Title

Prevalence and associated features of depression in women with Rett Syndrome

Abstract

Background: Little is known about depression among women with Rett syndrome (RTT) despite recent advances in knowledge about RTT. In this study, we aimed to establish the prevalence of depression among women with RTT as identified by a screening telephone interview and to explore the clinical factors associated with this.

Methods: The study employed the cross-sectional analysis of data from telephone interviews with carers of 56 women with RTT, using validated questionnaires for assessing mental health problems, challenging behaviour and RTT severity.

Results: Scores on the mental health assessment reached the affective/neurotic threshold in 8 cases (14.3%). No significant differences were found between those reaching the threshold and those who did not in terms of severity of RTT phenotype, health problems or social circumstances. There was a significant association between screening identified depression and higher lethargy and social withdrawal.

Conclusions:

Screening identified depression was found among a sizeable minority of women with RTT. Further investigation is needed to establish a clinically validated prevalence of depression among this group and to identify behavioural features that would lead to prompt psychiatric assessment.

Introduction

Rett Syndrome (RTT) is a profoundly disabling neurological condition usually caused by sporadic mutations of the *MECP2* gene (Trappe et al 2001). Almost exclusively affecting girls and with an incidence of approximately 1 in 10,000 female births, RTT is a relatively common genetic cause of profound intellectual disability in women (Hagberg 1985; Kerr & Engerström 2005). Neul *et al*. (2010) developed revised diagnostic criteria for RTT. Classic RTT requires apparently normal psychomotor development in the first 6 months of life followed by a period of regression (normally at around 12-18 months), which is not due to brain injury secondary to trauma, neurometabolic disease, or severe infection, and involves partial or complete loss of acquired purposeful hand skills and language, gait abnormalities and the development of stereotypic hand movements, followed by stabilisation or even some recovery. An important aspect of the regression is a period of social withdrawal or impaired communication. Atypical RTT requires a similar period of regression and subsequent stabilisation/ recovery, at least two of the above four behavioural manifestations and the presence of at least five, out of 11, supportive criteria. Other variant forms have also been described. Affected individuals remain dependent on others for many, if not all, of their daily needs.

Mental health problems are a considerable health burden and impact substantially on quality of life. Identification of mental health problems in people with intellectual disability, which is key for appropriate further investigation and treatment, however, can be difficult (Moss *et al*. 1998; Ross & Oliver 2003; Hurley 2006). Thus Cooper *et al*. (2007) found point prevalence rates for mental illness between 15.7% and 40.9% depending on the diagnostic criteria applied. Findings across diagnostic criteria were sensitive to whether problem behaviours and autistic spectrum disorder were included as indicative in themselves of mental ill-health. The reliance on behavioural signs of potential underlying psychopathology reflects both the inability in a sizeable proportion of the intellectual disability population to report internal states and the effects of developmental level on how psychiatric disorders

might present (Sturmey 1995). Assessment is particularly challenging among individuals with more severe intellectual disability, where different diagnostic measures may be required (Ross & Oliver 2003; Hurley 2006; Matson & Shoemaker 2011).

There is little evidence about mental ill-health among patients with RTT. Medline searches pairing Rett syndrome and either mental health or psychiatric diagnosis as key terms generated no articles where the mental health of people with RTT has been assessed. The most relevant papers either concerned autistic symptomotology (e.g., Kaufmann *et al*. 2012; Mount *et al*. 2003a) or a possible associated behavioural and emotional phenotype (e.g. Mount *et al*. 2001; 2003b; Matson *et al*. 2008). There is evidence that people with RTT have abrupt mood changes and periods of low mood (Mount *et al*. 2002; Halbach *et al*. 2013). Sansom *et al*. (1993) reported that individuals with RTT show patterns of anxiety and low mood characterised by brief rather than sustained episodes. The episodes of anxiety (reported in 76% of cases) seemed to differ from the episodes of low mood (reported in 70% of cases) and were reported to be precipitated by external events more so than the episodes of low mood. Mount *et al*. (2001) concluded that low mood was among behavioural and emotional features that required further detailed investigation.

Cianfaglione *et al*. (2015) measured mood, interest and pleasure among a sample of girls and women with RTT using the Mood, Interest and Pleasure Questionnaire Short-Form (Ross & Oliver 2003) and compared levels to a contrast group of individuals with other syndromes associated with severe and profound intellectual disability, matched for gender, age and functional level. They found no significant differences between the RTT and contrast groups either in total or in relation to its Mood or Interest and Pleasure subscales. However, analysis within the RTT sample (Cianfaglione *et al*. under review) showed that there was a significant deterioration in mood as individuals aged. Hence, it is important to consider depression as a possible comorbidity in women with RTT and to understand its

prevalence and whether there are any defining features of depression among individuals with RTT that would aid identification and appropriate management.

The primary aim of this study was, therefore, to assess the prevalence of depression among women with RTT as identified by a screening interview with carers. A secondary aim was to explore associated genetic characteristics, clinical severity and behavioural features of those who met the screening threshold for depression and contrast them with those who did not. To that end, we performed a cross sectional study analysing data from telephone interviews with carers of adolescents or women with RTT.

Methods

Survey sample

Before commencing the study, ethical approval was granted in May 2012. Individuals were recruited through the British Isles Rett Syndrome Survey (BIRSS). Inclusion criteria comprised women with RTT, aged 18 years and over, with a documented *MECP2* gene mutation, who were registered on the BIRSS and for whom consent had been received for invitation to participate in future research.

There were 93 individuals who met the inclusion criteria. Their carers (usually their parents) were sent a letter which detailed the research and invited them to participate. They were asked to return a form giving permission for their affected daughters to be included in the study as the affected individuals were over 18 years of age but lacked capacity to consent. Appropriate consent forms were returned by 56 (60.2%). Telephone interviews were then conducted between June and August 2012. Parents were respondents on behalf of 49 sample members (87.5%) and paid carers who knew the individual well responded for the remaining seven (12.5%). The individuals themselves were aged between 18 and 65 years (mean= 30.1, SD= 10.60) and had either classical (n=47, 83.9%) or atypical RTT (n=9, 16.1%). Simplified severity scores (see below) ranged from 3 to15 with a mean of 8.8 (SD=3.24). Half had mild (score ≤ 9) and half had more severe RTT (score>9).

Measurement

Demographic information and certain RTT specific data were abstracted from the BIRSS database. BIRSS information was confirmed at interview to ensure that it was up-to-date.

Simplified Severity Score (Smeets *et al*. 2009). Information was requested about six features of RTT: sitting, walking, hand use, speech, epilepsy and spine deformation. Each domain is scored from 0 to 3, where 0 indicates a normal situation, 1 indicates impaired ability to sit and walk, reduced hand use, some words, epilepsy is controlled with medication and scoliosis is mild; 2 indicates that the abilities to sit, walk, use hands and speak are lost, epilepsy is uncontrolled and scoliosis is severe; 3 indicates that the individual never acquired the abilities to sit, walk, use hands and speak, status epilepticus occurs and scoliosis has been operated upon. The score, which has a maximum of 18, evaluates the overall severity of the syndrome and indicates domains that are considered to influence evolution and severity in the long term. Scores of 9 or less are considered mild or less severe.

Psychiatric Assessment Schedule for Adults with Developmental Disabilities (PAS-ADD Checklist) (Moss *et al*. 1998) The PAS-ADD Checklist is a validated 25-question checklist for use by those who know the individual well to screen for mental health problems in individuals with intellectual disability (Moss *et al*. 1998; Taylor *et al*. 2004). Respondents are asked to consider the prior 4 weeks with answers reflecting whether a characteristic has been a problem and to what extent (Moss *et al*. 1998). The assessment generates total scores for organic, affective/neurotic and psychotic disorders, which can be compared to specified threshold levels to identify individuals requiring appropriate follow up by clinical assessment and specialist referral (Moss *et al*. 1998; Taylor *et al*. 2004). Scores above the affective/neurotic disorder threshold in this study were regarded to indicate ‘screening identified depression’.

Aberrant Behavior Checklist (ABC) (Aman *et al*. 1985a and b) The ABC is a62-item questionnaire addressing behavioural psychopathology in five domains: Irritability, Lethargy and Social Withdrawal, Stereotypic behaviour, Hyperactivity/Non-compliance and Inappropriate Speech.

Data analysis

Total scores for each individual were calculated for the Simplified Severity Score, PAS-ADD Checklist diagnostic areas and ABC domains. Those reaching the PAS-ADD Checklist threshold score for organic, affective/neurotic and psychotic disorders were identified. BIRSS characteristics and additional questions from the telephone interviews were also included in the analysis. The Statistical Package for the Social Sciences, version 20, was used to carry out Pearson chi-squared analyses for associations between categorical variables. Since the Simplified Severity Score and ABC Stereotypic Behaviour domain score met the assumptions of normality of distribution and homogeneity of variance, parametric t-tests were used for these variables. Non-parametric Mann-Whitney U tests were used for the other continuous variables. Statistical significance was considered at $p<0.05$. All 56 participants have been included in each analysis unless otherwise stated.

Results

Prevalence of depression

Table 1 summarises the PAS-ADD results. No individual reached the threshold of 5 for organic disorder or of 2 for psychotic disorder. Almost half of the sample group (n=27, 48.2%) scored 0 on the affective/neurotic domain but 8 individuals reached the affective/neurotic threshold of 6, giving a prevalence of 14.3% for screening identified depression.

Features associated with depression

Individuals reaching the threshold for possible affective/neurotic disorder were compared to those not reaching the threshold to determine if there were significant differences between the two groups. A summary of these results is set out in Table 2. The only statistically significant difference between the two groups was in the ABC Lethargy and Social Withdrawal domain score ($U= 291$, $z= 2.32$, $p<0.05$). Higher scores were associated with screening identified depression.

Seven individuals (12.5%) were currently prescribed anti-depressant medication (see Table 2). However, only one individual with screening identified depression was among those taking anti-depressants. Six women with screening identified depression were not receiving anti-depressive medication.

Discussion

The current study sought to establish the level of screening identified depression among women with RTT. It has a number of limitations. First, the use of the screening assessment is likely to overestimate the occurrence of depression. No follow-up of those screening positive for possible depression was undertaken and so further research is required to determine a clinically validated prevalence of depression. Second, the achieved sample was relatively small, albeit that it was taken from a national database with good diagnostic information. In addition, multiple comparisons were made in pursuit of the secondary research aim to determine if those screening positive for possible depression differed in other ways from those who did not. The small sample size meant that the study may well have been under-powered to detect differences between subgroups and applying a Bonferroni correction for multiple comparisons would have exacerbated the problem. As it was, only one statistically significant difference between the groups was identified and the association between lethargy and social withdrawal and depression makes intuitive sense. This may indicate social indifference, social avoidance, and lack of reactivity; perhaps those screening positive were more anxious or aloof.

The prevalence of depression of 14.3% as identified by screening is similar to the 14% found by Taylor *et al*. (2004), also using the PAS-ADD Checklist screen in a wider sample of people with ID. However a higher prevalence of 16.7% was found in women in that study, as is the case in the general population (Singleton *et al*. 2001). Taylor *et al.* (2004) were unable to assess intellectual disability severity and, due to the severity of intellectual disability among women with RTT, are likely to have included individuals with milder intellectual disability than our sample. This may account for the lower prevalence among women found here, as individuals with severe to profound intellectual disability may experience lower levels of depression than those with mild to moderate intellectual disability.. Cooper *et al*. (2007) give a point prevalence of 6.6% for affective disorders in a sample of people with intellectual disability and 8.6% for women with moderate to profound intellectual disability. These lower rates compared to our findings and those of Taylor et al. (2004) may be explained by the fact that Cooper *et al*. (2007) used clinical assessment for the diagnosis of depression rather than a screening tool, which is designed to be over inclusive.

An important finding was the lack of association between anti-depressant use and screening identified depression. Six of the seven individuals taking anti-depressants did not screen positive for depression. It is possible that individuals taking anti-depressants may not be identified by a screening assessment as having the symptoms of depression if treatment has been successful. Rather, they may be in need of medication review. However, the majority of those screened as having symptoms of depression were not receiving pharmaceutical treatment and this may indicate that greater awareness of the needs of this population is required.

Apart from the significant association between depression and lethargy and social withdrawal, a number of typical features of depression such as reduced food intake, sleep problems and mood variables were found in higher proportions in the screening identified depression group but differences did not reach statistical significance. It is possible that a future study with greater power would detect significant associations. It is important to

establish reliable behavioural signs of depression among those with severe to profound intellectual disability as they may have unusual presenting symptoms (Marston *et al*. 1997; Ross & Oliver, 2003; Hurley 2006; Matson & Shoemaker 2011). In particular, where lability of mood, social impairment and lack of activity may be seen as characteristic, as in RTT, it is vital to identify signs that could be used to trigger psychiatric examination for depression.

Conclusions

Women with RTT do appear to experience depression as identified by a screening interview with carers. Those screening positive for depression were also assessed as having greater lethargy and social withdrawal. Further research, with a larger sample, is required to establish a clinically validated prevalence of depression and to investigate characteristics of individuals with RTT possibly associated with the diagnosis that might indicate the need for psychiatric assessment.

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Table 1: PAS-ADD scores

Domain	Range (max. score)	Mean score (SD)	Threshold score	% Reaching threshold (number)
Organic condition	0-3 (8)	0.4 (0.65)	5	0 (0)
Psychotic disorder	0-1 (4)	0.1 (0.35)	2	0 (0)
Affective/neurotic disorder	0-11 (25)	2.2 (3.09)	6	14.3% (8)

Table 2: Features associated with depression

Variable		Below threshold (n= 48)	Above threshold (n = 8)	Sig.
Mean **age in years** (SD)		30.2(10.86)	29.8 (9.56)	NS
Mean **ABC domain** scores (SD)				
Irritability		8.2 (6.27)	13.8 (9.996)	NS
Lethargy and social withdrawal		11.5 (7.74)	20.1 (10.26)	0.019*
Stereotypic behaviour		7.8 (2.94)	9.6 (4.47)	NS
Clinical RTT variables				
Clinical diagnosis	Classic RTT	85.4% (n= 41)	75% (n=6)	NS
	Atypical RTT	14.6% (n=7)	25% (n=2)	
MECP2 mutation	Early truncating	33.3% (n=16)	25% (n=2)	NS
	Late truncating	14.6% (n=7)	25% (n=2)	
	Missense	33.3% (n=16)	12.5% (n=1)	
	C-terminal deletion	16.7% (n=8)	37.5% (n=3)	
	Large deletion	2.1% (n=1)	0% (n=0)	
Simplified severity score	Mean score (SD)	8.77 (3.204)	8.75 (3.694)	NS
	Mild	52.1% (n=25)	37.5% (n=3)	NS
	Severe	47.9% (n=23)	62.5% (n=5)	
BIRSS derived variables				
Communication				
Uses 0-1 word only		85.4% (n=41)	75% (n=6)	NS
Understands words without gestures		68.8% (n=33)	62.5% (n=5)	NS
Makes good eye contact		91.7% (n=44)	100% (n=8)	NS
Physical ability				
Use of hands	Uses spoon +/- mug	20.8% (n=10)	12.5% (n=1)	NS
	Finger feeds only	20.8% (n=10)	12.5% (n=1)	
	None	58.3% (n= 28)	75% (n= 6)	
Walking	Walks alone	43.8% (n=21)	37.5% (n= 3)	NS
	Walks with help	25% (n= 12)	12.5% (n=1)	
	Cannot walk	31.3% (n= 15)	50% (n=4)	
Sitting	Sits alone	64.6% (n=31)	50% (n=4)	NS

	Sits with help	12.5% (n=6)	12.5% (n=1)	
	Cannot sit	22.9% (n=11)	37.5% (n=3)	
Health factors				
Scoliosis		93.8% (n=45)	87.5% (n=7)	NS
Mean feeding difficulties score (SD)		3.3 (2.44)	5.3 (3.06)	NS
Breathing problems		89.6% (n=5)	87.5% (n=7)	NS
Epilepsy		75% (n=36)	62.5% (n=5)	NS
Medication	Regular medication	89.6% (n=43)	87.5% (n=7)	NS
	Anti-depressant medication	12.5% (n=6)	12.5% (n=1)	NS
Sphincter control	Total	25% (n=12)	37.5% (n=3)	NS
	Partial	37.5% (n=18)	25% (n=2)	
	None	37.5% (n=18)	37.5% (n=3)	
Emotional/behavioural factors				
Reported excitement		72.9% (n=35)	87.5% (n=7)	NS
Reported sadness		64.6% (n=31)	87.5% (n=7)	NS
Reported past depression		22.9% (n=11)	37.5% (n=3)	NS
Reported self-injury		27.1% (n=13)	25% (n=2)	NS
Reported injury to others *(total n=55)*		8.3% (n=4)	25% (n=2)	NS
Reported sleep problems		47.9% (n=23)	75% (n=6)	NS
Excessively sleepy		64.6% (n=31)	87.5% (n=7)	NS
Poor sleep		58.3% (n=28)	75% (n=6)	NS
Excessive appetite		37.5% (n=18)	50% (n=4)	NS
Poor food intake		27.1% (n=13)	37.5% (n=3)	NS
Other behaviours (in past 4 weeks)		16.7% (n=8)	37.5% (n=3)	NS
Social factors (events in past 2 years)				
Living with family		62.5% (n=30)	62.5% (n=5)	NS
Move of house or residence		12.5% (n=6)	12.5% (n=1)	NS

Death of first degree relative	2.1% (n=1)	0% (n=0)	NS
Death of family friend, carer/ other relative	22.9% (n=11)	0% (n=0)	NS
Serious illness/injury	25% (n=12)	37.5% (n=3)	NS
Serious illness/injury of relative/carer /friend	25% (n=12)	0% (n=0)	NS
Other event/ change in routine	12.5% (n=6)	25% (n=2)	NS
Parent respondent	89.6% (n= 43)	75% (n=6)	NS