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Rett Syndrome: some Behavioural Aspects and an Overview

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A brief review of the Rett syndrome is presented. The main clinical features are onset of mental deterioration, in girls only, between the ages of 6 and 18 months, all of whom later develop peculiar stereotyped repetitive movements resembling hand washing. The cause is unknown; the condition occurs more often than phenylketonuria and laboratory tests are normal. Random sequences of hyperventilation-apnoea-normal breathing appear in a considerable number of girls and are accompanied by certain EEG features. The nature of the repetitive manual and respiratory phenomena is discussed. We suggest that these behavioural peculiarities may be a form of communication, possibly pleasurable and to some extent interchangeable.

Introduction

It needed coincidence, serendipity, and the shrewd mind of a very observant paediatrician to make the world aware of the Rett syndrome which bears its discoverer's name.

Over 30 years ago two girls trying to wash their hands in thin air were simultaneously restrained by their respective mothers in a doctor's waiting room in Vienna. This very peculiar hand movement initiated a search for similar children and eventually led to a study of the first 21 by the doctor, Professor Rett (1966). Nearly two decades elapsed until the syndrome found its way to the English language medical literature (Hagberg *et al.*, 1983).

Clinical Features and Course

Rett syndrome is now recognized as a major form of mental handicap occurring in children with a normal family and prenatal history.

The peculiar repetitive hand movements are the hallmarks of the diagnosis and are unique to this condition. They appear most often in the form of hand washing or hand wringing; this may alternate with repetitive patting of the hands or the cheeks and is present for most of the waking state.

The children develop normally during the greater part of the first year of their life, the earliest age of onset being 6 months. Relatively abrupt cessation of development occurs usually during the first half of the second

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year of life when acquired microcephaly may develop owing to deceleration of head growth; regression follows and the children gradually lose the previously acquired motor skills.

Epilepsy—in the form of generalized convulsions and complex partial seizures—occurs in more than half of the children, usually starting after the age of 3 years. Responding well to the common anticonvulsants, especially carbamazepine and sodium valproate, epilepsy tends to improve or disappear after the second decade. During the age range when epilepsy is often a problem, daily periods of hyperventilation and apnoea may also occur. This breathing pattern appears independently from epilepsy although at times it may easily be interpreted as such.

The strict inclusion and exclusion criteria for establishing the diagnosis are seen in Table 1 (Trevathan and Moser, 1988). Some "formes frustes" are recognized but until biological markers become available these other forms are best accounted for separately. Life span is apparently not significantly impaired and several patients are known to have lived to the age of forty and beyond. For differential diagnosis by stages of the disease see Table 2 (Trevathan and Moser, 1988).

Epidemiology and Genetics

The aetiology is unknown.

Until now all known cases have been girls. However, in order to avoid future bias female sex was not included in the diagnostic criteria.

The condition is less uncommon than previously assumed. Epidemiological studies are incomplete; the prevalence is thought to be 1 in 15 000 girls (Kerr and Stephenson, 1985; Hagberg, 1985), twice as a common as the sex specific prevalence of phenylketonuria, a condition which is screened for in all neonates of developed countries. The disease is genetic but usually not familial. The question whether the syndrome is inherited has to be answered with a "don't know" but in summer 1989 a baby girl was born to a Swedish woman suffering from Rett syndrome (Witt-Engerström, personal communication, 1989). It is too early to say whether she will take her 50% chance to remain healthy or her equally 50% chance to develop the Rett syndrome. Scientifically it proves only that the reproductive system in the girls with Rett syndrome remains intact. This incident will not enhance our knowledge regarding the underlying genetic mechanism. With few exceptions the disease appears solitarily; the current thought is that Rett syndrome is caused by X-linked dominant mutation leading, in the case of the male embryo, to non-implantation or early abortion; every case would result from a new mutation (Hagberg *et al.*, 1983); Trevathan and Moser, 1988).

The theory of X-linked dominant mutation would well explain the extreme rarity of more than one affected person in the family, as the probability of the same mutation occurring twice is infinitesimal.

TABLE 1. *Diagnostic Criteria for Rett Syndrome*

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

Supportive Criteria
Breathing dysfunction
  Periodic apnea during wakefulness
  Intermittent hyperventilation
  Breath-holding spells
  Forced expulsion of air or saliva
EEG abnormalities
  Slow waking background and intermittent rhythmical slowing (3–5 Hz)
  Epileptiform discharges, with or without clinical seizures
Seizures
Spasticity, often with associated development of muscle wasting and dystonia
Peripheral vasomotor disturbances
Scoliosis
Growth retardation
Hypotrophic small feet

Exclusion Criteria[a]
Evidence of intrauterine growth retardation
Organomegaly or other signs of storage disease
Retinopathy or optic atrophy
Microcephaly at birth
Evidence of perinatally acquired brain damage
Existence of identifiable metabolic or other progressive neurological disorder
Acquired neurological disorders resulting from severe infections or head trauma

[a] Modified from Hagberg *et al.*
[b] Development may appear to be normal for up to 18 months.

Anatomy and Physiology

The noradrenergic and the serotoninergic systems arising in the midbrain and brainstem (locus coeruleus and raphe nuclei) and the dopaminergic system (substantia nigra) project to the forebrain, and are implicated in the Rett syndrome. As very few cases have reached autopsy, this implication is based on polysomnographic studies (Nomura and Segawa, 1986); on a number of single observations when lowered serotonin levels and low normal

TABLE 2. *Rett Syndrome: Clinical characteristics and differential diagnosis by stage*

Stages (after Hagberg and Witt-Engerström)	*Clinical Characteristics*	*Differential Diagnosis*
Early onset deceleration stage Onset: 6–18 months Duration: months	Developmental stagnation Deceleration of head/brain growth Disinterest in play activity Hypotonia	Benign congenital hypotonia Prader-Willi syndrome Cerebral palsy
Rapid "destructive" stage Onset: 1–3 years Duration: weeks to months	Rapid developmental regression with irritability Loss of hand use Seizures Hand stereotypes: wringing, clapping/tapping mouthing Autistic manifestations Loss of expressive language Insomnia Self-abusive behavior (e.g., chewing fingers, slapping face)	Autism Psychosis Hearing or visual disturbance Encephalitis Infantile spasms (West syndrome) Tuberous sclerosis Ornithine transcarbamylase deficiency Phenylketonuria Infantile neuronal ceroidlipofuscinosis

Duration: months to years	Seizures Typical hand stereotypies: wringing, tapping, mouthing Prominent ataxia and apraxia Spasticity Hyperventilation, breath holding, aerophagia Apnoea during wakefulness Weight loss with excellent appetite Early scoliosis Bruxism	Leukodystrophies or other storage disorders Neuroaxonal dystrophy Lennox-Gastaut syndrome Angelman syndrome
Late motor deterioration stage Onset: 10+ years Duration: years	Combined upper and lower motor neuron signs Progressive scoliosis, muscle wasting, and rigidity Decreasing mobility—wheelchair-bound Growth retardation Improved eye contact Staring, "unfathomable" gaze Virtual absence of expressive and receptive language Trophic disturbance of feet Reduced seizure frequency Dystonia and chorea	Unknown degenerative disorder

dopamine levels were found; on the isolated finding that the large cells in the substantia nigra, normal in number, have a very reduced melanin content; on some PET scan studies (Nomura *et al.*, 1984; Moser, 1988).

The involvement of these systems would explain the disturbance of sleep rhythms, in the form of irregularity of the REM and non-REM cycle; the initial decrease in muscle tone with more difficulty in crawling than in walking; it would give support to the assumption that the dementing process may be the result of the disturbed development of the frontal cortex caused by the early lesion of the midbrain and brainstem (monoaminergic neurones). Loss of hand dominance and the symmetry of the stereotypic hand movements indicate interference in the interhemispherical connections. The stereotypic movements are associated with rhythmic discharge at approximately 5 Hz (Nomura and Segawa, 1986), similar in frequency to the resting tremor of Parkinson's disease; both disappear on attempting voluntary movements and during sleep.

Laboratory Tests

A wide range of biochemical testing of blood, urine and CSF has not shown consistent abnormalities. The earlier finding of hyperammonaemia was most probably an artefact and is no longer considered to be a feature of the syndrome. So far the EEG is the only laboratory test which, though not pathognomonic, is often abnormal. Slowing of the ongoing activity and epileptiform discharges are frequently encountered. The abnormalities can be categorized in four sequential stages (Verma *et al.*, 1986). However, this categorization mainly serves as a general guideline and is not of diagnostic or prognostic help in individual cases. We have described a periodic EEG pattern consisting of lower amplitude faster rhythms frequently alternating with bursts of higher amplitude slow waves (Elian and Rudolf, 1989). This pattern appeared only in those girls with the hyperventilation-apnoea.

Intellect and Behaviour

Dementia refers to a global deterioration of mental functioning in its intellectual, emotional and cognitive aspects; intellectual decline is the central feature (Mayer-Gross *et al.*, 1969). In line with the above definition, in the Rett syndrome the intellectual deterioration is the central symptom of onset; in addition to loss of motor skill and speech the girls become rather indifferent to their environment, fail to respond in a specific way to close family members indicating that these are not any longer recognized as such. The facial mime is poor and the expression on the face changes very little in response to the environment. Sensory stimuli have to be strong to be perceived. The face however retains for many years a "knowing", "with-it" quality; the girls seem to look at the world with meaningful eyes. In contrast to other people with severe mental retardation or with psychoses, from glancing at the face alone one would not suspect the severe intellectual

deficit. This paradoxical preservation of normal facial expression is often seen in patients of all ages with dementia.

The majority of patients have a pleasant disposition. A substantial proportion of their waking hours is spent busy with the idiosyncratic hand movements. The speed and intensity of the movements is increased at either extreme of their emotional scale, i.e. when "bored" and when "excited" or alarmed. More explicitly, the repetitive hand movements are seen especially when the girls are left alone, or when "handled", for example when food, clothing or the pram is brought to their attention and activity anticipated, or when frightened.

A proportion of the girls shows an unusual respiratory pattern, with hyperventilation, apnoea and normal breathing occurring in a random sequence during the waking hours; associated low CO_2 levels prevail. It occurs only when awake, never during sleep, indicating that the behavioural voluntary respiratory control system is involved.

There is no systematic study as to how many girls with Rett syndrome show the unusual breathing pattern; however, according to various inspired opinions one-third and perhaps up to two-thirds of the girls between the ages of 5 and 15 years have hyperventilation, apnoea or both. We are now in the process of investigating the prevalence and the natural course of the idiosyncratic sequence of hyperventilation, apnoea and normal breathing among the popoulation of Rett girls. The extraordinary breathing pattern is not yet explained. Among the various concepts and mechanisms suggested we mention breathing apraxia; hyperpnoea compensating for periods of disorganized breathing and hypoxia; primary hyperventilation with secondary apnoea (Glaze *et al.*, 1987; Southall *et al.*, 1988; Elian and Rudolf, 1989; Lugaresi and Cirignotta, 1982).

In those children who do show this peculiar breathing pattern it appears in very similar circumstances to the hand movements, i.e. when bored and alone, or when excited, anticipating activities (Elian and Rudolf, submitted for publication). Some data we have obtained on the subject are now being analyzed and will be reported. At present our interim impression is that at least in some children the hand movements seem to be interchangeable with altered respiration, i.e. when mothers try to restrict the hand movements, then the hyperventilation-apnoea may take over.

The children do not seem to be distressed nor in a panic state during episodes of hyperventilation or of apnoea; even when an episode is accompanied by profound cyanosis, it may often end with a happy smile. From the above observations and from other data we propose that the hyperventilation – apnoea – is a form of stereotyped communication, a playful pastime under voluntary control; its meaning may be not dissimilar to thumb-sucking, hair curling or other repetitive activities.

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