ORIGINAL RESEARCH

Phenotypes in adult patients with Rett syndrome: results of a 13-year experience and insights into healthcare transition

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ABSTRACT

Background Rett syndrome is a complex genetic disorder with age-specific manifestations and over half of the patients surviving into middle age. However, little information about the phenotype of adult individuals with Rett syndrome is available, and mainly relies on questionnaires completed by caregivers. Here, we assess the clinical manifestations and management of adult patients with Rett syndrome and present our experience in transitioning from the paediatric to the adult clinic.

Methods We analysed the medical records and molecular data of women aged ≥18 years with a diagnosis of classic Rett syndrome and/or pathogenic variants in MECP2, CDKL5 and FOXP1, who were in charge of our clinic.

Results Of the 50 women with classic Rett syndrome, 94% had epilepsy (26% drug-resistant), 20% showed extrapyramidal signs, 40% sleep problems and 36% behavioural disorders. Eighty-six% patients exhibited gastrointestinal problems; 70% had scoliosis and 90% low bone density. Breathing irregularities were diagnosed in 60%. None of the patients had cardiac issues. CDKL5 patients experienced fewer breathing abnormalities than women with classic Rett syndrome.

Conclusion The delineation of an adult phenotype in Rett syndrome demonstrates the importance of a transitional programme and the need of a dedicated multidisciplinary team to optimise the clinical management of these patients.

INTRODUCTION

Rett syndrome (RTT, OMIM #312750) is one of the most common causes of intellectual disability (ID) in females, with an incidence of 1 in 10 000.1 According to the 2010 diagnostic criteria,1 typical RTT is defined by the presence of regression of purposeful hand use and spoken language, and development of gait abnormalities and hand stereotypes. In addition to the core neurodevelopmental manifestations, affected girls often show variable degrees of autonomic dysfunction,2 growth retardation, gastrointestinal (GI) discomfort3 and epilepsy.4 The clinical outcome is frequently complicated by variable motor impairment,4 skeletal abnormalities such as scoliosis,3 low bone density and increased risk of fractures.5 Approximately 60% of individuals with RTT from large cohorts from North America6 and Australia7 have been reported to potentially survive into middle age. Clinicians are therefore increasingly faced with managing the complexity of RTT in adulthood. However, little information has been available about these patients’ health status, and most studies were conducted using questionnaires completed by caregivers. In 2013, researchers from Maastricht University together with the Dutch Rett Syndrome Association reported a slow and progressive deterioration of gross motor functioning in contrast to better preserved cognitive functioning, less autonomic and epileptic features and overall good general health in adult patients.8 In 2010, we evaluated the main clinical features and health status of adult Italian patients with RTT, and identified sleep, behavioural issues, autonomic disorders, GI and musculoskeletal problems as major problems, whereas epilepsy tended to improve.9 The major limitation of our previous study was that data were obtained from the patients’ parents in most cases, introducing a bias in the interpretation of some clinical details. Nevertheless, that study taught us that the complex phenotype of individuals with RTT requires more careful and extensive medical care, although guidelines for clinical management of adolescents and adults with RTT are not available. The majority of adults with RTT are treated in paediatric centres because of lack of specialised adult clinics.

At our hospital, we have established a transitional programme from paediatric to adult care for girls with RTT. In this paper, we will discuss the functioning of our specialised adult RTT clinic, and present the results of a study that investigated the medical issues in adults 13 years after the clinic was established. Starting from our clinical observations, we will discuss the major healthcare issues described thus far in women with RTT and propose a follow-up protocol for these patients in adulthood.

MATERIALS AND METHODS

Rett clinic

At San Paolo University Hospital in Milan (Italy), a group of physicians has developed experience in caring for patients with RTT, and a multidisciplinary Rett clinic was established in 2006. Overall, we have been caring for about 130 patients, of whom half are paediatric and half adults.

A paediatric neurologist and a paediatrician coordinate clinical care for children up to age 18.
years, and a neurologist is in charge of the adult clinic. These physicians also serve as clinical managers and schedule clinical encounters based on individual needs and following the local guidelines on surveillance and management (http://malattierare.marionegri.it/images/downloads/PDTA/PDTA_schede/sclerosis_tuberosa.pdf). In addition to neurologists and paediatricians, the multidisciplinary team consists of cardiologists, internal medicine doctors, a general surgeon, a clinical geneticist, a physical medicine doctor and a gynaecologist, while other specialists are involved only when needed. A medical unit called Disabled Advanced Medical Assistance (DAMA) has dedicated spaces and personnel (internal medicine, general surgery and registered nurses) for individuals with ID and complex disabilities, and a phone line and fast track to the emergency room for these patients. All the patients with ID who are seen at DAMA also receive a yearly dental visit.

Ours is currently the only adult RTT clinic in Northern Italy, and receives referrals from several other paediatric clinics when patients turn 18. We have a formal programme for transition and transfer of care that takes into account external referrals and ensures continuity of care for those paediatric individuals who are already known to our staff.

Based on the model of the tuberous sclerosis complex clinic, individuals with RTT are usually seen as outpatients (children every 6 months, adults yearly), and we try to schedule all specialty visits during 1 or 2 days. The clinical manager performs the last visit, reviewing all notes from other specialists’ visits, discussing the results and making a follow-up plan. He/she keeps contact with family doctors, therapists and patient organisations to coordinate care. After each clinical encounter, the results of each visit are transferred into an ad hoc database, which we use for research.

### Patients’ data
We included in the study all patients aged ≥18 years who were in charge to our Rett clinic (mostly since it was established) and who received the last medical visit between January 2018 and December 2019. The diagnosis of RTT was made according to the diagnostic criteria in use.1 We recorded demographic and genetic information for each patient, and evaluated major clinical issues and interventions.

### RESULTS
We included in this study 56 adult patients with RTT. Median age was 29 years (range 19–49). Forty-seven out of 56 (84%) had a pathogenic variant in **MECP2** (all except four had a diagnosis of classic RTT: one with preserved speech variant, and three with early onset seizure variant). Two patients carried a pathogenic variant in **CDKL5**, and two in **FOXG1**. The characteristics of these patients are summarised in table 1.

Two patients were found to have pathogenic variants in genes encoding GABA receptor subunits (**GABRG2** and **GABRB2** respectively, one with atypical RTT and one with typical RTT), and have been recently described elsewhere.13 No pathogenic variants were detected in two individuals with a clinical diagnosis of classic RTT, and testing was not available in another one with classic RTT.

For consistency, we focused our analysis on the 50 patients with **MECP2** pathogenic variants or a clinical diagnosis of typical RTT.

The main medical problems of the adult cohort are represented in figure 1. With regard to motor ability, 27/50 girls (54%) had lost the ability to walk independently, 18/50 (36%)...
were able to walk with support, while 5/50 (10%) were able to walk unattended. As expected in Italy, where individuals with ID are usually taken care of at home, only two women from the present cohort lived in an assisted living facility or nursing home.

Probably due to the bias that our centre is dedicated to epilepsy, the most prevalent disturbances were related to neurological problems: epilepsy was diagnosed in 47/50 (94%), and was drug resistant in 12/47 (26%) (the pathogenic variants found in these patients are listed in online supplemental table S1), with 10 patients (21%) having monthly seizures. All but five patients were on antiepileptic drugs (AEDs). Ten out of 50 (20%) showed extrapyramidal signs, such as dystonia and tremor. Hand stereotypies were evident in all the patients.

Sleep disturbances were diagnosed in 20/50 (40%), and highly interfered with family habits because of frequent nocturnal awakenings in 7/50 (14%). They were usually treated with melatonin. In one patient mirtazapine was used, and in another one gabapentin was prescribed.

Behavioural problems, such as irritability, agitation or crying/screaming outburst, were recorded in 18/50 (36%). Six patients were treated with antipsychotic drugs, mainly risperidone. When suspected, depression was treated with sertraline or quetiapine.

The great majority of our patients have muscular-skeletal problems. Scoliosis was diagnosed in 35/50 (70%). Of these patients, 10 received surgery, 14 needed bracing and the remaining did not show a scoliosis that was severe enough to need treatment. The patients with severe scoliosis were wheelchair. All but six (88%) had low bone density at densitometry. For these issues, almost all patients received calcium and vitamin D supplementation, but none of them was treated with bisphosphonates.

GI disturbances were seen in 43/50 (86%); constipation in 42/50 (84%), gastro-oesophageal reflux (GERD) in 17/50 (34%); two required Percutaneous Endoscopic Gastrostomy (PEG) and 3/50 (6%) experienced cholelithiasis. Assessment of GI issues was generally clinical, and treatment consisted of a combination of behavioural indications (feeding strategies and posture for GERD; adequate fibres and fluid intake for constipation) and pharmacological therapy (proton-pump inhibitors or domperidone for GERD; psyllium or oral osmotic laxatives for constipation).

Regarding autonomic system disturbances, 30/50 (60%) women exhibited breathing irregularities. Most of them (27/50, 54%) experienced apnoeas, 12/50 (24%) associated with hyperventilation and 7/50 (14%) hyperventilation only.

Heart rate disturbances or other cardiac issues were not identified in any women from this cohort.

Interestingly, 6/50 (12%) women suffered from recurrent urinary tract infections.

Menstrual irregularities were frequently reported, although they did not usually require specific treatments. In two women ovarian cysts detected, and surgery was indicated in one case.

DISCUSSION

Although RTT is characterised by a recognisable phenotype, the clinical manifestations associated with this syndrome vary with age. Recently, an increasing number of studies have started to assess medical morbidities of adult women with RTT, but results are not consistent and the Italian population—and a Southern European cohort, more generally speaking—has been rarely evaluated. To better understand the medical problems and to evaluate the efficacy of our transitional model, we conducted a clinical study based on chart reviews of the adult patients with RTT from our clinic (in contrast with previous studies based on surveys completed by caregivers).

Here, we describe the main problems experienced by adults with RTT and potential therapies to address them.

Patients with a clinical or molecular diagnosis of classic RTT (MECP2)

Neuromotor features

Motor features are widely compromised in RTT, with variable degrees of impairment related to genotype and age. In our cohort, only 10% of women kept their ability to walk independently. The women who maintained relative good motor performances (eg, walking, climbing and go down the stairs) had presented with a mild neurological phenotype since their childhood: they never had seizures or epilepsy was easily controlled, and they were able to keep objects in their hands for a while. This finding is in line with the report that girls carrying pathogenic variants associated with a milder phenotype achieve better gross motor scores, and some maintain the ability to walk until adults.

Interestingly, neurological impairments such as bradykinesia, dystonia and parkinsonism can be frequently seen in older women, and were also present in our sample in 20% of the women, whereas stereotypic hand movements tend to persist throughout life, and were evident in all the women, with different characteristics. However, no clear correlations were found between dystonia and ambulation. Several patients with movement disorders (dystonia, tremor, parkinsonism) maintained their ability to walk.

Epilepsy

Epilepsy is common in RTT, with prevalence varying between 60% and 90%, although seizure frequency might be overestimated due to the difficulty in differentiating seizures from non-epileptic paroxysmal events. Epilepsy onset usually occurs around 3–5 years of age, but seizures can appear even after 10 years of age. This information should be kept in mind when caring for adolescent and adult patients with RTT.

Since our centre has a long history in treating patients with complex epilepsies, women with RTT followed at San Paolo Hospital probably exhibit a worse neurological phenotype. Indeed, epilepsy was present in 94% of our patients. Seizures were drug resistant in 26%, in line with wider studies involving patients at all ages.

Figure 1 Bar graph showing the medical issues of our cohort of 50 adult patients with classic Rett syndrome. Dark blue: percentage of patients presenting specific problems; light blue: percentage of patients without the specific problems.
Although previous works demonstrated significant improvement in seizure disorder after the age of 20 years, recent studies showed that the lifetime course of epilepsy is higher than previously reported. Seizure remission is not so common, and only a small percentage of individuals are seizure-free and off AEDs. Moreover, patterns of relapse/remission over the life span are emerging, and modifications of the drug regimens are often required to achieve seizure control. Therefore, clinicians should also consider age-dependency when prescribing appropriate antiepileptic drugs in RTT. We recently reported evidence that valproic acid could be the most effective anti-epileptic drug in younger girls, and carbamazepine in patients aged 15 years or older.

In general, no specific MECP2 mutation is significantly associated with either seizure prevalence or severity, while higher Clinical Severity Scores and nutritional/growth problems are frequently related to epilepsy.

Sleep disturbances
Sleep problems are present in nearly all patients with RTT. In our previously published cohort, sleep disorders were reported in the majority of adult patients (77%), even though they were considered a mild problem by the parents. Considering the most frequent sleep disorders in relation to ageing, the prevalence of night laughing and screaming tend to decrease with age, while waking remains similar across age groups. In the present cohort, 40% of women exhibited sleep disturbances, and in 14% of them this problem had a remarkable impact on daily habits. This number is consistent with the study by Wong et al., who found a decreased prevalence of sleep problems with age.

Regarding therapeutic management of sleep disorders, experience from the Australian group suggests that melatonin is used in <5% of cases and provides only little benefit to the patients. Another Australian study showed the importance of sleep hygiene strategies, such as environment modifications, sleep practices and physiological factors, to reduce sleep disorders in individuals with RTT. If behavioural interventions are inadequate, clinicians should consider the use of medications including chronobiotic regulators such as melatonin, or GABA agonists (eg, gabapentin, mirtazapine).

Behavioural problems
Individuals with RTT have difficulties in communicating symptoms and problems of which caregivers may not be aware. Behavioural problems might therefore be a symptom of a health-related disorder, for which a complete clinical evaluation is mandatory.

In our sample, a third of women with RTT presented behavioural disturbances, which could not be related to health problems or environmental situations despite careful assessment, and were mainly characterised by agitation, crying and irritability. Sudden mood changes or periods of low mood have been described in adults with RTT. Cianfaglione et al reported significant deterioration in mood as individuals aged. Therefore, depression should be considered as a possible comorbidity in women with RTT that requires identification and appropriate management.

Lastly, also agitation and anxiety have been described in adults with RTT, with the latter improving in women older than 30 years of age.

Scoliosis
As expected and in line with previous studies, which show that up to 75% of girls receive a diagnosis of scoliosis by the age 15 years, 70% of women from our cohort had scoliosis. Protective effects of walking ability and milder genotype (such as the p.R133C, p.R294X and p.R306C pathogenic variants) have been demonstrated.

In order to monitor the progression of scoliosis, 6-monthly X-rays are suggested if the Cobb angle is >25° before skeletal maturity and 12 monthly X-rays after skeletal maturity until evidence of no further progression, following a specific protocol.

Although not proven to modify spine curvature in RTT, bracing is recommended in order to reduce the progression of scoliosis when curves reach 25°, while surgery should be considered when the Cobb angle is approximately 40° to 50°. Surgical outcomes may improve if intervention is done before the development of severe scoliosis and before the effects of other comorbidities, such as age-related reduction in mobility. Additional non-surgical approaches, such as intensively structured physical therapy environment, have been suggested to improve the Cobb angle, but need further evaluations.

Bone health
Although altered bone mineral density has been reported in about 50% of individuals with RTT, low bone density was documented on densitometry in around 90% of the women in our cohort. We may speculate that this finding can be explained by the characteristics of the sample, with an over-representation of patients treated with antiepileptic drugs and neurologically impaired. Indeed, anticonvulsant therapy, especially with valproate, is an additional risk factor for low bone density and increases fracture risk by threefold in RTT, compared with no or any other prescribed antiepileptic drugs. Also, non-ambulatory patients have a decreased bone mass.

Patients with lower bone density are exposed to a higher risk of fractures, occurring much more frequently in RTT than in the general population. Fractures often occur spontaneously, after minimal trauma or a fall, and predominantly in the upper/lower limbs long bones.

A panel of experts in RTT has recently developed clinical guidelines for the management of bone health. The guidelines are divided in two sections: clinical and bone density assessment, and non-pharmacological and pharmacological intervention strategies. DEXA scans should be used to assess baseline bone mineral density, and monitoring should be done every 1–2 years depending on clinical presentation, and should consider Z-score results as well as previous occurrence of fractures. The increase of physical activity or at least encouragement of supported standing are recommended as non-pharmacological interventions, and the increase of dietary intake of calcium-rich or calcium-fortified food and vitamin D supplementation are advised. While no clear evidence of benefit from the use of bisphosphonates exists, new potential treatment with zoledronic acid in RTT has been recently suggested as it resulted in an increase in bone density and a reduction in the incidence of fractures.

Gastrointestinal issues
It is widely known that GI and nutritional problems persist throughout life in girls and women with RTT. However, the type of problems seems to differ between children and adults. Affected women are significantly less likely to present with vomiting or regurgitation and GERD than children. On the
other hand, underweight, prolonged feeding time and swallowing difficulty—thus considering the need of gastrostomy placement—are typical of older individuals. As expected, also in our cohort constipation was one of the most frequent complaints, experienced by 84% of women, while GERD only by 34%.

Interestingly, we diagnosed cholelithiasis, or gallbladder disease, in a small number of patients. This finding has been recently proven to be relatively frequent in RTT, and should be suspected as one of the causes of abdominal pain.

An international consensus developed guidelines on assessment and management of GI disorders in RTT, with specific focus on GERD, constipation and abdominal bloating. For these issues, conservative strategies together with pharmacological/surgical interventions are recommended.

Management of growth and nutritional aspects is often challenging in RTT, and needs to consider feeding difficulties and nutritional needs. Although no clear recommendations for affected adults have been established, risk of aspiration and prolonged feeding times are factors that should be considered for gastrostomy indication.

Breathing problems
Caregivers reported breathing disturbances in approximately two-thirds of RTT girls in a worldwide-based cohort and in almost all patients with typical RTT in the USA, with onset usually occurring during early childhood. The prevalence of hyperventilation decreases over time, while breath holding tends to persist, as seen in our cohort. This finding can be explained by the lower survival rate of individuals with more severe respiratory problems. Based on the American natural history study, one of the most striking findings is the strong association between prolonged corrected QT interval and severe breathing dysfunction, which links to increased risk for sudden death.

The majority of patients do not receive any treatment for their breathing abnormalities, although the use of topiramate, acetazolamide, buspirone and fluoxetine has shown some benefits. Besides autonomic breathing disturbances, individuals with RTT may experience more complex respiratory dysfunctions. Lower airway inflammation and ventilation and perfusion mismatch are thought to be the mechanisms involved, leading to lower respiratory tract infections that often require hospitalisation. Walking seems to have protective effects on respiratory health, beyond the influence of specific MECP2 variants, suggesting that the maintenance of activity programmes should be supported, especially during adolescence and adulthood.

Cardiac issues
Of note, no cardiac problems were present in our cohort, supporting the findings that heart problems may not be as common as previously thought. Individuals with RTT had been reported to show ECG and rhythm abnormalities including prolonged corrected QT interval (QTc) and reduced heart-rate variability. However, more recent findings demonstrated that the prevalence of QTc prolongation in RTT is lower than previously thought and around 7%. No correlation between QTc and genotype was identified, but a positive trend towards a slight increase of QTc with age was reported. However, the clinical significance of QTc prolongation remains unknown. To date, no specific consensus has been established, and treatment is based on individual needs.

Gynaecological issues
Little is known about gynaecological problems in people with RTT. Longitudinal population-based data showed that, at 14 years of age, the median age of menarche in girls with RTT was slightly older than in the general population. This finding could be probably related to body mass index and to genotype.

Menstrual disturbances in women with RTT from our cohort were similar to what is seen in the general population. Hormonal contraception may be used, in forms of oral pills or depot medroxyprogesterone. Dysmenorrhea can be treated with non-steroidal anti-inflammatory drugs at appropriate doses, since the communication disability can make it difficult to evaluate the severity of pain experienced by these girls and women.

Patients with CDKL5 pathogenic variants
Although patients carrying mutations in the X linked cyclin-dependent kinase-like 5 gene (CDKL5, chr. Xp22.13, OMIM # 300203) were originally diagnosed as having the early onset seizure variant of RTT, recent evidence suggests that this disorder should be considered a distinct clinical entity. One of the major medical issues in these individuals is epilepsy, which is almost universally present and frequently drug-resistant, also in adulthood, as in our two patients. Sleep difficulties as well as GI problems seem to be very common in the CDKL5 disorder. Scoliosis tends to develop with increasing age, while our experience confirms that breathing abnormalities seem much less prevalent than in classic RTT.

Patients with FOXG1 pathogenic variants
Since the identification of FOXG1 (chr. 14q12, OMIM # 164874) as the gene responsible for the congenital form of RTT, the combination of neurodevelopmental and brain imaging features observed in individuals with FOXG1 pathogenic variants may be sufficiently distinctive to allow clinical recognition of this disorder, considered as the FOXG1 syndrome. Less than 10 adults with FOXG1 mutations have been described so far, mainly within large series of patients. Their phenotype is characterised by severe postnatal microcephaly, severe ID, absent language, autistic traits, epilepsy and a typical hyperkinetic-dyskinetic movement disorder. Poor sleep patterns, irritability in infancy, unexplained episodes of crying, recurrent aspiration and GERD have also been reported. To date, no specific studies have evaluated the morbidities of these individuals in adulthood. The two women with FOXG1 pathogenic variants in our cohort experienced epilepsy, but seizures were controlled by AEDs. GI problems, scoliosis and severe osteopenia with fracture were the main problems in our two patients, in addition to ID.

Strengths and limitations
Although smaller in sample size and retrospective in nature, this is one of the first studies that evaluated medical morbidities in adult women with RTT by medical records review in a specialised clinic instead of by surveys completed by caregivers, thus possibly providing more accurate data. The results of this preliminary assessment confirm the utility of our multidisciplinary clinic, which ensures that all the main comorbidities are addressed. On the other hand, the identification of previously underestimated medical issues allowed us to understand what requires to be implemented, such as the presence of a sleep medicine specialist who has now joined the clinic.

Despite having some pitfalls and facing limitations in economic and staff resources, we try to target patients’ needs and family’s demands, adjusting international guidelines to the Italian reality.
This has resulted in the creation of local protocols, as seen in table 2, which we propose to the international community. Finally, women with RTT—like women with ID in general—may face several barriers in accessing preventive cancer screening (eg, breast and cervical cancer). Clinicians generally focus more on acute problems or chronic disorders associated with the specific syndrome than to age-related screening programmes. Indeed, these issues should be always kept in mind, especially for individuals with communication disability.

In conclusion, we have discussed the main clinical issues that should be considered when transitioning patients with RTT to adult care, based on data from our study and from the literature. We underline the importance of establishing a multidisciplinary team and educating the adult team members about RTT. Larger international studies assessing the medical problems of adult women with RTT and experiences from other adult clinics are highly encouraged.

Acknowledgements The authors would like to thank all the healthcare professionals involved in the RTT clinic of the San Paolo Hospital in Milan for their valuable work and participation in the care of the patients: Francesca La Briolet, Katherine Turner, Daniela Golasen, Clilo Oggioni, Massimo Corona and Cinzia Paolini. The authors would also like to thank the families for kindly participating in this study, and Airett, the Italian Rett Association, for the support.

Contributors Conceptualisation of the ideas, formulation and evolution of research goals and aims, and writing the article: AP and AV. Revision of the article: MPC.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Patients described in the study have been followed at the Epilepsy Center of the San Paolo Hospital, University of Milan (Italy). Data were obtained from a dedicated database of patients with RTT, and informed consent to participate was obtained from the patients’ parents. The Ethics Committee of San Paolo Hospital, Milan approved the study (2019ST/098).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The datasets analysed during the current study are not publicly available due to privacy policy, but are available from the corresponding author on reasonable request.

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Phenotypes


