Chromosomes were normal (46, XX) by G-banding analysis. Her life was relatively uneventful until 3 months of age, when she began to have right unilateral seizures, with episodes of 3 to 10 attacks in a day. These seizures persisted in spite of treatment with various antiepileptic drugs (AEDs). At the age of 5 months, she presented the first frequent episodes of apnea, especially in the early morning. Her apneic episodes lasted for about 30 to 60 seconds and were accompanied by cyanosis. She was therefore supported by assisted ventilation during cluste of apneic episodes.

At the age of 11 months, she was transferred to our hospital for the treatment of sporadic right unilateral seizures and frequent episodes of apnea with cyanosis requiring assisted ventilation. She was experiencing 10 to 20 apneic episodes a

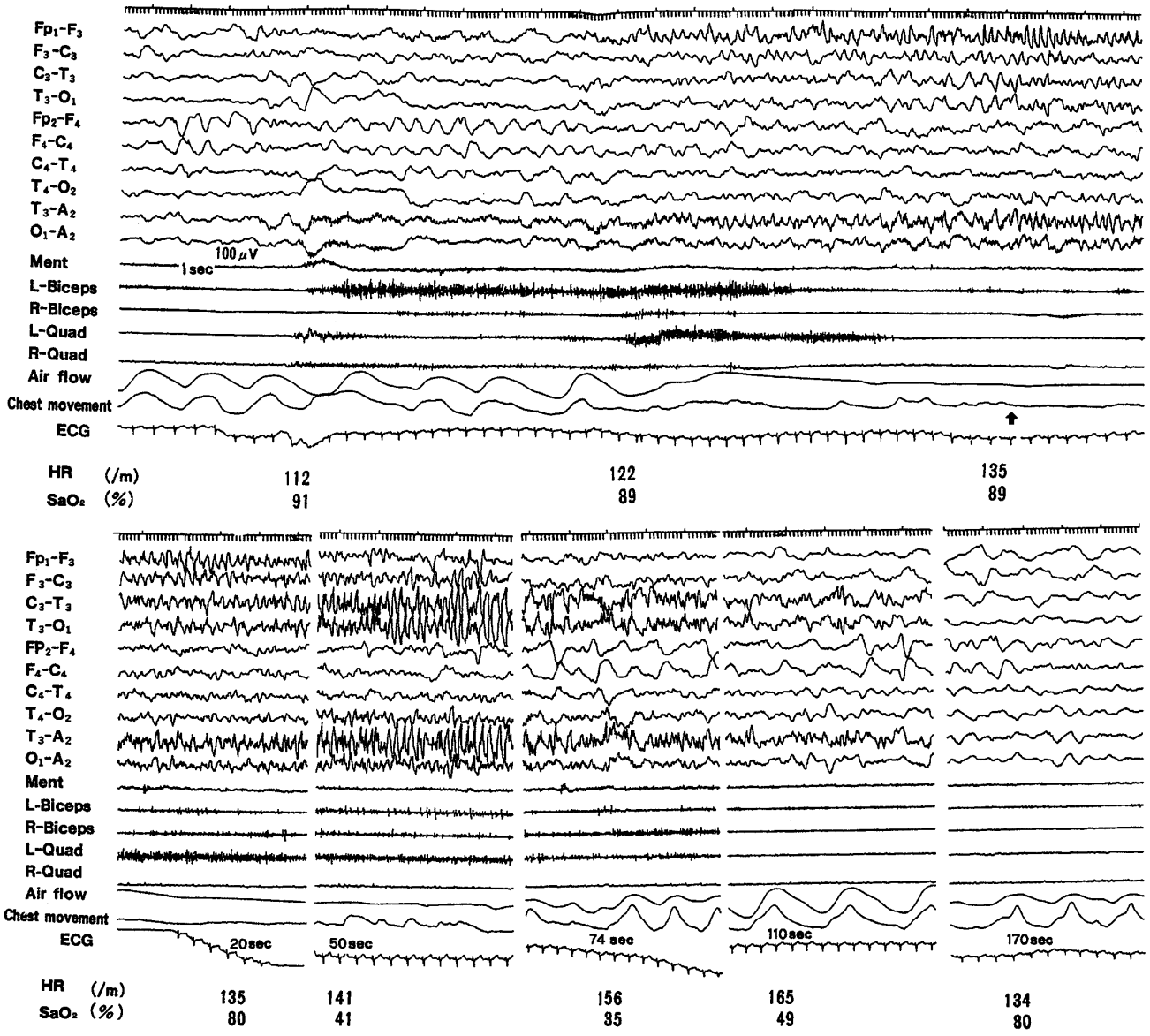

Figure Polygraphic recording during an attack of apnea manifested by mild stiffness of arms and legs, staring eyes, cyanosis, and tachycardia. The arrow indicates the onset of apnea. Paroxysmal 5- to 7-Hz theta-wave activity in the left frontal pole region was seen, followed by high-amplitude 6- to 7-Hz theta-wave activity mixed with spikes or sharp waves in the left temporal region. Respiratory monitoring showed that she stopped breathing about 10 seconds after the onset of the epileptiform discharge. The percentage of oxygen saturation dropped drastically and had decreased to 35% by the end of the apnea spell

day, each lasting for about 30 to 90 seconds. The first interictal electroencephalogram (EEG) showed moderately slow background activity and rare spikes in the left frontal pole and left occipital regions. She continued to have repetitive episodes of apnea after admission, each lasting about 60 seconds and requiring assisted ventilation.

A polygraphic recording was performed during a prolonged apnea episode, with changes in oxygen saturation measured by pulse oximeter (Figure). This ictal EEG revealed paroxysmal 5- to 7-Hz theta-wave activity in the left frontal pole region, while mild stiffness of arms and legs, eye

deviation to the left side, and head rotation to the left side appeared. Respiratory monitoring showed that she stopped breathing about 10 seconds after the onset of the epileptiform discharge. The ictal paroxysmal discharge was followed by high-amplitude 6- to 7-Hz theta-wave activity mixed with spikes or sharp waves in the left temporal region. The percentage of oxygen saturation dropped drastically and had decreased to 35 % by the end of the apnea spell. Three prolonged apnea episodes were recorded; all showed a left frontal pole paroxysmal discharge preceded the apnea.

Although clonazepam was relatively effective in reducing the right unilateral seizures and apneic seizures, other AEDs (carbamazepin, phenytoin, and valproic acid) were not effective, sometimes even increasing the frequency of these seizures. A brain CT scan at 11 months of age revealed more noticeable atrophy than at 5 months of age. She was severely retarded (DQ=8), and died from a convulsive status at home at 3 years of age.

Discussion

The Brachmann-de Lange syndrome is recognized on the basis of characteristic facies in association with prenatal and postnatal growth retardation. There are some reports which suggested the gene locus of this syndrome is at 3q26.3[5] and a case report with hyperthermia who showed multiple mt DNA deletions[6], however biochemical and genetic basis of this disorder is still unknown.

About 20% of patients with a clinical diagnosis of Brachmann-de Lange syndrome have seizures[7]. However, to our knowledge, there have been no previously published cases of this syndrome with epileptic apnea. Epileptic apnea is rare after the neonatal period[1]. This is the first report of an infant patient with this syndrome who had repeated life-threatening episodes of epileptic apnea. Diagnosis of epileptic apnea is usually difficult, and it is controversial if other signs of seizures are lacking. Interictal EEGs are often normal[1)8)], so the only way to make a conclusive diagnosis is by polygraphic ictal EEG recording during an apnea episode[1)~4)8)9)]. Ictal EEG during epileptic apnea in children shows a focal epileptic paroxysm predominant over the temporal region, suggesting an epileptogenic focus in the limbic system[1)8)]. Ictal EEGs of our patient showed unusual paroxysmal theta-wave activity in the left frontal pole region, which has been rarely observed during epileptic apnea[8].

Epileptic apnea is sometimes intractable in spite of various AED medication[8]. In our patient, clonazepam was relatively effective. Diffuse cortical atrophy may result from damage due to epileptic apnea. We conclude that epileptic seizures should be included in the differential diagnosis of apnea, and that the only way to make a conclusive diagnosis is a polygraphic ictal EEG recording during an apneic episode.

References

1) **Singh B, Al Shahwan SA, Al Deeb SM**: Partial seizures presenting as life-threateing apnea. Epilepsia **34**: 901–903,1993
2) **Coulter DL**: Partial seizures with apnea and bradycardia. Arch Neurol **41**: 173–174, 1884
3) **Watanabe K, Hara K, Miyazaki S et al**: Apneic seizures in the newborn. Am J Dis Child **136**: 980–984, 1982
4) **Monod N, Peirano P, Plouin P et al**: Seizure-induced apnea. Ann N Y Acad Sci **533**: 411–420, 1988
5) **Ireland M, English C, Cross I et al**: A de novo translocation t (3; 17) (q26.3; q23.1) in a child with Cornelia de Lange syndrome. J Med Genet **28**: 639–640, 1991
6) **Melegh B, Bock I, Gati I et al**: Multiple mitochondrial DNA deletions and persistent hyperthermia in a patient with Brachmann-de Lange phenotype. Am J Med Genet **65**: 82–88, 1996
7) **Smith DW** : Brachmann-de Lange syndrome. *In* Smith's Recognizable Patterns of Human Malformation (Smith DW ed) pp 88–91, WB Saunders

Co, Philadelphia (1997)
8) **Watanabe K, Hara K, Hakamada S et al**: Seizures with apnea in children. Pediatrics **70**: 87–90, 1982
9) **Navelet Y, Wood C, Robieux I et al**: Seizures presenting as apnoea. Arch Dis Child **64**: 357–359, 1989

てんかん性無呼吸発作を認めたBrachmann-de Lange症候群の1乳児例

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乳児期の無呼吸発作には様々な原因があるが，てんかん性無呼吸発作は極めて稀である．一方，Brachmann-de Lange症候群の約20%にてんかん発作を認めるが，我々の調べた限りではてんかん性無呼吸発作を伴った症例は報告されていない．我々は，頻回のてんかん性無呼吸発作を認めたBrachmann-de Lange症候群の1乳児例の発作時ポリグラフについて報告する．発作時ポリグラフでは，無呼吸に先だって左前頭極部に突発性θ波が認められた．部分発作は，無呼吸発作の鑑別疾患の一つであり，発作時ポリグラフが診断の唯一の方法である．