Case Report

Angelman syndrome

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ABSTRACT

Angelman syndrome is characterized by severe mental retardation, absence of speech, bursts of laughter, ataxia, seizure disorder and facial dysmorphism. This report describes the first 3 children with Angelman syndrome from Bahrain. The diagnosis was based on clinical features and confirmed by the presence of microdeletion of 15q11q13 using fluorescence in situ hybridization.

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Angelman originally described the syndrome in 3 children at 1965 and called them "Puppet children".[1] It is characterized by severe motor and intellectual retardation, ataxia, hypotonia, impaired speech, a happy disposition with bursts of laughter and facial dysmorphism. A small deletion of the maternal homology of chromosome 15q11q13 was detected in the majority of patients. Other cases are associated with paternal uniparental disomy or rarely a translocation or inversions involving the deletion site. We report the clinical, neurological and molecular cytogenetic of the first 3 recognized Angelman syndrome (AS) patients in Bahrain.

Case Report. ***Patient 1.*** A 9 and half year old Bahraini girl, the third child of healthy unrelated parents. The delivery was normal at term after uneventful pregnancy. Her birth weight was 2600 gm (3rd centile), length 49 cm (50th centile) and head circumference 33 cm (3rd–10th centile). Apgar score is 9 and 10 at one and 5 minutes. She presented with psychomotor retardation where she sat at 9 months and walked at 20 months of age. Her gait was unsteady with ataxia and frequent falls that have since improved. She has significant speech delay and mental retardation. She is hyperactive with inappropriate episodes of laughter. The patient developed recurrent tonic clonic seizures since the age of one and half years, which were well controlled with sodium valproate. Physical examination revealed a weight of 27 kg (25th centile), height 121cm (3rd centile) and head circumference 48 cm (2 SD below mean). She has microcephaly, deep set eyes, maxillary hypoplasia, large mouth with protruded tongue and prognathism, squint right eye. Her gait was unsteady, tone was increased and deep tendon reflexes were brisk. An MRI brain was normal, EEG during sleep revealed generalized high voltage slow activity delta wave of 3-4 Hz predominantly seen at the occipital region. In addition, there were frequent bursts of generalized spikes and slow wave complex. Chromosomal analysis was normal and fluorescent in situ hybridization showed an interstitial deletion of 15q11.2 SNRPN and D15S10 loci consistent with the clinical suspicion of AS. The test was performed at the Merieux Laboratoire, Paris, France (**Figure 1**).

Patient 2. A 6-year-old girl, was the fourth of 5 children, born to healthy first cousin once removed Yemeni parents. Her delivery was normal at term after an uneventful pregnancy. Birth weight was 2250 gram (below 3rd centile) with no neonatal problems. Her developmental milestones were delayed, she smiled at 5 months, rolled over at 8 months, sat at one year and walked at 3 years. Her

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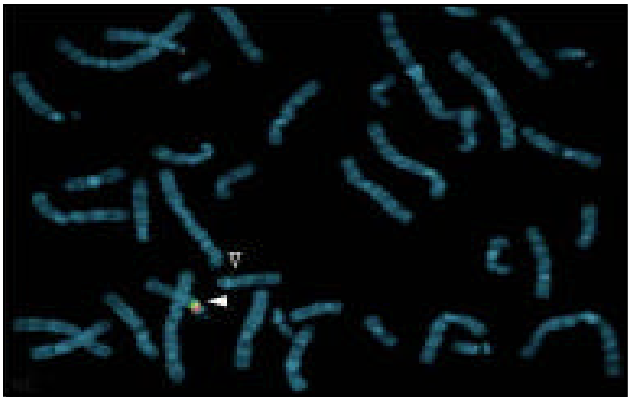

Figure 1 - Fluorescence in situ hybridization analysis of Patient 1 showing deletion of 15q11.2

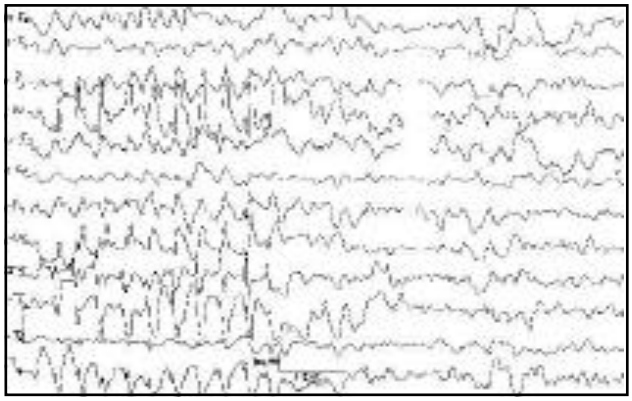

Figure 2 - Electroencephalogram findings in Patient 2.

gait was initially unsteady and ataxic but improved later on. Her cognitive function and speech were delayed, but her vision and hearing were normal. She was reported to be a happy and quiet child with episodes of inappropriate laughter. She developed recurrent generalized tonic clonic seizure from the age of one year; this was well controlled with clonazepam and sodium valproate. At 6 years of age, her height was 101.5 cm, weight 14 kg (both 2 SD below mean) and head circumference 43 cm (below 3rd centile). The face is dysmorphic: pointed chin, large mouth and deep set eyes. The gait was jerky, wide based and has generalized tremulousness. Her tone was increased, and deep tendon reflexes were brisk. An EEG showed intermittent bursts of high voltage slow waves of 4-5 Hz predominantly seen during eye closure at the occipital and posterior temporal region. In addition, there were paroxysmal bursts of generalized spike waves seen predominantly at the occipital region **(Figure 2)**. An MRI brain and chromosomal study were normal. Fluorescent in situ hybridization performed at Merieux Laboratoire revealed a deletion at the 15q11.2 SNRPN and D15S10 loci consistent with the clinical suspicion of AS.

Patient 3. A 7 and a half year old Bahraini boy, the fifth child of healthy unrelated parents. The pregnancy was complicated by gestational diabetes and was controlled by insulin. Delivery was normal and spontaneous at term. His birth weight was 2.5 kg (3rd centile). His motor development was normal, he sat at 6 months and walked at 15 months, however, his gait was unsteady with frequent falls. The speech was delayed but his hearing and vision were normal. He has mental retardation and abnormal behavior in the form of hyperactivity, destructiveness, inappropriate laughter and abnormal flapping hand movements. At 2 years of age the patient developed generalized tonic clonic seizure which was well controlled with Lamictal, carbamazepine and sodium valproate. On examination, the weight was 30 kg (90th centile), height was 115 cm (10th centile) and head circumference 47 cm (2 SD below mean). He had pointed chin and a large mouth. The tone was increased, and deep tendon reflexes were brisk with tight tendon Achilles. An EEG revealed generalized spike and wave discharges predominantly noted at posterior temporal and occipital regions. Metabolic screening was negative and CT scan of brain was normal. Fluorescent in situ hybridization performed at Merieux Laboratoire, showed deletion at the 15q11.2 SNRPN and D15S10 loci consistent with AS.

Discussion. Our patients represent the first 3 cases of AS reported in Bahrain. The diagnosis was based on clinical findings and was confirmed by molecular cytogenetics. The prevalence of AS was estimated to be one in 12,000.[2] Most AS patients showed at least 8 of the major characteristics of the syndrome (bursts of laughter, happy disposition, hyperactivity, micro and brachycephaly, macrosomia, tongue protrusion, prognathism, widely spaced teeth, puppet like movements, wide based gait, mental retardation and absence of speech).[3] The EEG changes in AS are characteristic and consist of high voltage slow wave activity (4-6 Hz) not related to drowsiness.[4] Our patients exhibited most of the major clinical features of AS and their EEG findings were consistent with the syndrome. The gait usually improves with age and the epilepsy is well controlled with anti-epileptic medications.

Several conditions can mimic AS, these include Rett syndrome (MIM 312750), alpha-thalassemia mental retardation syndrome (MIM 301040), Gurrieri syndrome (MIM 601187), ataxic cerebral palsy, (MIM 603513), and autistic spectrum disorders (MIM 209850).[5]

Angelman syndrome results from lack of maternal contribution of chromosome 15q11-q13

arising from de novo deletion or paternal uniparental disomy. (UPD).[6,7] Microdeletion can be detected cytogenetically in approximately 61% while using in situ hybridization can detect up to 73% of the syndrome.[3] Rarely, AS is due to paternal UPD, where the 2 segments of chromosome 15 are purely paternal in origin.[7] On the other hand, maternal UPD or deletion of the paternal 15q11q13 results in Prader Willi syndrome. Most cases of paternal UPD are due to meiosis II errors, while 82% of maternal UPD are due to meiosis I,[8] non-disjunction error UPD can be tested by the methylation technique, which relies on methylation sensitive enzymes differentially cutting maternal and paternal DNA.

Saitoh et al 1994,[9] classified 61 cases of AS into 4 groups: familial cases without deletion (5 patients), familial cases with deletion (3 patients), sporadic cases with deletion (37 patients) and sporadic cases without deletion (16 patients). The deletion, both in the familial and sporadic cases was exclusively maternal in origin consistent with the genomic imprinting hypothesis.[9]

A study shows that non-deletion cases usually have a less severe phenotype with regard to both physical anomalies and neurological manifestation. They have higher age of diagnosis, walk earlier, epilepsy starts later, verbal development is better and they have higher weight and head circumference for age.[10]

Rare cases of AS have been associated with microdeletion of the imprinting center (IC) that blocks the paternal-to-maternal imprint switch in the maternal germline.[11] Other associations include pericentric inversion with a breakpoint at 15q11q13,[12] balanced translocation t (15:22) (q13:q11),[13] translocation t (9:15) (p24:q 11)[14] and translocation 45 XY, t (15q:15q).[15]

The recurrent risk is less than 1% in both the deletion and UPD case. Parental transmission of a structurally or functionally unbalanced chromosome complement will result in case specific recurrent risk. The risk may be as high as 50% as a result of maternally inherited IC mutation or a mutation in the UBE3A gene loci.[16]

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