

Original article

Mind and brain in Rett disorder[☆]

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Abstract

Development and retention of speech is reported in 265 people with Rett syndrome: 30% (80) never gained real words, 55% (145) gained real words and lost them, 15% (40) retained some words and 6% of the total (16/265) continued to use phrases appropriately. Morphological studies of the cytoarchitecture of the speech areas in 14 cases indicate the existence of interhemispheric differences which form part of the infrastructure for speech processing. Ten adults with Rett syndrome and with meaningful speech are compared to age matched adults without speech. The profile of mind and strategies for coping with its problems are described by a family. Although the range in severity is wide the mental profile is remarkably consistent across the severity range with regard to both positive and negative aspects. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Rett and others first defined the syndrome from its associated mental and behavioural profile, recognisable even when the severity of the condition varies [1–7]. Early reports of monozygotic and concordant but dissimilar twins [8,9] and the clearly defined anatomy of the brain suggest that the many different mutations in *MECP2* lead to recognisably similar effects on brain structure [10–13]. The development of mutation testing [14–17] provides an opportunity to gain insight into the mental profile in Rett through recognition atypical presentations and experiences related by mildly affected individuals. This new knowledge will be of value in supporting those who are more severely affected.

The combination of motor and intellectual difficulties in Rett often makes it difficult to assess and support the learning capacities of the individual. Investigation of classic girls has usually suggested an infant level of understanding [18,19] but some studies have included less typical girls with preserved speech [20–22]. Zappella has suggested that people with preserved speech constitute a distinct, non-classic variant [23] however experience in the British survey suggests that there is no such clear distinction but rather a wide range in severity in the expression of the underlying disorder [8,24]. Examination of the normal brain indicates

that the anatomical infrastructures for speech and movement are closely related. Speech areas are activated when fine motor activities are undertaken or even considered without action [25,26] and primary motor areas are activated during speech and vocalisation without hand movements [27,28]. The thalamus is part of this integrative network and stimulation of the ventro-lateral thalamic nucleus disrupts speech articulation and increases the expiratory phase of respiration [29]. Basal ganglia disturbance may contribute to dysrhythmic breathing and the regression in speech skills in Rett [24,30,31]. Both motor and speech aspects of brain development therefore deserve careful scrutiny [32].

2. Aims

Our aim here is to establish the prevalence of speech in Rett in the UK, to survey these skills in the context of the mental and motor profiles and to consider the morphological basis for speech and implications for intervention.

3. Subjects and methods

The British Isles Rett Survey ($n = 967$, November 2000) consists of reports from physicians and families supplemented by direct clinical examination (AK). Many families take part in research studies and some have requested expert autopsy if death occurs. Routine mutation testing has recently become available (Angus Clarke, personal communication).

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Here one family (MW, TW) reports personally on the effects of a known Rett mutation.

Morphological studies of the speech areas are described in donated material (14 cases, 4–30 years) and 11 controls without previous history of neurological disease (4–59 years) [31–33]. In these cases cytoarchitecture and neuronal/ glial ratios were studied in Nissl stained sections. The architecture of synaptic vesicle proteins was studied by confocal microscopy using synaptophysin immunoreactivity (p-38-IR) as marker [30–33].

4. Results

Eighty-eight mutation test results had been reported to the British Survey by November 2000. Of people with classic Rett syndrome and full clinical data, 87.7% (50/57) had mutations identified and 12.3% (7/57) had not. Of 17 fully documented people with atypical Rett presentation 58.8% (ten of 17) have shown mutations and 41.2% (seven of 17) have not. Of cases not previously reported to the survey 2/10 (20%) had mutations and the others did not. Of four cases with full clinical data but judged not to have Rett none had mutations. Some mutations have been found by one laboratory but not by another. These figures give confidence in the clinical diagnosis of classic Rett, however clinically diagnosed cases with no mutation found clearly require a careful search for novel *MECP2* mutations and also for other genetic or external factors. Six of the 14 people (43%) with no mutation and either classic or atypical Rett belong to families with recurrences and it is clear that other mechanisms must still be considered in familial Rett.

Fig. 1 shows the proportions of people with classic or atypical Rett and full clinical data whose parents have reported their communicative behaviour longitudinally. ‘Words’ indicates two or more real words, clearly enunciated. ‘Kept speech’ indicates that such single words are still used, even if only rarely. ‘Speech in phrases’ indicates clear speech which can be understood by a stranger, used in context and in answer to some simple questions although some answers may have been practised. It can be seen that speech at some level is not rare in Rett. Also it should be

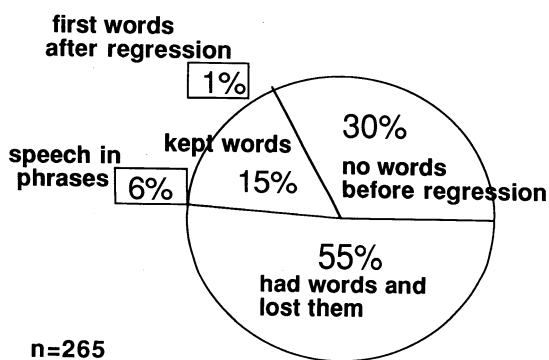


Fig. 1. Proportions of those acquiring and retaining clear words in 265 cases (classic and atypical) in the British Survey.

noted that it is not uncommon for an infant with Rett to fail to develop any words before regression even although regression has begun after the normal age for the first words to appear indicating significant delays before regression as demonstrated by earlier studies [4,24,34,35,36].

Table 1 compares the profiles of skill in ten fully documented British adults with Rett syndrome and speech in phrases (cases 1–10) and ten others (cases 11–20) age matched, but without such speech, selected randomly apart from cases 1 and 11 who are monozygotic twins with a *MECP2* mutation at position 255 (16). It can be appreciated that the women with speech have better head growth and gross and fine motor skills as judged by self feeding, feeding score, muscle tone, epilepsy, scoliosis and clinical severity score, compared to those without speech. However these two groups have the same mental profile, as judged by good vision, hearing, contact, responsiveness to music, sleep disturbance and proneness to agitation. It is noteworthy that preserved speech is frequently preceded by relatively good initial speech development. The feeding score (Fsc) gives points (maximum 20) for parent reported feeding difficulty due to shape or posture, mouth closure, chewing difficulty, swallowing difficulty, obstructing oral movements, vomiting or regurgitation, excessive secretions, poor appetite, difficulty accepting fluids and dependence in feeding. The severity score allocates points for muscle tone, locomotion, epilepsy, feeding difficulty and scoliosis, 100% indicating maximum severity [37].

Whereas, among the entire British cohort, classic Rett cases are in the majority [8,38], among those with preserved speech atypical cases predominate, their difference from the classic syndrome consisting in late or absent regression or lack of evidence that brain growth has slowed in early childhood. Since the people in this study without speech have reached adulthood it will be appreciated that they are among the most robust of the Rett cohort, some severely affected girls have died during adolescence [37]. Even allowing for this, the difference in motor severity between these and the women with preserved speech is quite clear.

Co-author, TW is a married woman of 33 years, with a daughter and son. TW has a Rett mutation 806 del G with skewed X inactivation, estimated at 85% in favour of the normal X. Her birth weight was 3.5 kg at term and head circumference was considered normal. She produced words at 2 years. There was no regression. At 8 years she learned to walk upstairs, one foot per step and first rode a tricycle. Neurological examination at that time recorded increased deep tendon reflexes with flexor plantar responses, low amplitude, high frequency tremor and poor recall of spoken figures. Intelligence quotient was estimated at 70. The assessment indicated ‘an attractive, pleasant child, anxious to please, with developmental immaturity and clumsiness’. Present OFC is 56 cm.

TW’s written contributions at 33 years, are reported verbatim here (questions in italics) maternal advice but no physical assistance was provided. Fig. 2 is sample of her

Table 1
Comparison of adults with and without preserved speech from the British Survey^a

| Case | Status | Yr | OFC | Regr | Speech | Self F | Resp | Fsc | Tone | Walk S | Ep | Scol | S (%) | Vis | Hear | Contact | Agit | Music | Sleep |
|------|----------------|----|-----|------|---------|--------|------|-----|------|--------|-----|------|-------|-----|------|---------|------|-------|-------|
| 1 | R** | 37 | 55 | 36 | Yes/Yes | Yes | Yes | 1 | N | Yes | No | No | 0 | Yes | Yes | Yes | Yes | Yes | NK |
| 2 | R** | 32 | 56 | 36 | Yes/Yes | Yes | Yes | 2 | Dys | Yes | Yes | No | 30 | Yes | Yes | Yes | Yes | Yes | NK |
| 3 | CR | 26 | 53 | 9 | Yes/Yes | Yes | Yes | 9 | Dys | No | Yes | Mild | 70 | Yes | Yes | Yes | Yes | Yes | Yes |
| 4 | CR | 37 | 53 | 24 | Yes/Yes | No | Yes | 5 | N | Yes | No | Op | 30 | Yes | Yes | Yes | Yes | Yes | Yes |
| 5 | CR | 28 | 52 | 18 | Yes/Yes | Yes | Yes | 5 | N | Yes | No | Op | 30 | Yes | Yes | Yes | Yes | Yes | Yes |
| 6 | R** | 17 | 52 | None | Yes/Yes | Yes | Yes | 0 | N | Yes | No | No | 0 | Yes | Yes | Yes | Yes | Yes | Yes |
| 7 | CR | 28 | 53 | 18 | Yes/Yes | Yes | Yes | 3 | N | Yes | Yes | Mild | 40 | Yes | Yes | Yes | Yes | Yes | Yes |
| 8 | R [†] | 24 | 56 | 8 yr | Yes/Yes | Yes | Yes | 5 | N | Yes | No | No | 10 | Yes | Yes | Yes | Yes | Yes | No |
| 9 | R [†] | 31 | 52 | 9 yr | Yes/Yes | Yes | Yes | 0 | Dys | Yes | No | No | 10 | Yes | Yes | Yes | Yes | Yes | No |
| 10 | R** | 31 | 49 | None | Yes/Yes | Yes | Yes | 1 | N | Yes | No | No | 0 | Yes | Yes | Yes | Yes | Yes | Yes |
| Mean | | 29 | 53 | | | | | 3.1 | | | | | 22% | | | | | | |
| 11 | CR | 37 | 52 | 24 | No/No | No | Yes | 5 | Hyp | No | No | Sev | 70 | Yes | Yes | Yes | Yes | Yes | NK |
| 12 | CR | 24 | 54 | 24 | Yes/No | No | Yes | 4 | Dys | Yes | No | Op | 40 | Yes | Yes | Yes | Yes | Yes | Yes |
| 13 | CR | 23 | 51 | 36 | No/No | No | Yes | 6 | Hyp | No | Yes | Mild | 70 | Yes | Yes | Yes | Yes | Yes | Yes |
| 14 | CR | 28 | 54 | 24 | No/No | No | Yes | 7 | Dys | No | Yes | Mild | 60 | Yes | Yes | Yes | Yes | Yes | Yes |
| 15 | CR | 19 | 49 | 15 | Yes/No | No | Yes | 5 | Dys | No | No | Op | 60 | Yes | Yes | Yes | Yes | Yes | Yes |
| 16 | CR | 32 | 51 | 15 | No/No | Yes | Yes | 10 | Dys | Yes | Yes | Sev | 70 | Yes | Yes | Yes | Yes | Yes | Yes |
| 17 | CR | 19 | 50 | 11 | No/No | No | Yes | 6 | Dys | Yes | Yes | Mod | 60 | Yes | Yes | Yes | Yes | Yes | Yes |
| 18 | CR | 37 | 51 | 18 | Yes/No | No | Yes | 5 | Dys | No | No | Mod | 50 | Yes | Yes | Yes | Yes | Yes | Yes |
| 19 | CR | 30 | 52 | 24 | No/No | No | Yes | 6 | Dys | Yes | No | Sev | 40 | Yes | Yes | Yes | Yes | Yes | Yes |
| 20 | Rep | 21 | 54 | 18 | No/No | No | Yes | 0 | Dys | No | Yes | Mild | 60 | Yes | Yes | Yes | Yes | Yes | Yes |
| Mean | | 27 | 52 | | | | | 5.4 | | | | | 58% | | | | | | |

^a Cases 1 and 11 are monozygotic twins with a mutation at 255. CR = classic Rett syndrome. R = atypical Rett. *Indicates no evidence of fall off in OFC. **Indicates no regression. [†]Indicates late regression. Ep (case no. 20) indicates epilepsy before regression. OFC = occipito-frontal circumference in cm. Regr = age in months at onset of regression. Speech/ indicates words used in early infancy and now. self F = able to feed unassisted with a spoon. resp = irregularity of breathing. Fsc = feeding score (see results section). tone = predominant abnormality of muscle tone at present, N = mildly increased, Dys = dystonic, Hyp = severely hypertonic. walk S = walks unassisted. Ep = epilepsy now present. Scol = scoliosis, Mod = moderate, Sev = severe. S (%) = severity score (see results section) higher% indicates greater severity. Vis: Hear = vision: hearing good. Contact indicates seeking face to face contact. Agit = agitation with severe unexplained excitement and sadness. Music = particularly responsive to selected music. Sleep = sleep disturbance, waking at night or sleeping by day. NK = not known.

careful drawing and writing. *Can you describe any difficulties with balance, walking, climbing etc?*

'I have a difficult time on ladders or chairs when I need something to climb on to reach something up high that I need. I can climb on high things if I have to but I rather not. Climbing is a very scary thing for me even now. When I was a teenager I used to trip over my own feet a lot. I was very clumsy at the time. I seemed to have gotten over most of my clumsiness'.

What problems do you have in using your hands and can you describe why you think this is difficult?

'I sometimes have a hard time picking up a coffee cup or anything heavy. I sometimes have a shake to my hands. The shakiness is more obvious in my right then it is in my left hand. The shakiness is more obvious if I haven't eaten in a while and are hungry. When I was a child my hands were kind of clumsy ...until I got passed being a teenager'.

What are your favourite TV programmes?

'My favourite TV programmes are the old ones from the fifties. I love musicals...I would like to add to this part of

the questionnaire that music has played a very large part in my life. I learned to do things by humming or singing. One example is I learned to set the table by humming and sometimes even singing'.

MW (mother of TW) relates:

My first concern about TW came immediately after birth when she failed to latch on to the breast well. The most noticeable thing about her was how passive and floppy she was. As an infant she was easily startled. She seemed to take longer to outgrow the difficulty that babies have when air is blowing in their faces. Starting at 9 months she developed problems sleeping at night. She would cry and cry... this became worse until about 6 years. These were called 'night terrors' but I called it inability to disengage from the world that hovers between sleep and consciousness. My solution.... a warm bath....to completely wake her up she quickly became tired and went into real sleep. ...

TW would learn by repeating. Her perseverance was incredible but the accomplishment was always one of rote – not of true comprehension....TW cannot perform, perceive, solve or simply hear more than one thing at a time. ...she has never been able to handle much noise, movement, crowds....Music



when I was a child my hands were kind of clumsy.
 I used to ~~not~~ accidentally break dishes when helping to
 wash them. I was kind of clumsy with things
 until I got up and being a teenager.

Fig. 2. Drawing and handwriting by TW aged 33 years.

was a godsend. It by-passed the standard routes for learning and gave her an avenue she could negotiate with ease.

TW's daughter has the same mutation as herself, random X-inactivation and classic Rett syndrome. TW's son had the same mutation and looked normal at birth, gained weight and made developmental progress which included smiling but then regressed. From birth he was hypotonic and suffered severe apnoeas during attempts to feed him. He died at 12 months during one such respiratory arrest. MW recognised the same problems as she had seen in the other children however in the boy they were much more severe [39].

This family's experience demonstrates how the same mutation may manifest as mild or severe disease depending on the pattern of X inactivation and also perhaps on other factors, genetic and non-genetic. In spite of this range of severity it is impressive that the mental and behavioural profile remains so consistent, making it possible to recognise the disorder at both extremes. Table 2 indicates the problems and strengths within this mental profile.

In a morphological study the cytoarchitecture of the speech areas in 14 Rett brains was compared to that in the controls [31–33]. There was no sign of abnormal migration of neurones. There was a reduction by 15–30% in the size of the largest neurones and the marker p38-IR was reduced in all the speech areas examined as compared to controls. Perineuronal satellitosis, which is the clustering of glial cells around neurones was increased. The interhemispheric difference was preserved in the motor speech areas 44 and 45. This interhemispheric difference is associated with the normal development of speech and in Rett is taken to indi-

cate that some morphological basis for speech processing is present [30–33].

5. Discussion

The fresh insights into difficulties and coping strategies in relatively mild Rett disorder provided by TW and MW illumine our understanding of more severe situations also. Their experience of the value of music is echoed by countless families and therapists. Sensitive used, this is certainly one of the foremost therapies for learning in Rett [36,40–43].

That music can be so effective indicates the presence of neural networks competent to receive and respond to its qualities. Trevarthen and Burford [41] have demonstrated that the girl with Rett responds well at an early infant level. Close interpersonal contact is very important to the infant and for this the brain of the new-born is well equipped with innate subcortical capacities to receive and invoke 'proto-conversations' [40,41]. The early responsiveness of the child with Rett is a genuine asset, developed, retained and accessible throughout life. The morphological studies indicate real although incomplete differentiation for speech in classic cases [30–33] and this, with the evidence of continued brain growth and the absence of major destructive processes [10–13], provides hope that appropriate intervention may encourage further brain development and learning [32].

The distinctive clinical deficits in people with Rett disorder direct attention to the normal processes of integration for movement, autonomic regulation and mentation [44–47]. Although the deficits in cortical connectivity may precipitate the late infancy regression crisis, these integrative functions rely on earlier developing, sub-cortical and brain stem functions [44–47]. The areas of competence in Rett are also informative, directing attention to some relatively spared receptive functions, vision and hearing and sexual capabilities including procreation. The Rett disorder appears to disable the forebrain and the related brain stem quite specifically. This predilection supports the concept of modular brain evolution and development which proposes that networks serving closely related functions have evolved

Table 2
The strengths and weaknesses in the mental profile in Rett

| Disadvantages in learning | Advantages in learning |
|------------------------------|---------------------------------|
| Poor postural awareness | Vision and hearing normal |
| Tremors and stereotypy | Accepts visual and tactile cues |
| Dyspraxic movements | Engages with people |
| Irregular breathing | Enjoys communication |
| Poor autonomic control | Very responsive to music |
| Inappropriate agitation | Learns through association |
| Epileptic seizures | Remembers what is learned |
| Problems receiving speech | Useful spontaneous actions |
| Problems producing speech | Patient and persistent |
| Lack of constructive thought | General health may be good |
| Sleep disturbance common | Improves around 20 years |

together and reflect comparable organisation at the genetic level [48].

In the development of the mammalian forebrain, cells disomic for the paternal genome contribute to those parts of the brain which are important for primary motivated behaviour (hypothalamus, pre-optic area and septum, maternal and feeding behaviour), relatively successful in Rett, while the cells disomic for the maternal genome contribute selectively to growth of the neocortex and striatum including the raphe nuclei, specifically disabled in Rett. It seems probable that in each case, development is co-ordinated by groups of genes which are themselves regulated by master genes. (Keverne, personal communication) [49,50] Such a role might be envisaged for *MECP2*.

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