Rett Syndrome — Two case reports

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Summary
Two cases of girls seen in Sarawak with the diagnosis of Rett Syndrome are reported. Their ages were 6 and 2 years respectively at the time of the report. Diagnosis is made clinically as there is as yet no scientific marker. Specific diagnostic criteria were met. There was a history of slowing of development followed by loss of previously acquired skills, changes in emotional development and behaviour and the definite emergency of stereotyped behaviour especially hand wringing in both girls. Onset was early in both girls, around nine months. Both girls are profoundly retarded mentally but the regression appeared to be static at present.

Key words: Rett Syndrome, case reports.

Introduction
Rett Syndrome was first described by Professor Andraes Rett of L. Boltzman Institute for Research on Brain Damaged Children in Vienna in 1966[1] as 'cerebral atrophy with hyperammonemia' affecting only girls. However it drew world-wide attention only after Professor Hagberb[2] of Sweden presented his series of 34 cases to neurologists in 1983. Since then there has been numerous reports from all over the world. A prevalence of 0.8 : 10,000 was noted in Western Scotland[3] by Kerr and 1 : 15,000 in Western Sweden by Hagberb[4].

In South East Asia, the first 3 cases were reported in Singapore[5] and the 2 cases were are presenting are the first reported cases in Malaysia. The condition is at present still underdiagnosed and we hope that in creating an awareness the condition may be more readily recognised.

Clinical Report
Case 1:
TCY, a Chinese girl is the elder in a family of 2 girls. The marriage is non-consanguineous and she was delivered at term vaginally on 31.3.1984. Birth weight was 3 kg. and head circumference 34 cm. The pre, peri and postnatal history was uneventful.

Developmental History:
TCY, developed normally in the first 9 months of her life. She held up her head at 3 months and could turn over at 4 months. She was able to sit without support at 8 months and at 8 1/2 months she could stand with support and cruise a little. She was able to hold toys with her hands and played with other children actively.

After the age of nine months, her parents noted that she refused to hold anything in her hands and instead tended to hold her hands and wring them. By one year she has lost all ability to use her hands purposefully and was unable to sit or stand without support. She said "papa" at 1 1/2 years but soon after that lost all ability to speak.

Emotionally she was noted to be more distant at one year and no longer responded to her parents' call by turning her head towards them. Her parents soon feared that she might be deaf. She also tended to burst into fits of laughter spontaneously or cried inappropriately. She had lost all interest in her surroundings as well. Feeding had become a problem from nine months of age. She was unable to suck and chew well at eight months. By 10 months she fed poorly and weight gain was low. She was unable to indicate her wants at all and if left alone, will not cry out in hunger. She showed marked bruxism at 1 1/2 years and gait became ataxic at 2 years. She started having generalised fits at the age of four years and is on phenobarbitone presently.

Presently at six years, she is profoundly retarded. She sits with support and walks with assistance but gait is ataxic. She is still uncontinent, feeds poorly and has constant bruxism. There is poor eye to eye contact but parents claim that she occasionally responds to their call with the movement of her eyes. Facial expression is minimal. Although she still smiles frequently there is little interaction with persons or object. Her hands are held in a stereotype wringing manner and purposeful fine hand function is lost. If one hand is restrained, the other will try to reach for an object placed close to the hand in a gross manner. There was no clinical observation of apnea or hyperventilation.

Clinical examination:
Clinically her head circumference is in the 25th percentile but there has been crossing of the centile chart. Her weight and height are in the 10th centile. The tone is increased in her lower limbs, tendoachilles are tight bilaterally and her reflexes are brisk in all four limb. Cranial nerves are intact, gait ataxic when supported and eye to eye contact is poor.

Her hands and feet are slim, small and smooth and there is constant hand wringing and rubbing and bruxism. There is no speech. Thoracolumbar scoliosis was noted.

Investigations
- CT scan and EEG were normal.
- Urine aminogram reducing sugar and ferric chloride were negative
- The brain stem evokved response was normal
- T4 level was 11.1 ug/dl

Case 2:
NSB, a Malay girl was born on 23.5.1988. She was the youngest in a family of five and the product of a non related marriage. Her birth history was normal. She was born full term by vaginal delivery. Her birth weight was 3 kg and head circumference 33 cm. The pre, peri and postnatal periods were normal.

Development history:
NSB had normal developmental till the age of 10 months. She held her head up at two months, turned over at four months, sat up at eight months and stood with support at 10 months. At 10 months she had a febrile fit and soon after her parents noted regression of milestones. She was unable to stand at one year but could sit with support. At six months she was able to reach out for objects and at eight months was playing very well. However after her 10th month parents noted that she was not reaching for objects and had begun to hold her hands together and wring them. At nine months she had said "papa" and "mama", but after 10 months she no longer spoke these words. Emotionally, autistic features have set in and she had become less responsive after 10 months. Eye contact with parents was poor. She had no interest in people or surroundings but instead tended to put her hands into her mouth. She stared into space a lot and facial expressions were minimal.

She had never been able to feed herself and is still incontinent. Feeding is slow but not much of a problem at the present moment. Bruxism was present since 1 year but no episodes of apnea or hyperventilation had been noted. At present, she is seizure free but is profoundly retarded and totally dependent on her parents.

Clinical examination:

NSB is presently well nourished. Her weight and height are in the 25th centile but her head circumference at 44.5 cm is less than the 3rd centile. The tone and reflexes are normal in all four limbs. Her plantars are downgoing. Cranial nerves are intact. The characteristic hand wringing is present with occasional mouthing. Her facial expressions are poor and there is minimal eye to eye contact. There is no intelligible speech.

Investigations: CT Scan was Normal but EEG showed multifacial discharges

Urine ferric chloride, reducing sugars and aminogram were negative.

The T4 level was 120 mmol/l (N)

Discussion

Since its first description in 1966 by Rett and its worldwide publicity in 1983 by Hagberg, neurologists have been trying to detect a possible scientific marker for Rett Syndrome. This has remained elusive. Diagnosis of Rett Syndrome is thus clinical, based on the fulfilment of specific necessary criteria. Supportive criteria and exclusive criteria have also to be considered. Hagberg & Witt Engerstorm set up a diagnostic criteria (Table 1) and this has since been enlarged on by the 41 member Rett Syndrome Diagnostic Criteria Work Group representing the Centers for Disease Control and the International Rett Syndrome Association set up in 1989 (Table 2A, 2B, 2C).[6]

Both our cases fulfil the necessary criteria. The first case had a number of supportive criteria i.e. seizures, spasticity of both lower limbs, scoliosis and small feet. The second case will have to be followed up longer to see how she evolves. Case 1 was diagnosed as Rett Syndrome at the age of four years and was previously labelled cerebral palsy with profound deafness and infantile autism. Case 2 was diagnosed as Rett Syndrome at the age of 23 months when first seen by a paediatrician. She was referred for delayed milestones.

There is no one single sign or symptom that is pathognomonic for Rett Syndrome. Hence differential diagnoses have to be considered and the patients followed up closely to see their evolution.

Table 1
Diagnostic criteria for Rett Syndrome (Hagberb and Engerstrom)

1. Female sex
2. Normal pre perinatal period, with normal development in the first 6 – 18 months of life.
3. Normal head circumference at birth, with deceleration of head growth between six months and 4 years.
4. Early behavioural, social and psychomotor regression, with evolving communication dysfunction and dementia.
5. Loss of purposeful hand skills, between ages 1 and 4 years.
6. Hand wringing/clapping/washing sterotypes, between ages 1 and 4 years.
7. Gait apraxia, truncal apraxia/ataxia, between ages 1 and 4 years.

Table 2A
Necessary criteria for Rett Syndrome

1. Apparently normal prenatal and perinatal period.
2. Apparently normal psychomotor developmental through the first 6 months of life.
3. Normal head circumference at birth.
4. Deceleration of head growth between ages 5 months and 4 years.
5. Loss of acquired purposeful hand skills between ages 6 and 30 months, temporarily associated with communication dysfunction and social withdrawal.
6. Development of severely impaired expressive and receptive language, and presence of apparent severe psychomotor retardation.
7. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and "washing"/rubbing automatisms appearing after purposeful hand skills are lost.
8. Appearance of gait apraxia and truncal apraxia/ataxia between ages 1 – 4 years.
9. Diagnosis tentative until 2 – 5 years of age.

Table 2B
Supportive criteria for Rett Syndrome

1. Breathing dysfunction
   (a) Periodic apnea during wakefulness
   (b) Intermittent hyperventilation.
   (c) Breath holding spells
   (d) Forced expulsion of air or saliva.
2. EEG Abnormalities
   (a) Slow waking background and intermittent rhythmical slowing (3 – 5 hz).
   (b) Epileptiform discharges, with or without clinical seizures.
3. Seizures.
4. Spasticity often with associated development of muscles wasting and dystonia.
5. Peripheral vasomotor disturbances.
6. Scoliosis.
7. Growth retardation.
8. Hypotrophic small feet..

Table 2C
Exclusion criteria for Rett Syndrome

1.	Evidence of intrauterine growth retardation.
2.	Organomegaly or other signs of storage disease.
3.	Retinopathy or optic atrophy.
4.	Microcephaly at birth.
5.	Evidence of perinatally acquired brain damage.
6.	Existence of identifiable metabolic or other progressive neurologic disorder.
7.	Acquired neurologic disorders resulting from severe infections or head trauma.

Differential diagnoses to be considered are neurodegenerative disorders e.g. the leukodystrophies, neuronal ceroid lipofuscinosis, spinocerebellar heredoataxias and infantile autism[7]

The presence of typical steretopic hand wringing self stimulatory behaviour should make one consider Rett Syndrome in any girl presenting with developmental delay. As in both our girls, the characteristic hand wringing were the pointers towards Rett Syndrome and on close scrutiny all other necessary criteria were fulfilled.

Hagberg and Engerstrom suggested a staging system (Table 3)[8] to help clinicians in diagnosis and prognosis. Case 1 is presently in Stage III – the plateau phase and Case 2 is in Stage II or the deterioration phase.

With the use of a set criteria and staging, uniformity may be ensured to allow for a clinical diagnosis and subsequently follow up and care of these girls.

Hyperventilation[9] is noted to be a prominent feature in Rett Syndrome though not noted in our case . It is generally present in the awake state and is said to be the primary problem. Hypoxemia that en' ..es is a consequence of prolonged apneic episodes induced by hyperventilation.

Investigations are also non-specific. CT Scan may show up cerebral atrophy and neuropa..iolgoical studies have shown many abnormalities.[10,11] EEG changes have also been noted to follow a certain pattern (Hagne et al 1989).[12] EEG, are normal initially. The first abnormality are rolandic spikes, often followed by other epileptic patterns and in more advanced stages a pseudoperiodic delta pattern and occasionally generalised periodic spike actively.

Rett Syndrome has been reported only among girls with concordance in monozygotic twins and discordance in dizygotic twins.

A possible genetic etiology – probably X linked dominant and lethal with a high mutation rate explains the number of cases that appears to present sporadically. Translocation between Chromosome X and 3 and between Chromosome X and 22 have been reported. The breakpoints appears to be in the region of the Duchenne Muscular Dystrophy gene and is abnormal.[13,14] The empiric recurrence risk is still low at present – 0.3%.[15]

Table 3
Staging system to help in diagnosis and prognosis of Rett Syndrome

1.	STAGNATION (age 6 – 18 months; duration : months) – developmental delay/arrest, personality change with diminished interest in play, decelerating head and somatic growth rates.
2.	DETERIORATION (age 1 – 3 years; duration : weeks to months) – loss of acquired abilities including cognition, speech, and use; autistic features; hand stereotypies, hyperventilation; clumsy movements (apraxia); seizures may begin.
3.	PLATEAU (preschool to early school age; duration :years) – no further loss of skills, less autistic, prominant gait apraxia/ataxia, seizures common (75%), severe mental retardation.
4.	MOTOR DETERIORATION (age 5 –25+ years; duration : decades) – decreasing mobility with spasticity, scoliosis, muscle wasting, vasomotor disturbance, cachexia in some, improved emotional contact.

The aetiology is unknown. No consistent metabolic, morphological or neuroradiologic abnormality has been found. As there is lack of effective treatment, treatment is mainly supportive and symptomatic. Music therapy has a calming effect.[16] Occupational therapy and physiotherapy are important for preserving existing capabilities and functions.[17] Seizure therapy should be started if clinically significant. Ketogenic diets appears to have a beneficial effect.[18]

Diagnosis will come as a relief to some parents as they would probably have been seeing many docotrs. This is so even if it will have no implication whatsoever for the future of the child. Knowing the diagnosis can help them to deal with the reality of the prognosis, plan for the future and seek help from parents' support group. The International Rett Syndrome Parents Association is such a body set up to enable exchange of information and may provide relief to the parental burden.

'Form Fruste' and atypical cases of Rett Syndrome has been reported by Hagberb[19] and Goutierres.[20] These girls fulfil the criteria partially and lack some of the essential characteristics.

Even as advances albeit slow are made in understanding this syndrome, it should always be considered in every girl who are assessed for development delay. Greater awareness leads to recognnition of more cases hence allowing for continued study and research to help better understanding this debilitating condition.

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