Abstract

Five girls aged 4 to 13 years presented with clinical features of classical Rett syndrome - loss of acquired developmental skills including speech and hand function, progressive microcephaly and characteristic stereotyped “hand washing” movements. Two patients had generalized tonic, clonic seizures and one had atonic seizures with electroencephalogram (EEG) evidence of Lannox Gastaut syndrome. Cranial CT was normal in all except two patients, which showed marked perisylvian atrophy, and metabolic screening revealed non specific mild hyperammoniaemia in three. The aim of the study is to illustrate the unique clinical features of Rett syndrome and reiterate the importance of the diagnosis of this rare condition, clinically.

Introduction

Rett syndrome (RS) is a unique progressive neurodegenerative illness occurring in girls. It has been recognized in all ethnic groups all over the world and the prevalence estimated in Sweden, Scotland and Texas ranged from 1:12,000 to 1:20,000. Originally described by Andress Rett, an Austrian Neurologist, in 1966 and later, in 1983 Hageberg from Sweden, reported 35 cases in detail with the characteristic clinical features, see below.

Diagnostic Criteria of RS (Hagberg 1988)

1. Female sex
2. Normal pre-post natal and even 6 to 12 months development
3. Normal head circumference at birth with later regression at 6 months to 4 years
4. Early regression including language and dementia
5. Hand stereotypes (wringing, washing,) 1-4 yrs
6. Loss of purposeful hand skills 1-4 yrs
7. Gait apraxia at 1-4 yrs
8. Diagnosis must be tentative till 3-5 yrs.

A clinical staging system of this disorder was made by Hageberg et al, which helps the clinician to diagnose at different age groups, table 1.

Methods

Five Omani girls aged between 4 and 13 years were examined in the Paediatric Neurology clinic at Royal Hospital in Muscat between 1999 and 2002. Though developmental regression was the major complaint, two girls were referred for uncontrolled seizures and the diagnosis of RS was made based on the defined clinical criteria, mentioned. Clinical features and the investigations are summarized in Table 2.
All five patients were normal at birth with no family history of similar illness and their initial developmental milestones were normal before the onset of clinical symptoms. However, one patient was referred to us for seizure control rather than developmental regression which was tonic/clonic and another had atonic, myoclonic seizures. The other three girls were asymptomatic despite grossly abnormal EEG, recorded during sleep. Six to eight months later, they manifested clinical seizures of tonic and clonic type. The clinical symptoms were almost similar in all these five girls with loss of acquired speech, developmental regression, characteristic stereotypic hand wringing, washing and clapping movements. Breathing disturbances were not observed during examination, in 4 of them, but one girl spat saliva forcibly following brief breath holding spells.

Gait was abnormal in all, ranging from wide based stance, aimless wandering and apraxia. All these abnormal movements disappeared during sleep except who two had extensive bruxism. One patient showed visual apraxia with a peculiar jerking of the head before fixing the gaze and motor restlessness (akathisia) was seen in the legs in another. Microcephaly was seen in three patients who presented early between 4 to 7 years.

Detailed neurometabolic tests including serum amino acid screening and urine organic acid estimation were normal in all; three showed mild increase in ammonia; the test was done in the immediate post ictal period which could be the reason for this rise. Electrocardiographs were done in all patients and were reported to be normal. Basic psychological evaluation revealed that their IQ was well below the standard norms for the age, mostly below 50. Electroencephalographs were abnormal in all, recorded during sleep as awake recording could not be done. The EEG changes included diffuse slow waves, absence of normal sleep patterns, bursts of spikes, sharp waves and multifocal slow sharp/wave of 2.5Hz/sec of Lannox Gastaut type. Computerized tomography of the brain was normal except in one patient who showed perisylvian atrophy.

**Discussion**

All these five patients fulfilled the established criteria of RS which include normal pre and perinatal period, normal development till 6-12 months of age, normal head circumference at birth with late deceleration, psychomotor regression including language skills, characteristic hand movements with loss of purposeful hand skills and gait apraxia. It is always necessary to rule out other causes of progressive neurodegenerative and metabolic disorders both clinically and by investigations, which were excluded in all our patients. Rett syndrome is a disorder seen in girls although it did not exclude male gender. In addition to the above clinical criteria, abnormal breathing patterns were observed in many patients, which include hyperventilation, or breath holding or both. These sometimes would precipitate seizures due to hypoxemia. The hyperventilation may be due to abnormal serotoninergic function in the brain. None of our patients had breathing abnormality except one who used to spit saliva with force after breath holding and all of them had seizures. Electrocardiographic abnormalities were reported in some patients which could explain sudden death due to autonomic nervous system disturbance. Neuropathological features are nonspecific, which include moderate cerebral atrophy and absence of pigmentation in substantia nigra suggesting monoaminergic system involvement. Recent reports reveal that arrest of neural development at the critical phase of synaptic elaboration and dendritic arborization could explain the reduction in size of cortical neurons in them. Most cases of RS are sporadic, but familial occurrence

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age of onset</th>
<th>Age of skill loss</th>
<th>Age of gait defect</th>
<th>Speech defect</th>
<th>Gait defect</th>
<th>Fits</th>
<th>Vision apraxia</th>
<th>Breathing defect</th>
<th>Akathisia</th>
<th>NH3 rise</th>
<th>EEG</th>
<th>Epile</th>
<th>CT brain</th>
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<tbody>
<tr>
<td>A.H</td>
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<tr>
<td>A.A</td>
<td>6yrs</td>
<td>3yrs</td>
<td>4.5yrs</td>
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<td>+</td>
<td>Rise 72</td>
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<tr>
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<td>2.4yrs</td>
<td>+</td>
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<td>++</td>
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<td>Perisylvian atrophy</td>
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<td>S.K</td>
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<td>7.5yrs</td>
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suggested an X linked dominant inheritance with possible male lethality. Recently, genetic mapping was used to mark Xq28 locus in familial cases; subsequently it was identified mutation in MECP2 gene ( methylated cytosine nucleotide) which would help in prenatal screening. Detailed molecular genetic evaluation is necessary to evaluate the exact prevalence of this disorder in Oman. Seizures were reported in 30-70% of patients with RS but almost all of our patients had seizure disorder. Interestingly multiple types of seizures of Lannox Gestaut type were seen in one of our patients and she needed multiple anti epileptic drugs to control them. Myoclonic seizures were also reported by some in the past. Apraxia of gaze was noted in one patient which has not been reported in the past. This could probably explain the supranuclear developmental gaze anomaly akin to gait apraxia due to neurotransmitter imbalance

Conclusion

The diagnosis of RS therefore depends upon fixed clinical criteria although mild variations do occur. However, due to the progressive nature of the illness, other causes of neuro degenerative disorders have to be ruled out. Though there is no specific treatment available for RS, supportive therapies for seizure control must be considered and family support is encouraged for physical rehabilitation, as significant number of these patients would develop spinal deformities, later. These five patients of RS are thus presented here for characteristic clinical features but with some unique variable findings.

References: