

Rett syndrome, motor development, mobility and orthostatic reactions

Loss of function, difficulties and possibilities

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Vancouver, swimming lesson

Every week I sit there and I watch with the other parents. We watch our kids and we talk a little bit. The pool is noisy, so it's not always the best place for a chat, but we still talk. This week we talk about school, about teachers, about special needs education, about parenting, and a lot more. It is a serious discussion, but we laugh a lot too.

We talk about how some people have a hard time teaching our kids, not because of our kids' special needs, but because these people feel sorry for them and assume they can't do things that they are actually capable of. "Oh poor you, you're not like the other kids! Let's lower our expectations right down to the floor for you!" That's pity and it doesn't help anyone, least of all our kids.

We talk about the other people, the really good teachers and instructors, educational assistants and therapists, who don't pity, who laugh and joke around with our kids and treat them like kids rather than special needs, the people who encourage them and help them achieve things they were always capable of, but were never given a chance to accomplish before. We talk about how each of them is such a kid, first and foremost, rather than "a kid with special needs".

And that's in 30 minutes. Meanwhile my son does a beautiful back float and then refuses to get out of the pool when his lesson is over. I'll be back next week for more, and so will he.

Maria Haskins Blog; Kids.Food.Life 2012-11-21

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Abstract

Rett syndrome (RTT) is a rare, severe neurodevelopmental disorder, which partly develops in a predictable way, and influences many bodily functions. Regression, i.e. loss of earlier achieved abilities, is one of the clinical criteria for RTT. Research on motor function has to some extent focused on this loss and less on the possibility to keep or develop abilities. RTT is mainly verified in girls/women and the prevalence of classic RTT in Sweden for girls born between 1965 and 1976 was 1 in 10.000-12.000 girls. There is no national register, and the true prevalence might not be known since the disorder can vary in severity and diagnosis can be missed. Clinical criteria are used for diagnosis, but since 1999 RTT can be confirmed by a genetic test. Several mutations on the MECP2-gene on the X-chromosome have been found. As there is no cure so far, development of clinical intervention and management is important and with good treatment it is possible to help and support people with RTT so that they can have good quality of life.

The main aim was to acquire more knowledge and understanding of motor development in RTT, both early development and development over time. Another aim was to study if there were deviating orthostatic reactions when rising from sitting to standing, and during standing, compared with normally developed, healthy people matched by sex and age, as a way of finding out if there is reason to limit standing and being active.

The two papers with case studies showed that it was possible for people with RTT to keep abilities, re-train abilities, and also learn new functions after regression. For good results the following were important: motivation, joint planning agreed upon for intervention, and understanding of the dependence on other people's initiatives due to dyspraxia in RTT. Information collected over several years showed the possibility to develop in some areas over time and the tendency to deteriorate in other areas. This was manifested further by reports from parents showing that some individuals with RTT had lost abilities, some had been able to keep abilities and some had been able to learn new abilities after regression. Movement transitions were difficult for many, even for those who were able to walk. Postural instability in sitting was reported for most people and the most common deformities were reported to be in the spine and feet. It was found that 73% started to walk; some stopped walking, some deteriorated, and some retrained walking after a period, in one case after many years. In order to find out if the deterioration in walking found in these previous studies was due to deviation in orthostatic reactions, a study was performed. Orthostatic reactions were defined as reactions of systolic blood pressure, diastolic blood pressure, mean arterial blood pressure and pulse, when rising from sitting and standing erect for three minutes. The results revealed that people with RTT mainly had the same reactions as the normally developed, healthy controls, matched by sex and age. The difference in resting values, with a tendency to higher heart rate and lower blood

pressures in RTT, was already known, but the quicker initial drop of systolic blood pressure when rising, in people with RTT, has not been documented earlier. Since those with RTT recovered their blood pressures in the same way as the healthy controls there is no reason to recommend limitations in standing.

In conclusion, these studies show that it is possible for some people with RTT to keep abilities, retrain/regain abilities, and learn new abilities after regression. In order to notice loss/deterioration or the possibility to keep or to develop abilities, individual analysis is important, as well as a good knowledge of the disorder's development and variation in expression, during a day and over time. The reactions of the pulse and blood pressures were the same in those with RTT as in healthy persons, but the quicker initial drop of systolic blood pressure in RTT should be noted. Helping or supporting people with RTT to remain standing might be important because their blood pressure recovered within the same time as controls. For individuals with a disability such as RTT, standing can be an important everyday activity for muscle workout and for keeping a range of motion in joints. For transitions such as standing up from sitting and moving to and from chairs, bed and toilet, the ability to stand is essential. Since most people with RTT live to adulthood, planning for intervention and care must be lifelong.

Since RTT remains a clinical diagnosis, physiotherapists working with newborn or young babies, with different or deviating development, have a special task. If they keep in mind the way RTT manifests itself early, as well as including parents' information, they can raise the question of RTT and initiate further medical examination which may confirm the diagnosis. Having an early diagnosis makes it possible to give early help and support to the child and to the family.

Svensk sammanfattning

Rett syndrom (RTT) är ett flerk Funktionshinder som orsakas av störning i den neurologiska utvecklingen. Syndromet utvecklas på ett delvis förutsägbart sätt, påverkar många av kroppens funktioner och tidig förlust av vissa funktioner ingår i kriterierna för diagnosen. Mycket forskning beträffande motorisk funktion har varit koncentrerad på förlusten av funktioner och mycket lite på vad som är möjligt att behålla eller utveckla. RTT har i huvudsak bekräftats hos flickor/kvinnor men enstaka pojkar och män har fått diagnosen. Efter att man 1999 upptäckt mutationer på MECP2-genen på X-kromosomen kan genetiskt test användas för att bekräfta en klinisk diagnos, men diagnosen är fortfarande baserad på kliniska kriterier. Prevalensen av klassiskt Rett syndrom i Sverige för flickor födda 1965-1976 var 1 på 10000-12000 och i Sverige har ungefär 270-280 flickor eller kvinnor fått diagnosen. Den verkliga prevalensen är osäker då syndromet varierar stort i uttryck och därför kan förbises och inget nationellt register ännu finns. Den återfinns i alla länder och är en förhållandevis ny och sällsynt diagnos. Då RTT är förhållandevis sällsynt har få studier omfattat stora grupper och fallstudier har varit ett sätt att dela med sig av erfarenheter. Forskningen har under senare år inriktats på genetiska frågor och mycket lite på grovmotorisk utveckling, grovmotorisk förmåga och kliniska insatser. Eftersom vi ännu inte kan bota RTT är utveckling av kliniska insatser och behandling ytterst viktigt. Goda behandlingsinsatser kan hjälpa och bidra till god livskvalitet.

Det övergripande syftet i dessa fyra delarbeten var att erhålla mer kunskap om och bättre förstå motorisk utveckling vid RTT, både den tidiga utvecklingen och utveckling över tid. Ytterligare syfte var att undersöka om det fanns avvikande reaktioner vid uppresning till stående och under stående, ortostatiska reaktioner, jämfört med friska personer av samma kön och i samma ålder.

Klinisk erfarenhet redovisad i artiklarna visade att det var möjligt att behålla rörelseomfång i fotleden över tid, återträna gång och förmåga till uppresning, liksom att lära ny förmåga, nytt sätt att resa sig från golvet, efter tillbakagången, regressionen. Det senare kunde sedan tillämpas självständigt och omväxlande med tidigare sätt. Viktigt för bra resultat var motivation hos individen med RTT, gemensam planering av insatserna och att alla förstod hur beroende personer med RTT är av att andra tar initiativ till aktivitet. I den fleråriga uppföljningen av en person med RTT fann man risk för försämring inom vissa områden som finmotorik och grovmotorik medan möjlighet till utveckling fanns inom andra områden som att lära sig och minnas. En enkät skickad till alla familjer med flickor och kvinnor med RTT i Sverige, visade på förlust av förmågor som gång, talade ord och förmåga att äta själv, men också att vissa hade behållit funktioner, några hade lärt nya funktioner efter en period av förlust och några hade lärt ny funktion efter tillbakagången, regressionen. Förflyttningar som att sätta sig i sängen, ställa sig upp från sittande och att sätta sig ner från stående, var svårt för ett stort antal,

även för personer som kunde gå. Osäker upprätning av kroppen i sittande gjorde att många lutade till sidorna eller framåt och vanligaste felställningarna rapporterades vara i fötter och rygg. Av de 73 % som lärde sig gå förlorade några sin gångförmåga, andra fick försämrad gång och några återtränade gången efter en tids uppehåll – i ett fall efter flera år.

De ortostatiska reaktionerna, dvs. reaktion och återhämtning av blodtryck och puls vid uppresning till stående, studerades för att undersöka om den förlust eller försämring av gången som konstaterats i tidigare studier kunde bero på avvikelser i denna funktion. Resultatet visade att personer med RTT reagerade i huvudsak på samma sätt som friska personer av samma kön och i motsvarande ålder, när de reste sig upp och stod i tre minuter. Att personerna med RTT tenderade att ha högre vilopuls och lägre blodtryck jämfört med kontrollpersonerna, var känt sedan tidigare, medan den snabbare sänkningen av det systoliska blodtrycket vid uppresning inte har rapporterats tidigare. Dock återhämtade sig personerna med RTT på samma sätt som de friska kontrollpersonerna och det finns ingen orsak att rekommendera begränsning av stående. De kan i stället vara viktigt att hjälpa/uppmuntra personerna med RTT att stå kvar då blodtrycket återhämtade sig inom samma tid som för kontrollpersonerna. För personer med ett funktionshinder som RTT kan stående vara en viktig daglig aktivitet för belastning av muskler, rörlighet i leder och är av stor betydelse vid förflyttning. Utifrån videofilmer tagna vid testtillfället framkom att personerna med RTT rörde sig mer jämfört med kontrollpersonerna och hade viss svårighet att behålla en rak kroppshållning under de tre minuter som testet pågick. De förstod tillsägelse att sträcka på sig och efterföljde uppmaningen.

Avhandlingen visar att det finns möjlighet för vissa att behålla funktion, återträna/återfå funktion efter en period av förlust, liksom att utveckla ny funktion efter regressionen, dvs. tillbakagången under småbarnsperioden. Reaktionerna av puls och blodtryck vid uppresning var densamma hos personer med RTT som hos den friska gruppen, men det snabbare initiala blodtrycksfallet som kan finnas vid RTT bör noteras. Vikten av individuell analys av motorisk funktion framhålls liksom medvetenhet om hur varierande symtomen kan vara, både inom en dag och över lång tid.

I det kliniska arbetet med barn och vuxna med ett så komplicerat funktionshinder som RTT, deras familjer, assistenter och lärare, är det mycket viktigt att ha god kunskap om hur syndromet utvecklas och hur varierande det kan yttra sig, för att inte förbise risk för förlust eller försämring – men inte heller förbise möjligheten att behålla eller utveckla förmågor. Då många personer med RTT lever upp till vuxen ålder är planering för livslånga insatser ytterst viktig.

Eftersom RTT fortfarande är en klinisk diagnos där utvalda kliniska symtom, kriterier, ingår, har personer som arbetar med nyfödda eller små barn med annorlunda eller avvikande utveckling, en speciell uppgift. Om

de har god kunskap om den tidiga utvecklingen av RTT och kombinerar det med föräldrarnas information, kan de väcka tanken på RTT och därmed ta initiativ till en fortsatt utredning som kanske kan bekräfta diagnosen tidigt. En tidig diagnos kan göra det möjligt att få tidig hjälp och stöd för barnet och familjen.

Abbreviations

ANS	Autonomic nervous system
BP	Blood pressure
CP	Cerebral palsy
CSB	Cardiac sensitivity to baroreflex
CVT	Cardiac vagal tone
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EEG	Electroencephalogram
HR	Heart rate
ISS	International Score for Severity
MAP	Mean arterial blood pressure
MECP2	Mutations of the MECP2 gene
MeCP2	Methyl-CpG-binding protein 2
SBP	Systolic blood pressure
VT	Vibroacoustic Therapy
WeeFim	Functional Independence Measure for Children

Original papers

This thesis is based on the following papers, referred to in the text by their Roman numerals I – IV

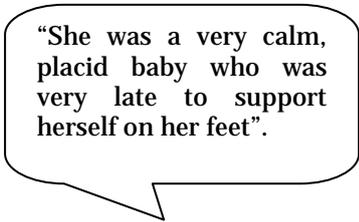
- I Larsson G, Witt Engerström I. Gross motor ability in Rett syndrome – the power of expectation, motivation and planning. *Brain Dev* 2001; 23: S77-S81.
- II Hagberg B, Erlandsson A, Kyllerman M, Larsson G. Odd MECP2-mutated Rett variant- long-term follow-up profile to age 25. *Eur J Paediatr Neurol* 2003; 7: 417-421.
- III Larsson G, Lindström B, Witt Engerström I. Rett syndrome from a family perspective: The Swedish Rett Center Survey. *Brain Dev* 2005; 27: S14-S19.
- IV Larsson G, Julu POO, Witt Engerström I, Sandlund M, Lindström B. Normal reactions to orthostatic stress in Rett syndrome. *Res Dev Disabil* 2013;34:1897-1905.

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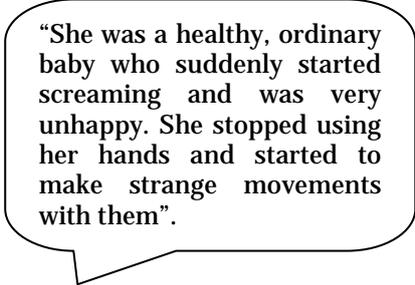
Figure 1 is used by kind permission of Oxford University Press, Oxford.

1 Introduction

In 1966, Austrian paediatrician Andreas Rett described 32 females with specific symptoms, for example specific repetitive hand movements (Rett, 1966a). This was published in German and did not attract much attention; nor did a report from Japan on three girls with similar symptoms (Ishikawa et al., 1978). Not until 1980 at a meeting in Manchester, when Bengt Hagberg reported on 16 Swedish females and their symptoms to “The Council Group of the European Federation of Child Neurology Societies”, was it noted that similar patients were also documented in Lisbon and Paris. Together they reported on 35 cases (B. Hagberg, Aicardi, Dias, & Ramos, 1983). In Sweden Bengt Hagberg had named this syndrome Morbus Vesslan after the first girl he had examined, but after a meeting in Vienna and a report on suggested diagnostic criteria in 1988 it has been called Rett syndrome (Diagn.Criteria & Group, 1988).



“She was a very calm, placid baby who was very late to support herself on her feet”.



“She was a healthy, ordinary baby who suddenly started screaming and was very unhappy. She stopped using her hands and started to make strange movements with them”.

(Comments from parents describing the early development of their child with Rett syndrome)

1.1 Rett syndrome

1.1.1 Epidemiology

Rett syndrome (RTT) is a severe neurodevelopmental disorder that is mainly verified in girls and women. It is found in all countries and in all races (B. Hagberg & Hagberg, 1997). The prevalence of classic RTT in females in the world ranges from 1:10.000 to 1:20.000, and reports on incidence are few and varying. In Sweden the prevalence for girls born between 1965 and 1976 was 1:10.000-12:000 (B. Hagberg & Witt-Engerstrom, 1987). The estimated prevalence in the United Kingdom was reported to be 1:10.000 females at 14 years (A. M. Kerr, 1995). In France a prevalence of 0.6:10.000 females aged 4-15 years has been reported and this is in line with other European studies based on clinical examination. (Bienvenu et al., 2006). The true prevalence may not yet be known, since the disorder can vary in severity and diagnosis may be missed (A. M. Kerr

& Witt Engerström, 2001). From Australia a prevalence of 0.88:10.000 females aged 5-18 years was reported (Laurvick et al., 2006). Next to Down syndrome, it has been suggested that RTT is the most common severe cognitive disability in females (B. Hagberg & Hagberg, 1997).

1.1.2 Development of Rett syndrome

Children who later develop RTT are generally born after a normal pregnancy and delivery. They are considered to reach normal developmental milestones up to 6–18 months, after which comes a period of stagnation, followed by loss of abilities they have achieved (A. M. Kerr & Witt Engerström, 2001; Witt-Engerstrom, 1990). The loss is in communication, fine motor and gross motor skills, but the loss in communication and fine motor skills is often more obvious and complete than the loss in gross motor skills. The latter is in most cases more subtle and combined with some development. However, recent research has shown that the newborn period may not be normal after all (Einspieler, Kerr, & Prechtel, 2005a, 2005b; Leonard & Bower, 1998; Marschik et al., 2012). There may be varied soft signs that are difficult to observe, leading to a risk of missing this initial stage (A. M. Kerr & Prescott, 2005). Parents are reported to have concerns due to subtle, atypical development in their child and there are reports that even individuals with the Preserved Speech Variant of RTT, may not develop normally from birth (Fehr et al., 2011). Also, Kerr (2005) states that "there can be no remaining doubt that the pre-regression period contains important signs which should not be missed and are of value in both diagnosis and prognosis" (A. M. Kerr & Prescott, 2005). A stationary phase follows the regression and can last for years, though for some it is followed by later deterioration (A. Kerr, 2002; Y. Nomura & Segawa, 2005).

Included in the diagnosis of RTT are autonomic dysfunction, seizures, weight loss, contractures, scoliosis, dyspraxia/apraxia and unexpected fractures indicating deviating bone structure, all with different severity and at different ages (S. Ager et al., 2006; S. S. Budden & Gunness, 2001, 2003; Julu, 2001). Because of dyspraxia and motor disability it may be difficult to decide on the severity of the motor function unless repeated assessments are made and one gets to know the individual (Baptista, Mercadante, Macedo, & Schwartzman, 2006; Trevarthen & Burford, 2001; von Tetzchner, 1997; G. Woodyatt & Ozanne, 1997).

A study using a questionnaire and including the WeeFim Functional Independence Measure for Children concluded that people with RTT have major limitations in self-care, surpassing Down syndrome (Leonard, Fyfe, Leonard, & Msall, 2001).

In all, this means that after the regression, people with RTT have a severe disability that acts on the whole body, on most body functions.

1.1.3 Diagnostic assessments

1.1.3.1 Clinical diagnosis

Since RTT is a complex syndrome which varies over time, and even during a day, it has been difficult to interpret different symptoms and confirm the diagnosis. Due to this, diagnostic criteria were set up early and have later been revised over the years (Diagn.Criteria & Group, 1988; B. Hagberg, 2002; B. Hagberg, Goutieres, Hanefeld, Rett, & Wilson, 1985; B. Hagberg, Hanefeld, Percy, & Skjeldal, 2002; A.K. Percy et al., 2010). The different revisions point out that with time there is more to learn about RTT and the way it develops. The criteria for classic RTT were defined as “necessary criteria” and “supportive criteria”. There were also “exclusion criteria” in order to distinguish RTT from other disorders. In 1986, a staging system was suggested in order to describe the impairment and changes over the years (B. Hagberg & Witt-Engerstrom, 1986). In addition to criteria for classic RTT there are specific criteria for variants of RTT, sometimes called “atypical” RTT and also for the Preserved Speech Variant, sometimes called the Zappella variant, at times seen abbreviated as PSV or Z-RTT (Marschik et al., 2012; Neul et al., 2010; Renieri et al., 2009).

1.1.3.2 Mutation and diagnosis

In 1999, a mutation was found on the gene MECP2 locus Xq28, which can be used as a confirmation of RTT (Amir et al., 1999). This mutation can now be identified in more than 95% of individuals with criteria for classic RTT, and more than 250 different mutations associated with RTT have been identified. Since it has not been confirmed in everyone tested and has been found in healthy people, although with skewed X-inactivation, we still rely on clinical criteria for diagnosis, but the body of knowledge is growing (Amir et al., 1999; Chapeau et al., 2013; Colvin et al., 2004; Percy, 2008, 2011). In at least 99% it is a sporadic mutation, and even if there are familial cases, most are de novo mutations of paternal origin (Chahrour & Zoghbi, 2007; Huppke & Gärtner, 2005; A. M. Kerr & Witt Engerström, 2001).

Genotype-phenotype

Over the years, research about genotype-phenotype has been carried out, and this knowledge is developing, but so far it is not possible to use this for prediction of development or severity of RTT; it still has to be used with caution. The mutation R133C is found to be a milder type of RTT, while R270X is said to be the most severe. There is considerable functional variation, even for individuals with the same mutation. An increased risk of fractures for all individuals with RTT has been reported, though especially in subjects with mutations p.R270X and p.R168X. Some protection against development of scoliosis was found in those with the mutation p.R294X (S. Ager et al., 2006; J. Downs et al., 2008). Others have found p.R133C as well as p.R294X to be the least severe

phenotypes; this is in line with Halbach et al (2012). Even so, the latter recommend caution in using this information when talking about prognosis (Bebbington et al., 2008; Colvin et al., 2004; Halbach et al., 2012; Ham, Kumar, Deeter, & Schanen, 2005; Leonard et al., 2003).

Other mutations with Rett syndrome picture

In later years, it has been found that variants which were previously called “congenital” or “early onset epilepsy” are caused by different mutations. It has been found that the “congenital” variant, also called the “Hanefeld variant”, is caused by the mutation, FOXP1, while the variant with early onset of epilepsy has been connected to mutation CDKL5, the clinical picture still being RTT (Ariani et al., 2008; Evans et al., 2005; Pini et al., 2012; Rajaei et al., 2011).

Rett syndrome in males

Very early in the history of research on RTT it was stated that only girls could develop this syndrome, but in the revision of criteria published in 1988 this was deleted (Diagn.Criteria & Group, 1988; B. Hagberg et al., 1985; B. Hagberg & Witt-Engerstrom, 1986; Rett, 1977; Witt-Engerstrom, 1990). There have been reports on males with suspected RTT over the years, and the typical mutation leading to RTT in females has been thought to cause severe symptoms and early death in infancy or early childhood in boys. This has later been reconsidered and it has been suggested that MECP2 mutation in boys does not seem to result in prenatal death but might manifest itself as a Rett-like phenotype. The Klinefelter syndrome has been discussed as a way for boys to have classic RTT since they have two X chromosomes (Erlandson & Hagberg, 2005; Meloni et al., 2000; Schanen, 2001; Schanen & Franke, 1998). There is still a lack of knowledge, as Villard reported in 2010, on males with mental retardation having MECP2 mutation and great variation in phenotypes, from mild mental retardation to severe neonatal encephalopathy (Villard, 2007).

Current research on the mutation

Recent research on RTT using mice is ongoing and extensive. The possibility to reactivate MeCP2 in mice after deletion and thus regain some lost functions has been reported; and when restoring it in mice there was improvement in functions (Cobb, Guy, & Bird, 2010; Robinson et al., 2012). Research on mutant mice showed that an early enrichment of the environment was beneficial, and the authors conclude it might also be beneficial in humans with RTT (Lonetti et al., 2010). One important question to answer, concerning regression, has been put forward, since regression is a main feature in RTT: “Do animal models have regression, or do they simply display fixed phenotypic abnormalities?” (Samaco & Neul, 2011).

1.1.4 Temporal profile of Rett syndrome

It was recognized early on that RTT changes over the years, and with more research and more knowledge this has been revised. In 1986 a four-stage system was introduced, which is still commonly used, describing development over the years. This was later amplified (B. Hagberg & Witt-Engerstrom, 1986; Witt-Engerstrom, 1990). Stage I=early onset stagnation, Stage II=rapid developmental regression, Stage III=pseudo-stationary stage, Stage III/IV=not yet ambulant, Stage IV=late deterioration stage, Stage IV-A= previous walkers, Stage IV-B=never ambulant. In later revisions the words “rapid” or “sudden” have been excluded in connection with regression (B Hagberg, 1993; B. Hagberg et al., 2002; B. Hagberg & Witt-Engerstrom, 1986). Even so it still appears, although it has become more evident that regression is not always sudden but may be more subtle, and can occur both suddenly and gradually (Fehr et al., 2011; B. Hagberg, 2002; B. Hagberg et al., 2002; Jackowski et al., 2011; Lotan, 2006b). Another way to describe how RTT develops is also used. Some authors use the terms “pre-regression”, “regression” and “post-regression” to describe the temporal profile in RTT, see figure 1 (A. M. Kerr & Witt Engerström, 2001).

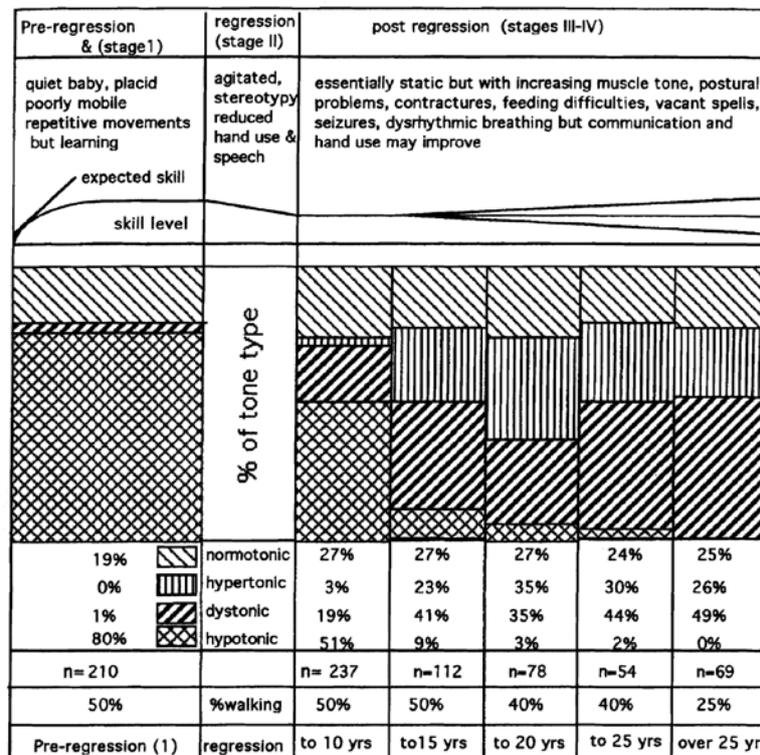


Figure 1. The figure shows the different ways symptoms of Rett syndrome appears over time (Kerr and Witt Engerström 2001)

1.1.5 The central nervous system in Rett syndrome

Although in his early descriptions of the syndrome, Rett considered RTT to be progressive, the consensus nowadays is that it is to be described as a neurodevelopmental disorder and not a progressive encephalopathy. The consensus is primarily about neurons having less dendrites and increased neuronal packing density in RTT, causing the brain to be small. Dendrites are few but there is no sign of progressive decrease in volume over time. The small size of the brain is presumed to be the result of arrested brain growth and development. Something interferes with development in the late stages of pregnancy or early in infancy, and it is not a result of degeneration. According to Kaufman (2001), the basic disturbance occurs early and it is not supposed to severely affect later cortical growth. This may explain the relative stabilization after regression (D. D. Armstrong, 2001, 2005; D.D Armstrong & Kinney, 2001; Kaufmann, 2001).

There are some conflicting results on whether there is a reduction in volume with age. In a report on results from autopsy of 51 brains there was no evidence of decline in weight with increasing age. Another study using MR imaging, reported on progressive atrophy of cerebellum with age but not in cerebrum or brainstem. Reiss (1993) found significantly reduced cerebral volume in 11 females with RTT; loss of grey matter was greater than loss of white matter, and there was also regional variation in cortical grey matter where frontal regions showed more decrease. There was also reduced volume of the caudate nucleus and midbrain but, notably, no evidence of an ongoing degenerative process (D.D Armstrong & Kinney, 2001; Murakami, Courchesne, Haas, Press, & Yeung-Courchesne, 1992; Reiss et al., 1993). Kaufmann (2001) concluded that when the brain is impaired, as in RTT, this could either be caused by atrophy or because of reduced dendritic/synaptic development, and he concludes that the latter is present in RTT. Reduced dendritic development has been discussed by others, suggesting that it is due to cholinergic deficiency, imbalance in neurotrophic factors/glutamate imbalance. Later studies support that RTT is “a genetic disorder of synapse development”, also concluding that there is reduction in size in cerebellum in accordance with motor deficits in RTT. Later MR imaging showed an expected grey-matter involvement, but also a marked reduction of grey matter in the dorsal parietal region. A greater reduction in the anterior frontal lobe had a correlation with severity of RTT. Grey matter reduction in parietal and frontal areas was negatively correlated with clinical severity and gait abnormalities. No evidence of progressive reduction of brain tissue was found, and the study supports the hypothesis of early arrest in dendritic growth (Carter et al., 2008; Johnston, Blue, & Naidu, 2005; Kaufmann, 2001; Riikonen, 2003). In a report on studies conducted on *Mecp2* knockout mice with early motor problems, similar to those in RTT, there was a deregulation in noradrenergic and serotonergic systems. These were especially in regions for motor control, i.e. prefrontal and motor areas, and their research

indicated involvement of cortical as well as brainstem regions as the origin of RTT (Santos et al., 2010).

In a study of regional blood flow in RTT and healthy controls, profound hypoperfusion in frontal areas was found in people with RTT compared with controls. There was no correlation with age and it was concluded that there is a developmental arrest in midbrain and brainstem in RTT. Another study also found hypoperfusion in frontal lobes and parts of the midbrain, concluding that these structures in the brain have relevance for the way RTT develops (Bieber Nielsen, Friberg, Lou, Lassen, & Sam, 1990; Bjure, Uvebrant, Vestergren, & Hagberg, 1997).

A description has been published of different features developing due to an immature brain in RTT: Cortical origin: mental retardation and epilepsy; Extra-pyramidal origin: dystonia, orthopaedic deformations, secondary muscle wasting and uncoordinated movements; Monoaminergic dysfunction in the brainstem, causing dyspraxia, aberrant sleep pattern; Immaturity of brainstem/not working inhibition, causing abnormal breathing, dysautonomia. The “developmental slurring” in babies that later develop RTT and the difficulty for the general practitioner or the paediatrician to discern these early signs are also highlighted (Julu et al., 2008). This difficulty to discover early symptoms has been explained as a consequence of neural systems having to reach certain levels of maturation for symptoms to become manifest. According to this, it has been suggested that the onset of RTT is between 36 gestational week and 3-4 months after birth (Y. Nomura, 2001; Y. Nomura & Segawa, 2005).

1.1.6 Autonomic nervous system

Some signs of autonomic dysfunction in RTT were described early on: different breathing irregularities as well as bluish small feet (Southall et al., 1988; I. Witt Engerström, 1990). A study on genotype-phenotype found disturbed peripheral circulation in 71% and no relation to a specific type of mutation (Bebbington et al., 2008). With time, research has elucidated the immaturity of the central nervous system in RTT and proved that it is especially severe in the brainstem, causing poor control of the central autonomic nervous system (Bieber Nielsen et al., 1990; Julu, 2001; Julu, Kerr, Hansen, Apartopoulos, & Jamal, 1997a; Y. Nomura, Kimura, Arai, & Segawa, 1997). This immaturity mostly remains throughout life and is manifested as irregular breathing, variation in heart rate and blood pressure, agitation, flushed face, dilated pupils, peripheral vasomotor disturbance and gastrointestinal problems (Julu et al., 2001; Julu et al., 2008; A. M. Kerr & Witt Engerström, 2001). Sleep patterns may also be affected (Y. Nomura, 2005).

The autonomic nervous system (ANS) consists of the sympathetic system, “the driver”, and the parasympathetic system, “the brake”. It is essential that the systems work in balance according to physiological need, but in those with RTT there is a deficient control with the sympathetic system being normal or near normal and the parasympathetic system poor (Julu,

2001; Low & Benarroch, 2008; Y. Nomura, 2001). Sympathetic and parasympathetic functions are mainly controlled in the brainstem. Evaluation of how these systems work can be made by assessing how the heart reacts to some activities such as deep breathing, characterizing the cardiac cycles. Mean arterial blood pressure (MAP) can be used as a measure of how the sympathetic system works and cardiac vagal tone (CVT) as a measure of the parasympathetic system. The parasympathetic system has been described as a promoter of growth and restoration of systems, and the sympathetic system as a promoter of increased metabolic output in order to manage challenges from outside the body (Dampney, 2008; Porges, 1992; Wieling & van Lieshout, 2008). There are different ways of measuring autonomic reactions but an advantageous way is to measure it heartbeat by heartbeat in real time; at the same time for blood pressures (systolic, diastolic and MAP), breathing rhythm, oxygen, carbon dioxide, cardiac vagal tone (CVT) and cardiac sensitivity to baroreflex (CSB). This can be done non-invasively (Julu, 2001; E. E. Smeets et al., 2006; Wieling, 1992). For some areas it has to be clinically described (D. G. Glaze, 2005; Y. Nomura, 2001; Y. Nomura et al., 1997).

1.1.6.1 Agitation and stress

In RTT, as the sympathetic system is often normal or near normal and the parasympathetic system weak, people with RTT are easily subjected to stress and/or agitation (Julu, 2001; A.M. Kerr & Engerstrom, 2001). This often manifests itself as a flushed face, dilated pupils, increased breathing disturbance and increased intensity in hand stereotypies. Stress is described as withdrawal of the parasympathetic activity causing a disruption of homeostasis, the autonomic balance. In RTT, stress can be triggered by events that would not cause stress in those with well-functioning autonomic control; stress also takes longer until it is restored back to where it was before the event occurred. A stressful event can be something alarming, scaring or something pleasant and joyful. It is not an act of will, but something that happens that is out of their control (A. Kerr, 2002). It has been suggested that decreasing the repetitive purposeless hand movements seen in RTT can be a way to help relieve agitation (S. S. Budden, 1997).

1.1.6.2 The heart

A well-functioning autonomic system adapts heart rate according to activity performed. Compared with healthy people, individuals with RTT have a higher heart rate when resting, and research is mostly conducted when individuals with RTT are resting. This means we have no information about what happens when they are moving, e.g. standing up, keeping standing or walking. There are reports on prolonged QT intervals in Rett and for this reason a connection to sudden death is made in some reports (D. G. Glaze, 2005; Guideri, Acampa, DiPerri, Zappella, & Hayek, 2001; Guideri, Acampa, Hayek, Zappella, & Di Perri, 1999; Julu, Kerr, Hansen, Apartopoulos, & Jamal, 1997b; Madan, Levine, Pourmoghdam,

& Sokoloski, 2004; Rohdin et al., 2007; Sekul et al., 1994). Prolonged QT intervals may have different causes apart from “real disease” of the heart. The cause can be genetic and it can be affected by electrolyte imbalance and/or medication – the consequence is a heart arrhythmia, but the proper treatment is different. It also causes diminished heart rate variability. An annual ECG control for individuals with RTT has been suggested, checking for the presence of prolonged corrected QT interval (QTc), degree of it, and recommended caution with certain drugs (Ellaway, Sholler, Leonard, & Christodoulou, 1999). One report summarizes a longer list of medication that should be avoided, for example some anaesthetics and some antibiotics (Weaving, Ellaway, Gecz, & Christodoulou, 2005). Even if some authors recommend medication such as β -blockers McCauley (2011) found that β -adrenergic receptor blockers did not prevent ventricular tachycardia in male mice lacking MeCP2 function (McCauley et al., 2011). A recent study of RTT reported on reduced preload and subclinical myocardial dysfunction, and speculated that this may be related to many different factors such as enhanced oxidative stress, hypoxia, and/or autonomic dysfunction, breathing disorders or motor dysfunction (De Felice et al., 2012).

1.1.6.3 Blood pressure

In general, blood pressure in the group with RTT has a tendency to be lower than in healthy individuals of the same age. This is due to immaturity in the brainstem and the deviating control of the autonomic nervous system (Julu, 2001). Blood pressure may be influenced by breathing abnormalities observed in RTT, and for individuals having frequent Valsalva manoeuvres, which cause sudden changes in heart rate and blood pressures (Julu et al., 1997a; A. Kerr, 2002; E. E. Smeets et al., 2006).

1.1.6.4 Breathing

Breathing irregularities have been described in RTT and have been categorized in three different cardiorespiratory phenotypes: forceful breathers, feeble breathers and apneustic breathers, each of which can have the complication of Valsalva manoeuvres (Julu et al., 2001). The different types of breathing were initially found when the person was awake but some research has shown divergent breathing also during sleep (Rohdin et al., 2007; Weese-Mayer et al., 2008). Forceful breathers tend to have low levels of pCO₂, hypocapnia, causing increased nerve and muscle excitability, sometimes ending in muscle cramps, hypocapnia attacks, which can mimic epileptic seizures. Feeble breathers have high levels of pCO₂ due to inadequate ventilation which can cause headache, confusion and lethargy (Julu, Witt Engerström, Hansen, Apartopoulos, & Engerström, 2012). Apneustic breathers also accumulate CO₂, since expiration is delayed and not adequate, but treatment may be different compared with that for feeble breathers (Julu et al., 2008). Valsalva manoeuvres cause sudden changes in intrathoracic pressure, both when

trying to exhale against a closed airway, increased pressure, and when suddenly exhaling causing a sudden drop. This affects the heart and blood pressure. Healthy people can perform this as an act of will, but individuals with RTT who are subjected to this cannot stop it (Y. Nomura, 2001; E. E. Smeets et al., 2006).

1.1.6.5 Bowels/gastrointestinal problems

Problems with gastrointestinal tract and bowels are common in RTT and it is suggested that they are related to imbalance of the sympathetic and parasympathetic systems (Dahlström, 2001; A. M. Kerr & Witt Engerström, 2001), causing constipation, gastroesophageal reflux and swallowing problems (Lotan & Zysman, 2006; Reilly & Cass, 2001). In an Italian study, constipation was reported in 89% and reflux in 25% (Vignoli et al., 2012). Air swallowing, and bloating, is also a complication and a possible cause of pain or discomfort in this area of the body (R. Morton, Pinnington, & Ellis, 2000).

1.1.7 Epileptic/non-epileptic seizures

A common feature of RTT is epilepsy, or seizures of some kind, though not all can be verified by EEG. Even if the seizures are not verified for epilepsy, the EEG is mostly abnormal with divergent rhythms. Early changes can be seen, including Rolandic spikes (A. M. Kerr & Witt Engerström, 2001; I. Witt Engerström, 1990). A Swedish study reported that 28 out of 30 females with RTT had had seizures originally and eight had stopped when they became older (Steffenburg, Hagberg, & Hagberg, 2001). It has been suggested that epilepsy in RTT might be overestimated, since seizures confirmed by parents were not verified on EEG; this is in line with later findings that disturbances in the autonomic control and breathing can cause seizures that mimic epilepsy (D.G. Glaze, Schultz, & Frost, 1998; Julu, 2001). In a paper reporting on 346 cases of RTT from different countries, the incidence of epilepsy was reported to be 58% and no significant correlation with a specific mutation was found (Bebbington et al., 2008). This is in contrast to Jian et al who found a correlation with specific mutations and age of the individual with RTT (Jian et al., 2007). As non-epileptic vacant spells have been reported, one study concluded that EEG has been extensively studied in RTT but it cannot be used as a diagnostic tool (D. G Glaze, 2002). In some cases with serious epilepsy, an implanted vagus nerve stimulator has been used (Wilfong & Schultz, 2006). Variations in percentage of seizures have been reported and the discrepancy may be due to difference in age or stage of RTT in the reported groups (Cooper, 2001; D. G Glaze, 2002; Jian et al., 2007).

1.1.8 Sleep

A deviating sleep-wake pattern is common in RTT (Segawa & Nomura, 1992). Among British families, 80% reported sleep problems (A. M. Kerr & Witt Engerström, 2001), and an Australian study using an international dataset reported 67.3%, and no relation to a specific mutation (Bebbington et al., 2008). A normal sleep-wake pattern in young girls with RTT was described, but in that study a deviating sleep rhythm was found in older individuals, where irregular times of waking up in the morning and of falling asleep at night were reported, and daytime sleep was long compared with healthy age-matched controls (Y. Nomura, 2001; Y. Nomura & Segawa, 2005). Indications of disrupted sleep stages have also been reported. Melatonin has been helpful for some to improve their sleep at night (S.S. Budden, 2001; McArthur & Budden, 1998).

1.1.9 Morphologic findings / Anatomical changes

1.1.9.1 Growth

Deficient growth is described in RTT, for growth of the head and the feet, and for growth of total body. Low weight, short height and low energy intake has been reported, although the girls in that study had good appetite but were not able to feed themselves. Different strategies to prevent malnutrition were recommended and extra vitamins, calcium and iron were also suggested (Thommessen, Kase, & Heiberg, 1992). Difficulty in feeding and swallowing is a concern for those helping people with RTT. A study using video fluoroscopy reported on reduced movements and delayed swallowing, and another reported on 13 females with RTT, of whom 100% had oropharyngeal dysfunction and 69% gastroesophageal dysmotility (R. E. Morton, Bonas, Minford, Kerr, & Ellis, 1997; Motil, Schultz, Browning, Trautwein, & Glaze, 1999). A Swedish study reported on guided eating as a way to prepare for food intake and enhance participation by girls with RTT; eating behaviour differs depending on whether the individual is being fed or having guided eating (Qvarfordt, Witt Engerström, & Eliasson, 2009). It has been proposed that resting metabolic rate is higher in RTT compared with other disabilities, and intensive nutritional therapy is said to improve growth. Mutation in *MECP2* is related to growth failure in RTT, and is more evident in those mutations associated with more clinical severity (Tarquinio et al., 2012).

1.1.9.2 Bone

Deficient bone mass and osteopenia in RTT was documented early on, and some connection was made to mobility, but in later years this has been related to the mutation or to autonomic imbalance (Leonard, Fyfe, & Ellaway, 2001). In a study of bone age in 16 people with RTT, aged 2 years 9 months to 24 years, walking is not declared, but according to declared Stages of RTT there were probably nine walking participants. Skeletal age

matched chronologic age, but due to the limited number of subjects, authors found the results unreliable (Hennessy & Haas, 1988). In a later study, 20 subjects with RTT were compared with healthy people and a group with CP, and it was concluded that there was reduced bone density in the RTT group (Haas, Dixon, Sartoris, & Hennessy, 1997). Bone age was reported to match chronological age in a group of young girls with RTT, and it was speculated that delayed bone age may occur in older people with RTT. Five subjects had had ten fractures in both upper and lower extremities, and the authors recommended that patients were mobilized rapidly (Loder, Lee, & Richards, 1989). Another study reported on three females with RTT who had osteopenia and a low bone formation rate, presumably caused by genetic factors (S. S. Budden & Gunness, 2001). A population-based Australian study using radiographs of second metacarpal bone in 137 females with RTT, showed decreased cortical thickness related to increasing age and use of anticonvulsant medication. One third of the group had had fractures (Leonard et al., 1999).

Osteopenia was reported to develop at an early age and absorption of calcium might not account for osteopenia in RTT. Four of the ten girls with RTT in this study could walk at the time of the study (Motil, Schultz, Abrams, Ellis, & Glaze, 2006).

In a Danish study of bone mineral density and bone size in RTT, low bone mass, low bone density and small bones were found. There was no association with a specific mutation, but association with epilepsy and treatment for that. There was indication that mobility status was important, especially for bone mass in the proximal femur (Roende, Ravn, Fuglsang, Andersen, Bieber Nielsen, et al., 2011). The same authors reported on low energy fractures and risk factors in a Danish group of females with RTT, matched by age and pubertal or menopause status. The results showed a significantly greater number of low-energy fractures in RTT, from an early age. This was associated with reduced mobility and walking, but not with epilepsy or anti-epileptic drugs. The group with RTT had lower levels of vitamin D compared with controls during summer but not during wintertime. Weight-bearing and daily physical activity were recommended in order to stimulate muscle functioning, bone development, growth and strength (Roende, Ravn, Fuglsang, Andersen, Vestergaard, et al., 2011). Contrary to that report, a study using the Australian Rett syndrome database found a correlation with epilepsy. There was also an increased risk of fractures in individuals with mutations p.R270X and p.R168X (J. Downs et al., 2008).

1.1.9.3 Face

Few have reported on morphological features in RTT, and as babies there is nothing in the way they look that causes suspicion. When Rett reported on his group of 32 females with joint features in 1966, he did not find any specific anomalies except for small head, poor mimic and repetitive hand movements (Rett, 1966b). In a recent study of the face in 37 females with RTT, aged 2 to 20 years, there were few measurements that deviated from

normal or were dysmorphic (Allanson, Hennekam, Moog, & Smeets, 2011). The authors' conclusion is that a diagnosis of RTT cannot be made on facial phenotype but, as now, should be made on history of development, neurology and behaviour.

1.1.9.4 Head

Occipito-frontal circumference (OFC) is within the normal range at birth but head growth later slows down. In a Swedish study, 7 out of 20 girls showed decelerating head circumference before 12 months, though since it was a subtle gradual change this was only confirmed retrospectively. It has been suggested that stagnation of head circumference can be found at 3 months to 4 years (B. Hagberg, 2002; I. Witt Engerström, 1992). In a report from the USA on growth and growth failure in RTT, head growth was seen to fall below normative mean by 1 month, and by 2 years it was - 2 SD (Tarquinio et al., 2012). A correlation between almost normal head growth and good gross motor ability has been suggested and also a gradual deceleration of head circumference with stabilization by 8 years of age. There was individual variation and a conclusion that OFC should not be considered a necessary criterion for diagnosis of classic RTT (G. Hagberg, Stenbom, & Engerström, 2000; G. Hagberg, Stenbom, & Witt Engerström, 2001).

1.1.9.5 Body/ Spinal deformity

Since early reports on RTT, there have been annotations on small stature compared with people of the same age (A. M. Kerr & Witt Engerström, 2001). Correlation has been made for low weight, short stature and feeding difficulties, but in recent years a correlation with mutation has also been made (Reilly & Cass, 2001; Tarquinio et al., 2012). It has been suggested that this pattern of growth could be the earliest clinical sign of RTT (R. J. Schultz et al., 1993).

In clinical work, asymmetries are often noted and already in 1990 Witt Engerström and Hagberg reported on scoliosis being common in RTT and dystonic signs being asymmetrical in extremities in adult women with RTT (Witt-Engerström & Hagberg, 1990). Later, asymmetry with functional incapacity in the right side of the body was described, advancing in the late teens and more evident in lower extremities (Cass et al., 2003; B. Hagberg & Romell, 2002). Other authors also reported that regarding scoliosis in RTT the convexity was more often to the right. There were reports on asymmetric pelvis, and asymmetries increasing with age. Right-sided convexity of scoliosis was found in almost two-thirds of those included in an investigation. It was reported that scoliosis was more often C-shaped than S shaped (Huang, Lubicky, & Hammerberg, 1994). The C-shaped curve was more disabling and more progressive than the S-shaped curve, and females with an S-shaped scoliosis or kyphosis were more likely to walk in a Norwegian study (Riise, Brox, Sorensen, & Skjeldal, 2011). It has also been found that severity of scoliosis increases with increased age (Bassett & Tolo, 1990).

Since the scoliosis is concluded to be of neuromuscular origin it may continue to develop in adult life; severity of scoliosis may be more dependent on neurological factors than on age and scoliosis may develop earlier than for idiopathic scoliosis (Lidstrom, Stokland, & Hagberg, 1994).

The percentage of scoliosis and/or kyphosis varies in different studies, but is always high (Harrison & Webb, 1990; Hennessy & Haas, 1988; A. K. Percy et al., 2010; I. Witt Engerström, 1990). In later years a possible relationship between scoliosis and mutations has been reported. An Australian survey, using information from a database, found that scoliosis was present in 79%, with scoliosis developing later in mutations p.R133C, p.R294x and R306C, though only significant for p.R294x (S. Ager et al., 2006). Earlier development of scoliosis was found in p.R168X, p.R255X, and p.R270X and large deletions. An American study, with several centres collaborating, investigated data on 554 classic RTT (A. K. Percy et al., 2010). Assessment of scoliosis was made by direct examination and x-ray, Cobb angle; clinical severity scores were also examined. Among participants aged 16 years or older, 85% had some degree of scoliosis. Prediction of scoliosis was correlated with location of mutation of MECP2, clinical severity, and motor skills. Concurrent with the Australian results they found reduced risk of scoliosis in individuals with mutations p.R294x and p.R306C (S. Ager et al., 2006; A. K. Percy et al., 2010). There are few reports of interventions with the purpose of slowing down or stopping development of scoliosis. In a report on parental experiences of scoliosis management, parents rated physiotherapy as favourable, even if it did not have an impact on development of the curve (S. Ager, Downs, Fyfe, & Leonard, 2009). The benefit was reported as maintaining or developing flexibility in the spine, which was seen as important for later surgery, keeping their daughter mobile, retaining good posture and making her feel more comfortable after a session. "She seems to enjoy the therapy". This was similar to conclusions by an expert panel consisting of orthopaedic surgeons, paediatricians, occupational therapists and physiotherapists from all over the world when preparing clinical guidelines for scoliosis in RTT through evidence review and consensus (Downs, Bergman, et al., 2009). This was published in 2009 and includes recommendations on monitoring, therapy, bracing, surgery and post-operative considerations. This work was initiated and headed by Jenny Downs et al. A case study reported on physiotherapy having successfully reduced scoliosis "by asymmetrical activation of trunk muscles through equilibrium reactions" (Lotan, Merrick, & Carmeli, 2005). In concordance with the previous study, it was suggested that physiotherapy was valuable for flexibility and strength, but had no effect on curve progression in RTT (Koop, 2011). Bracing was suggested for slowing down progression of curves. The author calls attention to the benefits of successful spinal surgery and speculates that if there is a correlation between specific mutations in MECP2 and severity of scoliosis, it might be possible to perform surgery before the need for both

anterior and posterior operation arises. This is a way to reduce the risk of serious complications. RTT has been reported to differ from other disabilities, where it is possible for people to have severe scoliosis and still be ambulant (Holm & King, 1990).

1.1.9.6 Joints/Hips/Feet

Contractures of joints may develop and most were reported to be in the feet but also in the hips (A. M. Kerr & Witt Engerström, 2001). This is not often reported for upper extremities, but some individuals are subject to this. In an Italian study, the incidence of deformities of joints was reported to be 36%, while for scoliosis the incidence was 83%. Joint deformities became worse with age (Vignoli et al., 2012). Dystonia can be seen early in feet and this can later develop into shortening of Achilles tendons, making walking difficult (Cass et al., 2003; A. M. Kerr & Burford, 2001). Toe walking is one way to compensate; other ways may be to hyper-extend the knees and flex the hips (Hanks, 1990). One study found no heel cord contracture in a girl with RTT Stage II, but in 6 out of 7 individuals in Stage IV. Severity varied, but the risk of contractures in lower extremities was found in all those with RTT (Hennessy & Haas, 1988). A larger study with 87 participants found tight Achilles tendons in more than half of those aged five years and younger, even if they had hypotonia (Cass et al., 2003). A tendency for people with RTT to have greater instability in the hips than age-matched healthy controls was reported, but there were no major differences. More recently there has been a report on higher prevalence of hip instability and/or displacement in RTT, and early, regular and careful surveillance of this is recommended (Hennessy & Haas, 1988; Tay et al., 2009).

Disproportionately small feet and hands in comparison to height is reported, though hands to a lesser degree (B Hagberg, 1993; A. M. Kerr & Witt Engerström, 2001; R. Schultz, Glaze, Motil, Hebert, & Percy, 1998). This may be related to autonomic dysfunction causing inadequate peripheral circulation (Leonard, Fyfe, & Ellaway, 2001). Schultz et al did not find that ambulatory status had any effect on foot length (R. Schultz et al., 1998). A study found that 20% in a Rett clinic group had a short fourth metatarsal, but this was also found in 16% of males and females with Down syndrome (A. M. Kerr, Mitchell, & Robertson, 1995). An Australian study with 17 participants using radiological examination, found that 65% had a short fourth and/or fifth metatarsal and 57% had a short fourth and/or fifth metacarpal; this was more common in individuals older than 14 years of age (Leonard, Thomson, Bower, Fyfe, & Constantinou, 1995).

1.1.10 Development and changes in motor function

1.1.10.1 Early development

In most cases, a child who is later diagnosed with RTT is considered to be normal at birth, and born after a normal pregnancy (A. M. Kerr & Witt

Engerström, 2001; I. Witt Engerström, 1990). Loss of function, regression, is a main feature in this syndrome and this loss follows a period of stagnation in development. Although the point of time when regression occurs may vary, it is mostly within 24 months. A distribution of 13-25 months with a median age of 17 months has been reported, as well as a mean age of 19.3 months. Since it is difficult to establish the point in time when RTT appears, it will take time before diagnosis is confirmed, even if it can be supported by a genetic test. The time when developmental milestones are lacking is a common period when RTT is suspected and clinical diagnosis is made, though Fehr et al found no relationship between time for diagnosis and acquisition of sitting (Fehr et al., 2011; A. M. Kerr & Witt Engerström, 2001). The report by Fehr et al showed that if a child was unable to walk, diagnosis was confirmed earlier than if she or he was able to walk, but there was no relationship with the time of learning to walk. Not learning words but only using babble indicated earlier diagnosis. In this study, 81% of parents were concerned about their child's development or behaviour within the first 10 months, and a large number of parents reported that their child's development or behaviour had never been "normal".

1.1.10.2 Muscle tone

Hypotonia and failing postural control may be observed, though low muscle tone was not observed in a study using spontaneous movements on early videos, and not by clinical assessment (General Movements). There were instances of other indistinct, divergent motor behaviour, but these were not specific enough to be used for diagnostic purposes (Einspieler et al., 2005a; A. M. Kerr, 1995; A. M. Kerr & Witt Engerström, 2001; Witt-Engerstrom, 1990). In recent years, research has questioned whether people with RTT are normal at birth (Einspieler et al., 2005b; Fehr et al., 2011; Leonard & Bower, 1998). Change in muscle tone over the years is documented in individuals with RTT, starting as hypotonia and changing into a more hypertonic muscle tone or even rigidity in some. Dystonic muscle tone may be present in all age groups (A. M. Kerr & Witt Engerström, 2001). In a report of 87 females with RTT, nearly half of the children aged less than five years had low muscle tone; this became more uncommon with age (Cass et al., 2003). Noradrenalinic deficiency has been related to hypotonia (Y. Nomura, 2001).

1.1.10.3 Working against gravity

Most babies are able to sit unsupported, but sitting in a "frog position" is common (I. Witt Engerström, 1990). Few crawl on their hands and knees, and shuffling while sitting is preferred by many (Y. Nomura & Segawa, 1990b). One study reports that 79.9% out of 199 participants developed sitting within the normal time frame, and a study in 2008 declared sitting balance to be the strength in RTT (J. A. Downs et al., 2008; Fehr et al., 2011). The later changing from the rather normally developed sitting into pulling to standing and struggle against the force of gravity turns out to

be more difficult. Cass et al found that most needed help when moving from supine to sitting and sitting to standing (Cass et al., 2003). These transitional movements are reported to be difficult for most individuals with RTT (Foley et al., 2011).

1.1.10.4 Walking

Walking ability is reported in various numbers but it is not always reported whether the walking is assisted or unassisted. Unassisted walking was achieved by a little less than half, according to two different Australian studies (J. A. Downs et al., 2008; Fehr et al., 2011), as compared with 20% in an Italian study (Vignoli et al., 2012). Another study reported on problems in walking in all age groups, but half of their group of 87 participants were still largely independent walkers at about 20 years of age (Cass et al., 2003). Walking is often broad based and there is a balance problem and often an element of ataxia that influences walking (Hanks, 1990). Dyspraxia also affects walking and the ability to initiate walking. Moving from side to side instead of regular weight shift forward to initiate a step is often used, as well as holding the body stiff with no trunk rotation. The common problem of walking up and down stairs, down being more difficult than up, seems to be of both motor and perceptual origin (Lotan, Isakov, & Merrick, 2004).

1.1.10.5 Postural control

Keeping the body position in space is often a problem that is added to postural weakness. Spatial orientation seems to be disrupted and equilibrium responses are slow or inadequate (Hanks, 1990; A. M. Kerr, 2006).

1.1.10.6 Dyspraxia

A pronounced dyspraxia is common, even if it may vary between individuals and situations. Dyspraxia is what to some extent separates RTT from other severe disabilities, making it difficult for individuals to use abilities they have. The confusion that is sometimes reported concerning people with RTT may be caused by their ability to overcome dyspraxia sometimes and be locked by it at other times (Hanks, 1990; A. M. Kerr, 2006).

1.1.11 Hands/hand stereotypies and handedness

Loss of hand function and development of various stereotypical movements is a main symptom in RTT (Rett, 1966b). The hands are involuntary locked in these movements, making it difficult to have any real use for them. The most common movements are with the hands together, squeezing, patting or wringing, often also engaging the mouth and/or tongue. Finger movements can be very intricate. All these movements are very intense and may injure the skin but tend to decrease in intensity with age. Development of hand function has been reported to occur at around the four-month level, involving being able to grasp and

bring the hands to midline but not performing a pincer grip. However, a Swedish study reported that 11 out of 20 had developed a pincer grip before regression (I. Witt Engerström, 1992). The stereotypic hand movements develop between eight months and three years and handedness is undetermined in most cases. In a British study with 87 participants, only two did not have any hand stereotypies (Cass et al., 2003). In an Australian study reporting on hand use in 129 participants with RTT, two-thirds had purposeful hand use ranging from minor ability to manipulating small objects, but one-third had no hand function (J Downs et al., 2010). When studying early videos in retrospect, few individuals really use their hands or handle objects in a normal way, even if it was regarded normal at that time (A. M. Kerr, 1995). Nomura and Segawa point out that hand stereotypies appear after purposeful hand use is lost, and that most are undecided about handedness (Y. Nomura & Segawa, 1990a, 2005).

Handedness is observed to change over time in RTT, but description of expression varies, though a predominance of left-handedness after regression is reported, as well as a large proportion with no decided preference of hand (Umansky et al., 2003; I. Witt Engerström, 1992). There is consensus that hand dominance in RTT differs from the general population, but whether this is related to a specific age is not clear (Y. Nomura & Segawa, 2005; Olsson, Rett, Opitz, & Reynolds, 1986). A connection to deviating blood flow in the brain has been proposed (Bieber Nielsen et al., 1990).

1.1.12 Teeth clenching/teeth grinding

Teeth grinding and/or teeth clenching is a common involuntary muscle activity in RTT (Lavás, Slotte, Jochym-Nygren, van Doorn, & Engerström Witt, 2006; Mount, Hastings, Reilly, Cass, & Charman, 2002). It is proposed to move back in the jaws with increasing muscle tone (A. M. Kerr & Witt Engerström, 2001). Since this is a continuously ongoing muscle tension, at least when awake, it may be presumed to cause pain (Kjoerholt & Salthammer, 1990).

1.1.13 Hearing, vision and sensation of pain

Assessing hearing and vision is not easy in a disability such as RTT, but reports from parents indicate that these abilities function rather well; especially vision, since eye pointing is often a way to communicate. In a study using evoked potentials, intact peripheral pathways were found, both auditory and visual ones. The conclusion was that if there was a dysfunction, it should be found in central cortical pathways (D. G. Glaze, 2005).

1.1.13.1 Vision

It has been suggested that vision in RTT might not be severely affected because the deficient synaptogenesis might not be as serious in the occipital cortex as in other parts of the brain (Nomura & Segawa, 2001). Also, no severe visual defects were found by Saunders et al (1995), though refractive errors were common and many lacked the corrections they needed (Saunders, McCulloch, & Kerr, 1995).

In everyday life, people with RTT often hesitate in front of stairs or when there are changes in the colours of the floor or ground. Walking downstairs is more cumbersome and it could be suspected that this is caused by an affected perception of vision, as deviation in processing both auditory and visual tasks has been reported. It was concluded that for participants with RTT, visual processing did not become easier with age as it did for controls, since the visual encoding was less efficient in RTT (Stauder, Smeets, van Mil, & Curfs, 2006). In a study where seven females with RTT, aged nine to 21 years, were examined, none had abnormalities of ocular structures, five had abnormalities that could be treated, but no one had correction for this. Visual tracking was absent in five and poor in the remaining two. Since there was no deficiency in the eye muscles, the authors recommend intervention in order to improve visual tracking. They call attention to spectacle corrections (Koslowe, Bergwerk, Yinon, & Merrick, 2009).

1.1.13.2 Hearing

A study reporting on hearing impairment in girls with RTT presumed there was a connection with the development of the disorder and the use of certain drugs (Pillion, Rawool, Bibat, & Naidu, 2003).

1.1.13.3 Sensation of pain

Common reports from parents indicate a deranged sensitivity to pain (I. Witt Engerström, 1990). These reports are mostly concerned with lower extremities but upper extremities are also reported. It is not clear if the nociceptive perception is disrupted or has a delayed reaction (B. Hagberg, 2002). In an Australian study, 75% reported an abnormal response to pain and 65% reported decreased sensitivity to pain. Decreased sensitivity to pain was more often reported in those with C-terminal mutation and mutations p.R306C and p.R168X (Jenny Downs et al., 2010). Only minor signs of peripheral nerve damage have been found, even in advanced stages of RTT (Bader, Witt-Engerstrom, & Hagberg, 1989). In 2001, Nomura suggested that indifference to pain may be due to the autonomic nervous system or central nervous system, since peripheral motor and sensory nerve conduction are normal (Y. Nomura, 2001).

1.1.14 Cognitive functions/ Communication

Even if there are variants of RTT called preserved speech or Zappella variants, most individuals with RTT have no speech (Zappella, Meloni, Longo, Hayek, & Renieri, 2002). This makes deciding on level of cognition very difficult in RTT, as the hands are locked in stereotypies. Most instruments that are used to test level of cognition are designed for verbal use or for using hands, but since this is most often not suitable for people with RTT, eye pointing is used, even if it is not always reliable (Baptista et al., 2006; von Tetzchner et al., 1996). In a report by Cass et al on 87 people with RTT, two-thirds were able to use eye pointing (Cass et al., 2003). There is consensus that there is a severe intellectual disability in this disorder and some have found the level to be at the individual onset of the regression (Fontanesi & Haas, 1988). The individual's level of language before regression varies; however, after regression there is practically no expressive language but more passive language, more understanding of verbal communication than is first understood. Social and emotional situations are favoured (Dahlgren Sandberg, Ehlers, Hagberg, & Gillberg, 2000; Lavás et al., 2006; G. Woodyatt & Ozanne, 1997). It has been questioned whether learning is possible, but research taking into account the level to start from, motivation and the importance of adapting to the individual's speed as well as numbers of repetition, has shown that it is possible for some people with RTT to learn and remember, within their limitations (Demeter, 2000; Elefant & Wigram, 2005). As always in this syndrome there are individual variations (G. C. Woodyatt & Ozanne, 1993). It has been reported that communication worked better for younger girls, those who lived at home and had no epilepsy (Didden et al., 2010). Intervention in the form of coaching communication partners during mealtime led to an increased number of bids for communication from the girl with RTT; feeders waited longer for the girl to respond and there was increased eye contact and choice-making (Bartolotta & Remshifski, 2012). It has been suggested that there are better conditions for learning if hand stereotypies are controlled (Fabio, Giannatiempo, Antonietti, & Budden, 2009).

Literature

Since RTT is a rare disorder, there are few large studies on therapists' clinical interventions. Most are case reports or studies with few participants. Riise comments that when researchers actually meet and examine someone with RTT, the groups are inevitably small (Riise et al., 2011). Studies with larger groups most often use data from questionnaires or registers. Literature searches have been conducted continuously over the years and a table has been put together in order to show what clinical interventions, carried out by therapists, have been found. Colleagues at the Rett Center were also asked for information about intervention studies from their field of competence.

See Appendix 1. and Appendix 2.

Rationale behind the thesis

The first time I met a girl that was later diagnosed with RTT was in 1978. Since then my experience of this syndrome has developed and I have met many females with RTT of different ages; and a few males. Unfortunately, there are still few physiotherapists publishing their experience and doing research, and therapists working clinically still come across old information contradicting the new research they need, in order to plan correctly for someone with RTT. This is why I wanted to try to make my contribution.

When working with children and adolescents with varying disabilities I became aware of the lack of information when it came to this specific girl, who did not have Cerebral Palsy (CP) and was not autistic, even if her medical record said so. Her muscle tone was not really spastic but more like the rigidity seen in Parkinson's disease; she also had ataxia, breathing dysrhythmia, dyspraxia and strange repetitive hand-mouth movements. There was also more ability than was first evident, but she could very seldom start activities by herself. Her parents had not been believed by healthcare professionals when they insisted that she had been healthy and normal as a baby and later developed this disability. This caused distrust and a feeling of not getting any help with their daughter's problems. After working with the girl for a couple of years I was trusted to see their family films, i.e. to see the girl when she was six months and 12 months old. In these films she looked quite different from the girl I had met since she was four years old and I discussed this with the girl's paediatrician. By this time the girl was losing weight in a way that worried the paediatrician. Looking for more information, the paediatrician found the article by Hagberg et al (1985) and the girl was referred to Professor Hagberg for assessment. The diagnosis was not easy for the parents to receive, because at that time RTT was said to be a progressive encephalopathy. The parents were, however, happy to meet someone who knew about this disorder, someone who believed them when they told him about the way she looked as a baby. Parents of girls with RTT I met later did not have the same struggle since the diagnosis has become more known to paediatricians. However, there is still a lack of knowledge, especially regarding adults.

When I started to look for information I realized there was very little to be found – little information for me as a physiotherapist, no one to ask about this syndrome that is so rare. Later I came to work with another girl with RTT, and it was intriguing and challenging to discover her abilities and realize that she also could keep these abilities, even if she could not always initiate them, or only perform them spontaneously. It was also possible for her to learn and retain a new way of getting up from the floor with some help. She developed this ability and used it in different settings but could also use the “baby way” she used earlier. It was important to plan for her everyday activities because it looked as if she would forget abilities if she did not use them regularly. With more experience I became aware of the very limited number of people with this syndrome and the

variation in the way their disorder manifested itself. My conclusion was that case reports, reports on clinical intervention, might also be of importance. Meeting more individuals with RTT was a way for me to increase my knowledge, so I was happy to start working at the Rett Center at Frösön. There I could meet and assess many people of all ages with the diagnosis. There was the opportunity to learn more and attempt to develop clinically important areas for people with RTT and those helping them in their everyday life. Collecting good information from colleagues was important, as well as supporting with my knowledge. Over the years there have been some more reports on intervention for people with RTT, but there is still very little “hands on” information for therapists.

Rett Center

The Rett Center was built up with the support of a state subsidy for stimulation of support for rare disorders, and it was started by Dr. Witt Engerström after she completed her PhD on Rett syndrome. After having worked as a consultant physiotherapist for the Rett Center for some years I was later employed there. At the Rett Center the multiprofessional team who worked together was very important, in the same way as at my earlier work at a habilitation unit. The difference was that this work was for all ages and only for people with RTT. Work at the centre has three objectives: 1. Research and development, 2. Education, knowledge and information, 3. Highly specialized medical care. The Rett Center is now administrated by Jämtland County Council and the clinical activities take place in Östersund. The Swedish state took over the long-term financial responsibility for the Rett Center in 2003. People with RTT are referred to the centre by their paediatrician or physician for different reasons, for a cross-professional assessment during a week, for a cortico-bulbar brainstem assessment during 2-3 days, or for diagnostic or orthopaedic purposes. The people with RTT and those accompanying them stay together in an adapted, homelike unit at the centre during the visits. On the last day of the visit, the family and others attending during the stay are given a summary of recommendations. This is later complemented with a written report to the referring doctor and to the family, the importance being to cooperate with doctors and therapists where the person with RTT lives.

Working at the Rett Center has been very stimulating, constructive and gratifying, in that I have been able to concentrate on one disorder and have been encouraged to perform research in combination with clinical work. Later on, it was a requirement for all those working clinically at the Rett Center to carry out research, making it possible for me to perform PhD studies within my work.

Aims of the thesis

Overall aim

The main aim of the thesis was to acquire more knowledge and understand more about development, first and foremost motor development, in RTT, and to find out if there is cause for limitations in standing and being active.

Research questions relating to specific aims

In what ways have gross motor development been described in RTT? (Papers I, II, III)

How early have particular deviating signs been noticed by parents or others? (Paper III)

Is there partial deterioration or is loss of skills always complete? (Papers I, III)

What about loss of skills or abilities - is it possible to keep abilities after regression? Can some be kept? Regained/re-trained? Can skills be achieved after regression? (Papers I, III)

How do females with RTT control their orthostatic reactions? Does severity of RTT, using ISS score, affect how the individuals with RTT react to the different orthostatic positions (Paper IV)

What would be important for physiotherapeutic intervention? (Papers I, II, III, IV)

2 Methods

This thesis is based on four different papers, of which Papers I and II are case reports, Paper III is based on a questionnaire and Paper IV is an experimental study.

For an overview of methods and participants, see each paper and Table 1.

Table 1. Methods included in the thesis

Paper	Method	Subjects (n)	Assessment/analysis
1	Case reports Empirical and clinical experience	3	Video recording was used regularly and also clinical assessment. Medical records were scrutinized. Parents provided early films and information
2	Case report Longitudinal study	1	Medical records, films and videos from childhood to 25 years of age were studied. Present motor and behavioural development was assessed Tests for neurometabolic and neurological status were made over the years A genetic test later confirmed a Rett syndrome variant
3	Questionnaire	125	The questionnaire contained 14 main subject fields and 34 subgroups. For this study these subgroups were used: background data, deformities, feeding, first symptoms, mobility, motor function, postural control, retraining of abilities. Also some about communication, failing autonomic nervous system and fine motor function Descriptive data was presented
4	Experimental study	21/14	Orthostatic reactions in 21 females with Rett syndrome and 14 normally developed females matched by age, were investigated when they rose from a sitting position, and during standing for three minutes. Reactions of the heart, the blood pressures and the time for recovery of systolic blood pressure, were studied in real time, heartbeat by heartbeat, simultaneously The Multilevel linear mixed models (LMM) as well as Mann-Whitney U Test were used

2.1 Participants

In Study I, three individuals with RTT were described; they were 35, 16 and 10 years old, respectively, and diagnosed as classic RTT. Study II reported on a woman who was 25 years old and diagnosed as a variant of RTT. In Study III, a questionnaire was sent to all families (176) in Sweden who had a child diagnosed with RTT at that time. There were 125 answers but no information as to whether they were diagnosed as classic or variants. For Study IV, in which orthostatic reactions in RTT were investigated, 21 females with RTT and 14 healthy females matched by age participated. Of those with RTT, 18 were diagnosed as classic RTT and three as variants of RTT. The median age at assessment in Study IV was 20 years (min-max 5-46 years) for participants with RTT and 24 years (min-max 5-43 years) for controls. Only the participants in Study IV were females with RTT who were referred to the Rett Center for assessment of the central control of the autonomic nervous system. They had to be able to get up from sitting to standing, with support or by themselves, and be able to keep standing for three minutes. If they were unable to meet these conditions or showed discomfort in the situation they were excluded. Age-matched females were recruited as controls through friends and colleagues in the Östersund area. These were recruited on the basis that they were healthy and did not have any medical complaints. They were to be excluded if the assessment showed any reactions that might be pathological.

2.2 Procedure, assessments and devices

For the four participants in Studies I and II, background information was studied as well as a personal assessment performed by this author. Parents contributed with statements, photos, films and videos from an early age. Medical records and physiotherapists' reports were also studied with parents' permission. Study III was a questionnaire to all 176 families in Sweden who at that time, 1996/97, had a daughter with RTT, and 125 answers were received. The questionnaire was comprehensive with questions concerning all professionals working at the Swedish Rett Center at that time, all of them experts on RTT in their profession. The questionnaire contained 14 main subject fields and 34 subgroups such as background data, deformities, feeding, first symptoms, mobility, motor function, postural control, retraining of abilities. The different professionals at the Rett Center had contributed with questions concerning their own field of work; this author participated as a physiotherapist and also selected areas to report in this study (Table Method).

For the experimental study, Paper IV, a non-invasive method was used where all measurements were carried out heartbeat by heartbeat, simultaneously. In order to measure BP waveform a photoplethysmograph was attached to a finger, PortapresTM (Finapres

Medical Systems BV, Amsterdam, The Netherlands). The beat-by-beat systolic (SBP), diastolic (DBP) and mean arterial (MAP) blood pressures were derived from the BP waveform by the Neuro-Scope™ (MediFit Instruments Ltd., London, UK). The MAP was calculated as the true arithmetic mean of pressures throughout the whole cardiac cycle. A height compensation unit was used to compensate for change in level when a person is not able to keep their hand at heart level the whole time. To examine the orthostatic reactions, standing up from a sitting position was used, since people with RTT have difficulty in standing up quickly from lying down. The participants sat in an ordinary chair, with their feet supported on the floor. They would sit for at least three minutes, then stand up and remain standing erect for three minutes, and then sit down again. This procedure was repeated once more. In this study, orthostatic hypotension (OH) was chosen as the difference between the DBP in sitting position and after standing up for three minutes (i.e. less than 10 mmHg drop in DBP after standing for three minutes). Continuous video recordings were used for further analysis. These were time-locked with the physiological measurements. Severity of RTT, according to the International Severity Score (ISS), was also studied to examine whether severity could predict orthostatic reactions.

2.3 Analysis and statistics

In Papers I and II, observation and mixed descriptions were used, and in Paper III descriptive statistics with percentages, medians as well as min and max values were presented. Areas analysed and reported from the questionnaire were: background data, first symptoms related to RTT, who suspected that the girl's development deviated from what is normal, time when these suspicions arose, best ability before regression, walking, feeding, hand function, communication/social interplay, movement transitions, posture, postural control, deformities, autonomic dysfunction connected to feet and breathing, senses, retraining of abilities and achieving new abilities after regression. For statistics in Study IV, the IBM SPSS statistics version 20 was used. Multilevel linear mixed models (LMM) were constructed in order to analyse general differences in orthostatic reactions between positions and groups. A two-level mixed model was applied for each variable with "group" (RTT/controls) and "position" (sit, get up, and stand) as fixed factors. The interaction between group and position was also included in the analyses. Since assessment was performed with repeated trials from the same individual, the intercept for each individual was set as random to create a hierarchical structure (i.e. the individual was treated as a two-level variable). To analyse if severity of RTT could predict the outcome in the BP variables and HR, separate models were created for the participants with RTT. In these two-level models, the "position" was also treated as a fixed factor, while the ISS score was added as a covariate, together with the interaction between position and ISS. When there was only one value

for each individual, the Mann-Whitney U Test was used for comparisons between groups. For all analyses a significance level was set to $p \leq 0.05$.

2.4 Ethical approval

For papers I and II, parents were asked for permission to describe their daughters in the papers, and also concerning the use of pictures.

Study III was approved by the Ethics Committee at the University of Umeå (Section 15/97, dnr97-1).

Study IV was approved by the Regional Ethical Review Board in Umeå 2010-03-02, Dry 09-192M.

3 Results

This is a summary of the results from the included papers. The complete report on results and data are presented in each paper.

From the results of this thesis it became obvious that even if individuals with RTT lost functions and skills, it was also possible for some to keep, develop and regain or retrain abilities. In addition, the orthostatic reactions when standing up from sitting and during standing were similar to those of healthy controls.

Time for early signs

From the 125 returned questionnaires in Paper III, it was found that deviation in development was observed at 0-4 years of age, median age 0.75 years, and 65% were less than 1 year old when someone first suspected something was not quite normal in the child's development. The ages when loss had occurred varied from 7 months to 7 years. Loss of developed ability was reported to be sudden in only 35 out of 116 answers; the rest reported a gradual loss.

Motor development and deviations

Family members were most often the ones to call attention to the deviations, and second came medical staff. The most common reason for suspicion was deficient gross motor ability (n=60), such as being late in developing functions or never developing functions, low muscle tone, weak postural control, balance problems, not putting weight on the legs. Deficient fine motor ability, repetitive hand movements and divergent behaviour in play situations came second (n=22), while change of behaviour such as screaming, agitation, fright was less common in our study (n=18). "Best abilities" before regression are displayed (Table 2). In some cases these "best abilities" were lost, in some they were kept, and in others regained/retrained. Hand dominance after regression was reported to deviate from normal since participants with RTT were distributed into three almost equal groups for preferring right hand, left hand or both/none. A prominent result was difficulty in transferring from lying down to sitting, or from sitting to lying down, and to sit down from a standing position or rise to standing from sitting. In Paper II a special deviation was shown where the girl could ride a tricycle, at speed, when she was eight years old, although there were suspicions that her development was not according to standards at that time. It was also shown that it was easier for her to "take in", i.e. remember, than to perform activities.

Results

Table 2. Best ability during the early development, distributed into the three areas, gross motor function, fine motor function and communication/social interplay. More than one area was reported for each of the received 99 answers

Gross motor function	n	Fine motor function	n	Communication/social interplay	n
Walk	17	Grab objects	11	Had social interplay	11
Run, jump, climb	13	Turn pages	9	“Had words”	9
Sit	11	Pincer grip	8	Could say words in two languages	2
Crawl	9	Feed herself	8	“Could talk”	2
Shuffle	7	General fine motor ability	8	Babble	1
Move lying on floor	5	Play with toys	6		
Stand	2	Undress	2		
Others	5	Others	2		

Loss and regain of abilities

Thirty-six out of 114 reported on new abilities achieved after regression. In both Papers I and III it is shown that, for some, loss of skills is not always complete and some abilities can be kept, regained or even achieved after regression. From Paper III in our study it was shown that some had retrained feeding, see figure 2, and walking ability, see figure 3. One grown-up woman in Paper I had been able to regain the ability to move from the floor into her chair after practising for a long time. A single “code word” had to be used, but most important was returning to a place where she had been able to perform years ago. Another of the participants in Paper I was introduced to a new way of getting up from the floor, after which she developed this further. Being able to keep some abilities, develop others such as remembering information, and a slow deterioration in fine motor skills, was shown when assessing the participant in Paper II.

Development and changes in feeding

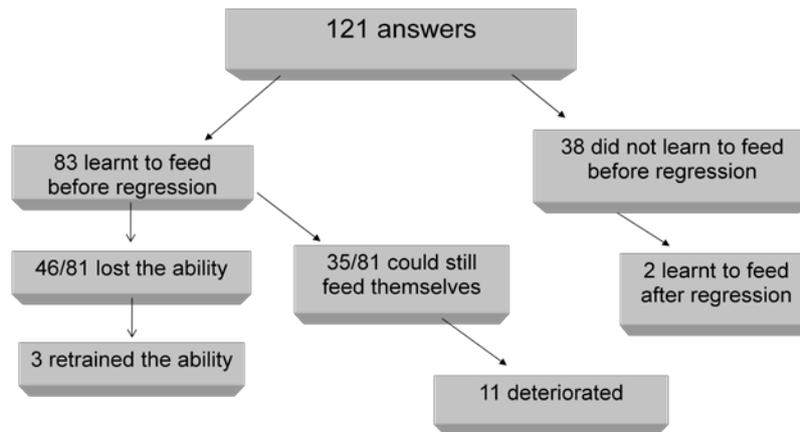


Figure 2. Reported development and changes of feeding ability in 121 girls/women with Rett syndrome

Development and changes in walking

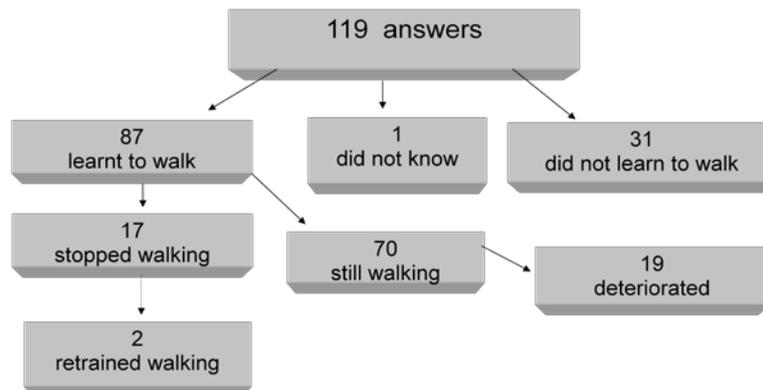


Figure 3. Reported development and changes of walking ability in 119 girls/women with Rett syndrome

Deformities

The most common deformities were in the back and feet. In Paper I, the adult woman regained walking after surgery to correct a foot, it took long time and well fitting shoes were important to keep the good result. Also a girl with RTT is reported to have maintained a good foot position when using foot orthoses, which made a good standing position possible. Scoliosis was reported in 74% and kyphosis in 24% of people with RTT. Age when scoliosis was first noticed ranged from 0 to 20 years. Many of the girls/women with RTT were reported to be leaning to one side or forwards when sitting. This postural instability in sitting was reported to start at an early age. To our knowledge this has not been highlighted earlier. It has not yet been investigated whether this is an early sign for development of scoliosis or due to other reasons.

Autonomic dysfunction/senses

In Paper III, disturbance in the autonomic nervous system in RTT was expressed as different kinds of breathing disturbances and disturbance in peripheral circulation. Families reported doubts about the extent to which the senses functioned for a person with RTT, especially the feeling of pain.

Orthostatic reactions

Results in Paper IV showed that the reactions of participants with RTT did not differ significantly from those of the controls with regard to their responses by the heart and blood pressures when standing erect for three minutes. There were differences in resting values, with a tendency to higher HR and lower BP in RTT compared with controls. Severity of RTT did not affect orthostatic reactions, i.e. how individuals with RTT reacted to the different orthostatic positions: sitting, rising to standing and standing erect for three minutes; although those with higher ISS score, i.e. more severe RTT had lower BP values when position was taken into consideration. The specific immediate response by the heart to standing up, the 30:15 ratio, showed lower values for the group of RTT compared with controls, indicating that the individuals with RTT had a weaker response of the heart to standing up.

Physiotherapy

Reports about physiotherapy or physical activities showed that 57% had individual physiotherapy, 19% were reported to have no gross motor exercise at all, and no correlation was stated between severity of RTT and physiotherapy offered.

4 Discussion

RTT is a rare disorder, found all over the world. The fact that there are few in each area makes it difficult to have large populations in research and even more difficult to perform intervention studies involving assessment, intervention and then reassessment to document the result. Each therapist meets few individuals with RTT, and thus few have the opportunity to enter more deeply into the syndrome. The variation of expression and severity makes it even more complicated, and this is why case reports can be of value. Case reports on the effects of intervention in RTT may be helpful for the individual therapist, when trying to support the individual with well-planned interventions leading to good health and good quality of life, whatever their expression of RTT may be.

Time and early signs

The early signs in RTT are not very evident, and also in retrospect it is not always evident that a child has this syndrome, even if it can be seen that something is not according to the general course of development (Einspieler, Kerr, & Prechtl, 2005a, 2005b). In our studies, 65% of families reported that some deviation was noted before one year of age, and one Australian study reported that 46.5% of parents noticed unusual development or behaviour in the first 6 months (Leonard & Bower, 1998). Another Australian study reported that 81.5% of parents (n= 237) had concerns about their daughter's development or behaviour within the first 10 months (Fehr et al., 2011). This in contrast to most descriptions of people with RTT, stating that the first period is normal or "seems normal". This information about normal development during the first 18 months may be confusing for therapists assessing babies with delayed or deviating development, preventing them from discussing the baby's problems with RTT in mind, which may delay diagnosis (Fehr, et al., 2011). There is a time profile in the development of RTT, but the variation is extensive, both when development starts to slow down, when regression first appears and when the more stable period starts. In 116 statements, our study showed only 35 reports of sudden loss of abilities, sudden regression. In an early description of the syndrome, Rett (1977) only mentions slow development and "in no case was there a dramatic onset", although he also states that most of these patients came to the clinic "in an advanced state of the disease" and there was little information about early development (Rett, 1977). Regression has later been emphasized as a main symptom in RTT, and is still expressed as "rapid" or "sudden" in some papers, although as early as in 1986 and 1990, regression is described as sudden for some and slower for others (Hagberg & Witt-Engerstrom, 1986; I. Witt Engerström, 1990). Our study is in line with Fehr et al who state that loss can be sudden or gradual; and they conclude that even if regression is a main feature in RTT, knowledge is deficient (Fehr, et al., 2011). They also call attention to lack of information about early development of gross motor and communication

abilities in people who later develop RTT, as well as a risk for children who acquire more milestones to have their diagnosis later. This is in accordance with our report in Paper II.

Deviation in development

Few earlier studies have called attention to a major problem in RTT found in our studies, i.e. difficulties in transitional movements such as moving from supine to sitting, sitting to lying down, rising from sitting to standing or sitting down. This problem was even present in those who could walk. In a study of 87 females with RTT, Cass et al (2003) reported that 32.8% were not able or needed major help to move from supine to sitting. This corresponded to 71% in our study, and their 37.5% who had difficulty moving from sitting to standing corresponded to 57% in our study (Cass et al., 2003). Hanks (1990), being a clinical physiotherapist, points out that transition is as important as ambulation and recommends activities to enhance spatial orientation and equilibrium, emphasizing verbal and physical support to make the person feel safe and confident during these activities (Hanks, 1990).

People with RTT are reported to have limited voluntary use of their hands in everyday activities because of stereotypic, repetitive hand movements, or hand-mouth movements. Cass et al (2003) reported that despite these movements, there were some hand skills in all ages; though in adults there was a tendency for less stereotypies as well as decline in hand use. It was evident that they found it difficult to look at the object they wanted to grasp (Cass, et al., 2003). An Australian study reported on limitations in hand use, with participants having more difficulty reaching out from the body than touching the body, for instance scratching or rubbing their eyes (Umansky et al., 2003). The restricted use of hands is also evident in our research, and the woman in Paper II showed decreased hand skills with age. However, in Paper III there are also reports on 3 out of 46 who had retrained feeding ability and 2 out of 38 explicitly declaring that they had learnt to feed after regression. Hand dominance after regression was reported to deviate from normal, since our group was divided into three almost equal groups for preferring the right hand, the left hand or both/none. Deviation of hand dominance is also reported for a British group and an Australian group, even if percentages are not completely concordant (Kerr & Witt Engerström, 2001; Umansky, et al., 2003).

In our study, reports on “best ability before regression” indicate sitting, crawling and walking, but there are few reports in each subject field. Earlier studies have reported that few people with RTT learn to crawl on their hands and knees but rather use “bottom-shuffling” as a way of moving on the floor (Kerr & Burford, 2001; Nomura & Segawa, 1992; I Witt Engerström, 1987).

Loss of abilities, kept - regained or re-trained abilities, abilities achieved after regression

In this thesis, apart from losing abilities, it was found that abilities could be kept or partly kept, retrained or regained, and there were also abilities that were developed after regression. Whether or not it was possible for some individuals to develop motor function depended on good knowledge of the person as well as of the syndrome. As shown in Paper I, it was essential to find what was motivating for the individual with RTT and that all those who were helping worked together.

There are few papers reporting on clinical physiotherapy intervention in RTT and of those few, most report on different loss of abilities. This is obvious since regression, i.e. loss of skills, is a main feature in RTT. But this should not keep us from reporting skills that are kept or partly kept, or skills that are achieved, whether before regression or after. Foley et al (2011) found loss more frequent in younger people with RTT, while gross motor abilities were more stable in older individuals and not dependent on whether they could walk or not. They also state that their result contradicts earlier reports about RTT having arrested development. They found some abilities kept and some developed after regression (Foley et al., 2011). The results of an Italian study including 84 females with RTT agreed with our results, stating that in some individuals there is loss of abilities, maintenance of abilities and development over time. The authors ask for more data on the long-term development of RTT, in order to highlight and evolve some issues in their study: hand stereotypies were stable over time, autonomic features persisted in adults, epilepsy tended to improve over time and musculoskeletal problems got worse with time. They demand programmes for younger people with RTT in order to provide early prevention (Vignoli et al., 2012). Cass et al (2003) ask for therapists to expect mobility to be maintained and not deteriorated, since this would help adults with RTT to function according to their best ability (Cass, et al., 2003). Successful intervention in the gross motor area was seen by Hanks and Lotan respectively; albeit in studies that have few participants or are observational studies (Hanks, 1990; Lotan, 2006a; Lotan, Isakov, & Merrick, 2004). It is important to disclose these potentials in the complexity of RTT (Kerr, 2006). Pizzamiglio et al (2008) reported on sensory-motor rehabilitation where a person with RTT partially regained the use of her hands after three years of intervention (Pizzamiglio et al., 2008). Reports on keeping or regaining abilities or learning something new after regression are few, but Jacobsen et al (2001) reported about a woman with RTT who was unable to walk for 23 years. With intervention she regained walking and also improved her hand use (Jacobsen, Viken, & von Tetzchner, 2001). This is in accordance with results from Papers I and III and with an English study of 87 people with RTT, where some were reported to have gained new skills (Cass, et al., 2003).

Fehr et al (2001) described that most children who later develop RTT have learnt to sit, although few have reported if it is within the

recommended time frame. The same authors also reported that 20% of children who learnt to sit were delayed (Fehr, et al., 2011). In many papers there are reports of different numbers of individuals learning to walk, and it is not always stated whether this is with or without some support. In our study, Paper III, 73% started to walk and in the questionnaire it was formulated as walking without support, while another study reported that 46.2% walked unassisted (Fehr, et al., 2011). In our study, 20% stopped walking, there was deterioration in some who continued to walk, and two regained their ability to walk. In our study it is not reported when they were able to start walking, but this may be delayed. Fehr et al (2011) state that a mean age is 19.6 months with a range of 9-50 months, and Kerr and Burford comment that walking is often delayed but some learn to walk in a swimming pool with the support of the water (Fehr, et al., 2011; Kerr & Burford, 2001).

Deformities

In our study, deformity of the spine and feet were reported to be the most common problems. Scoliosis was reported by 74% and kyphosis by 24% kyphosis. The percentages may differ between studies but nevertheless scoliosis presents a major issue for those with RTT. The degree of scoliosis or kyphosis varies between individuals and a correlation to specific mutations has been suggested (Ager et al., 2006). There is consensus that the cause is neuromuscular, indicating a risk for development of curves, even in adulthood, with more rapid development if the curve is C-shaped. Bracing is not likely to stop the development of curves and may be difficult for those with RTT to use (Kerr, Webb, Prescott, & Milne, 2003). In some cases it may help to delay progression and can provide support in sitting (Downs, Bergman, et al., 2009). Spinal surgery is an extensive operation but often recommended when curves exceed 40° of Cobb angle (Bassett & Tolo, 1990; Huang, Lubicky, & Hammerberg, 1994). In our study, scoliosis was reported to be first noticed at 0-20 years of age, but there were few answers. Another study reported a peak for developing scoliosis at age 8 (Harrison & Webb, 1990). Surgery for scoliosis is a major event and stressful, but when necessary it is reported to be successful and a help to maintain ambulation (Kerr, et al., 2003). A Swedish study reported improved sitting and reduced time of rest during the day in a follow-up study (Larsson et al., 2009). This is in line with a report by Downs et al (2009), who found that surgery was associated with improved activities in daily living, especially in those who did not walk. Those who walked with support needed less support after surgery (Downs, Young, et al., 2009). If development was affected before 10 months of age, or if someone never could walk, they were at greater risk of developing scoliosis at an early age (Ager, et al., 2006).

Leaning when sitting, presumed to be postural instability, was a pronounced feature in our study and reported in 88%, starting at an early age. To our knowledge this has not been highlighted earlier. It has not yet

been investigated whether this is connected with the early development of spinal deformity. When reporting on the use of active spinal orthoses, Shook and Lubicky (1991) distinguish between individuals having an intact righting reflex and those who do not have normal righting reflexes. When provided with a brace, the person is instructed to “pull away” from the pad placed on the convex side of the spinal curve (Shook & Lubicky, 1991). This is not possible for those with RTT to perform; whether it is because of deficient righting reflexes or other reasons is not known.

The risk of early development of foot deformities in RTT may be due to early hypotonia, but also later due to the common walking or standing posture in RTT, with the legs apart and the feet in a fixed position. Cass et al (2003) reported tight Achilles tendons even in people with RTT who have hypotonic muscle tone (Cass, et al., 2003). In Paper I we have reported on the possibility of using ankle-foot orthoses to maintain range of movement over time in the ankles and feet of a young girl with RTT; this was for a girl who could not stand or walk unassisted. The orthoses were changed with time according to needs, with the aim of maintaining her ability to stand and provide help in walking. In fact, they did give a good standing position and she could regularly walk with help. According to our study, hips were not reported to be a major issue, but concern has been expressed by orthopaedic surgeons (Hennessy & Haas, 1988). A recommendation for regular assessment of hip displacement and spinal deformities has been put forward (Tay et al., 2009).

Hearing, vision, sensation of pain, central autonomic function and orthostatic reactions

Uncertainty about how the senses function in people with RTT has been reported, and in our studies there has been most doubt about indifference to pain. Indications of intact peripheral visual and auditory pathways have been reported, as well as the possible occurrence of involvement in sensory pathways in older people with RTT (Glaze, 2005). Koslowe et al (2009) found no major ocular abnormalities in RTT, though corrections were lacking for many and they emphasized the benefit for better quality of life if appropriate treatment is provided (Koslowe, Bergwerk, Yinon, & Merrick, 2009). Longer latency for event-related potentials in auditory- and visual tasks has been reported (Stauder, Smeets, van Mil, & Curfs, 2006). Latencies in many areas are evident in clinical practice and lack of well-functioning perception may cause insecurity and hesitance that may explain some reactions seen in those with RTT. A report using the Non-Communicating Children's Pain Checklist, reported increased and overlooked risk of pain in RTT. One quarter of parents reported that their daughter had experienced pain for a total of 8 days during the last 30 days, and most often communicated with facial expression or vocalization (Symons, Byiers, Tervo, & Beisang, 2013). The question is still whether individuals with RTT do not feel pain, or whether they have latency in experiencing it and communicating it to others. In a report on the neurophysiology of RTT, Nomura (2001) states that the indifference to

pain seen in some people with RTT does not have pathological origin in peripheral nerves. It might be due to involvement by the autonomic nervous system, presumably brainstem, or the central nervous system (Nomura, 2001).

Central autonomic dysfunction is observed in RTT and may be exhibited in many ways (Julu & Witt Engerström, 2005; Julu et al., 2008; Nomura, Kimura, Arai, & Segawa, 1997). In Paper III, only two topics were at issue: peripheral circulation being inadequate, causing bluish, cold and sometimes swollen feet, and breathing disturbances, the latter found in more than half of the participants in. Most often reports describe that breathing disturbances appear when the individual is awake and breathing during sleep is assumed to be normal (Julu et al., 2001; Southall et al., 1988). Even so, there are also reports on breathing being affected during sleep, though Weese-Mayer et al (2008) report that breathing during the night is less irregular than during the day (Rohdin et al., 2007; Weese-Mayer et al., 2008). All the different breathing disturbances cause severe problems in daily life for people with RTT, both physically, for instance by causing unbalanced levels of oxygen and carbon dioxide, and by making it difficult to concentrate in different situations. We could observe, analyse and report on the orthostatic reactions in a group of females with RTT compared with healthy females matched by age. We used standing up from sitting position, since people with RTT find it difficult to rise quickly from a supine position. From the measurements of reactions of the HR and blood pressures (SBP, DBP, MAP) in Study IV, we found that people with RTT mainly had the same reaction as age-matched healthy controls when rising from sitting and standing erect for 3 minutes. These reactions were in line with values of other healthy groups (Wieling & van Lieshout, 2008). The differences in resting values, with a tendency to higher HR and lower BP in RTT, was already known, but the quicker initial drop of SBP has not been described before. This has to be considered when helping people with RTT in the morning or after resting. Since BP recovered in adequate time for participants in our study, compared with controls, standing could be used as an important activity in RTT. Reduced physical activity may cause increased orthostatic intolerance, and practising standing, using leg muscles, may be used as a way of enhancing activity and further developing orthostatic tolerance (Low, Sandroni, Joyner, & Shen, 2008; Low & Singer, 2008)

When comparing for severity of RTT, using the ISS score, no difference was found in reactions to standing up for participants in our study, depending on whether their symptoms were severe or less severe. However, severity was correlated to lower BP, indicating that individuals with severe RTT can use standing as an activity if given time when standing up. Our group of RTT displayed no medical conditions limiting their ability to stand up and keep standing for 3 minutes. It has been reported that activity might be positive in RTT, as it was shown that a person's respiratory pattern and heart-rate function improved when

walking or listening to music, i.e. during activity (Rohdin, et al., 2007). The technique for measuring all parameters simultaneously, heartbeat by heartbeat and non-invasively using the NeuroScope™ (MediFit Diagnostics Ltd, London, UK), US patent No. 6442420, 2002, is relatively new, but has been validated over time (Julu, Cooper, Hansen, & Hainsworth, 2003; Murray, Hamilton, & Macfarlane, 2001). A doctoral thesis described a validation made for a female with RTT, comparing measurements using the NeuroScope™ and measurements using an indwelling arterial catheter for 48 hours. The latter confirmed the observations from assessment by the NeuroScope™ (Smeets, 2005).

What would be important for physiotherapeutic intervention?

Already in 1977, when discussing treatment in what has later been known as RTT, Andreas Rett pointed out that physiotherapy and “continued physical activation” was essential (Rett, 1977). Later, in a joint article, occupational and physical therapists conclude that “scientific research on the efficacy of therapy for girls with Rett Syndrome is critical to guide pediatric physical and occupational therapists toward effective, quality intervention programs” (Stewart, Brady, Crowe, & Naganuma, 1989). Unfortunately few physiotherapists have reported practical clinical intervention research since then. Intervention studies are needed, as they may improve everyday life for people with RTT, their families and those helping them. Areas that are important for intervention may differ during different periods in the life of someone with RTT, but analysis of abilities, possible development and risk of deterioration is the main issue. With a severe disability like RTT it is important that every function or part of function works. In Stage I, it is important to document development, help families to initiate activities they know the baby has been able to do and enjoyed. In Stage II, if the child has become insecure or scared of movements, it needs help with stability so that it dares to play as it has been doing up till now. It is important to help families and daycare to find activities that the child can enjoy, activities for keeping skills and developing new ones. During Stage II, the most important factors are feeling safe, retaining confidence and motivation in activities. In order to analyse and find out what is right for this particular child it is very important to have a team that works together. In Stage III, most children with RTT have left the anxiety and uneasiness in Stage II and activities can be in groups with other children in different surroundings. Individual assessment is still important, but now it is rather the family, teachers or carers who will need support to find proper activities, or they may need someone to ask if there are issues or changes in the child’s behaviour or performance. For those who do not walk, Stage IV, daily activities and keeping abilities, is as important as for those who can walk. Most people with RTT live a long life into adulthood and lifelong plans with regular activities are needed. Since they most often cannot take the initiative themselves they need help to initiate activities. In line with our research, Fabio et al (2011) found structure and motivation very important when

supporting and helping people with RTT to develop (Fabio, Giannatiempo, Oliva, & Murdaca, 2011).

Early diagnosis is a way of providing early help and support, both for the child with RTT and for the family. Even though prediction of the development is difficult due to the wide variation of severity and expression in RTT, an early diagnosis may provide better quality of life, both for people with RTT and for their families (Halbach et al., 2012).

4.1 Methodological considerations

Since RTT is such a rare disorder it is not possible for researchers to have many participants in a study, especially not in research on clinical intervention. This means that case reports are important in finding and disclosing new knowledge and may signify best possible evidence.

Being case reports, Papers I and II only include few people, making it difficult to draw generally applicable conclusions. However, long-term follow-up for the woman in Paper II with access to early films and videos, medical records, family reports and personal assessment enhanced knowledge about the syndrome over time.

In Paper III, the questionnaire, there were some internal dropouts and some variation in answers to different questions. Responding parents with a grown-up daughter might have difficulty remembering specific developments during childhood, and for some participants there were no parents, implying there was very little or even no knowledge about early development. When studying dropouts there was no indication of a specific group choosing not to answer.

For Paper IV, participants with RTT were a consecutive selection of girls and women referred to the Rett Center for assessment of the central control of the autonomic nervous system. When studying videos that were time-locked with the test, it was found that those with RTT moved more when standing, compared with controls. Even if most movements were in the upper body, this might have caused BP for RTT participants to decrease less than if they had been standing still. A bias could also be the difficulty in standing up quickly from sitting experienced by people with RTT. For some participants with RTT, continuous recordings were not obtained throughout the assessment because repetitive hand movements sometimes caused artefacts or interrupted readings, resulting in fewer readings. There was substantial variation for severity of RTT, but nevertheless the orthostatic reactions for the group of RTT did not differ significantly from the group of age-matched healthy people.

Individuals taking part as controls were recruited through friends and colleagues in the Östersund area. Even if they originally came from different parts of the country this was not specified. For financial reasons it was not possible to assess more people for the group of controls, making it smaller than preferable.

4.2 Ethical considerations

Participants with disorders such as RTT are vulnerable, since they have difficulty showing their will, and protesting or understanding what will happen. Parents or guardians are the ones to give consent, also for adult RTT participants. This has to be taken into consideration in research; it is important to try and explain in a way that is understandable to the participant, as well as ensuring that informed consent is obtained from parents or guardians. In Paper I, personal data were disclosed, which is regrettable, even if parents had consented to data and pictures being published.

Marked attention was paid to the vulnerability of participants with RTT in the experimental study (Paper IV). Parents or other persons close to them observed participants during activities, to make sure they were feeling comfortable in the situation; if not, they were to discontinue the assessment. The possibility to discontinue was stressed for all parents/guardians answering for someone with RTT or young children, as well as for those taking part as controls (Paper IV).

4.3 Clinical implications and future research

Clinical implications

In a disorder as complex as RTT, and with such variations in symptoms and severity, it is not always easy to discover what really works. The variation between different occasions and during the day makes it even more difficult. This varying picture of RTT often causes confusion about best intervention, and thus highlights the importance of adequate knowledge about the syndrome, in order to support abilities and help keep or develop them over the years. In such a disorder even small changes can make a big difference in daily life, both for the individual with RTT, their family and those helping them.

Knowing that it is possible for some individuals to keep, regain or develop abilities, therapists have a better basis for providing good interventions.

Regular individual analyses are an absolute condition in order to perform an intervention that works well for the individual.

Joint planning, where all those helping the person with RTT have agreed upon what intervention there is, may have a better chance to be effective.

Motivation was found to be important for people with RTT, which should not be surprising since it is important to all, the difference being that when working with people with disabilities it takes time to find their motivation, and motivation might not be consistent on every occasion.

Regularity, repeating activities in order not to forget how to perform, has been a way to keep abilities. Also returning to a place where it was performed earlier was a way to regain ability.

The knowledge that people with RTT react the same way as healthy people when standing up and standing for three minutes, is a good basis for helping them to stand, keep their standing ability or develop this

ability. The quicker drop of SBP for some individuals has to be taken into consideration when helping those with RTT get out of bed in the morning or after resting in daytime.

Good foot position should be planned for early, since deformities in the feet were common in this research, as well as in other reports. When standing, a good basis for support on the floor is helpful. Standing barefoot may also be beneficial, if the person prefers this; though this was not the case for a person in our studies. Early orthopaedic assessment is recommended.

It was difficult for most participants reported on in Paper IV to keep a straight back and an upright position for a long period of time. It is not known whether there had been any early intervention concentrating on the strength of back muscles, experience of postural control and perception of the body in relation to the room. This might be something to plan for in early intervention.

For all interventions it is important to communicate and inform people with RTT. The expressions on their faces may not be distinct, so we have to look for other signs. Does she or he comply and take part, or is she or he tense or resisting? Is this motivating; is she or he enjoying this? Is she or he engaged in this activity? Compliance, participation and engagement are most important, in order to perform an activity and do it regularly. Personal contact, face to face, or music makes an intervention more agreeable.

Activity does not have to mean walking, but it has to be according to the individual's ability; anything more than what is usual will enhance reactions in the body. Sometimes a tilt table is used for standing in clinical work. The difference between standing up with help, putting weight on the feet, and being placed upright on a tilt table, has to be considered. Reactions in the body are not the same, though there is a lowering of BP and the person should neither be raised too quickly nor lowered too quickly.

When planning for intervention for people with RTT, the planning ought to be for life, since the majority of those with RTT today survive into adulthood.

Future research

Walking on a treadmill could be used to investigate how people with RTT manage their HR and BP in such a situation; this would give an important contribution to knowledge about walking and exertion in RTT. Research on intervention over time would also be useful in order to study effects of training. This could add more knowledge about possible physical activities to help people with RTT maintain their general health.

Dislocation of the hips has a great impact on the severity of the disability and how active a person with RTT can be. More research should be carried out to disclose risks for dislocation in time, in order to take preventive actions.

Discussion

Little is still known about perception in RTT; about pain, postural instability and its potential correlation to scoliosis. More knowledge in these matters would enhance the quality of life in people with RTT and their families.

Repetitive hand stereotypies are reported for many individuals, but little is known about possible intervention

5 Conclusions

Our research has shown that:

- It is possible for some people to keep abilities over time
- It is possible for some people to regain or retrain lost abilities, even after some years
- It is possible for some people to learn or develop new abilities after the period of regression
- Motivation was of major importance in order to keep, regain or develop skills
- Returning to a place where an activity was performed earlier was a way of regaining an ability
- Early use of foot orthoses, before contracture was manifest, was a way of maintaining range of movement
- It may be easier for some people with RTT to understand and remember information than to actively perform
- Orthostatic reactions were the same as in healthy persons of the same age, indicating that there are no autonomic limitations for people with RTT in rising from sitting and during standing for three minutes
- The fast initial fall of SBP in some people with RTT has to be considered
- Repeated individual analysis is most important because of variation of severity and variation during a day and over time

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Appendix

Dissertations written by physiotherapists, Umeå University 1989–2013

Birgitta Bergman. Being a physiotherapist - Professional role, utilization of time and vocational strategies. Umeå University Medical Dissertations, New Series no 251, 1989 (Department of Physical Medicine and Rehabilitation)

Inger Wadell. Influences from peripheral sense organs on primary and secondary spindle afferents via gamma-motoneurons - A feedback mechanism for motor control and regulation of muscle stiffness. Umeå University Medical Dissertations, New Series no 307, 1991 (Department of Physiology)

Jessica Elert. The pattern of activation and relaxation during fatiguing isometric contractions in subjects with and without muscle pain. *Arbete och hälsa* 1991:47. Diss. 1992 (sammanfattning). (Departments of Clinical Physiology, National Institute of Occupational Health and Physical Medicine and Rehabilitation)

Gunnevi Sundelin. Electromyography of shoulder muscles - The effects of pauses, drafts and repetitive work cycles. *Arbete och Hälsa*, 1992:16. Diss. (sammanfattning). (Departments of Anatomy, National Institute of Occupational Health, Division of Work and Environmental Physiology, Divisions of Occupational Medicine and Applied Work Physiology and Occupational Medicine)

Birgit Rösblad. Visual and proprioceptive control of arm movement - Studies of development and dysfunction. Diss. (sammanfattning) 1994 (Department of Paediatrics)

Charlotte Häger-Ross. To grip and not to slip - Sensorimotor mechanisms during reactive control of grasp stability. Umeå University Medical Dissertations, New Series no 429, 1995 (Department of Physiology)

Lars Nyberg. Falls in the frail elderly – Incidence, characteristics and prediction with special reference to patients with stroke and hip fractures. Umeå Medical Dissertations, New Series no 483, 1996 (Department of Geriatric Medicine)

Margareta Barnekow-Bergkvist. Physical capacity, physical activity and health -A population based fitness study of adolescents with an 18-year follow-up. Umeå University Medical Dissertations, New Series no 494, 1997 (Departments of Physiology and Technology, National Institute for Working Life and Epidemiology and Public Health)

Britta Lindström. Knee muscle function in healthy persons and patients with upper motor neurone syndrome. Umeå University Medical Dissertations, New Series no 505, 1997 (Departments of Physical Medicine and Rehabilitation and Clinical Neuroscience)

Monica Mattsson. Body Awareness - applications in physiotherapy. Umeå University Medical Dissertations, New Series no 543, 1998 (Departments of Psychiatry and Family Medicine)

Hildur Kalman. The structure of knowing. Existential trust as an epistemological category. Umeå studies in the humanities. 145, 1999 (Department of Philosophy and Linguistics)

Hamayun Zafar. Integrated jaw and neck function in man: studies of mandibular and head-neck movements during jaw opening-closing tasks. Umeå University Medical Dissertations, New series no 74, 2000 (Departments of Odontology, Clinical Oral Physiology and Centre for Musculoskeletal Research, National Institute for Working Life, Umeå)

Lillemor Lundin-Olsson. Prediction and prevention of falls among elderly people in residential care. Umeå University Medical Dissertations, New Series no 671, 2000 (Department of Community Medicine and Rehabilitation, Physiotherapy and Geriatric Medicine)

Christina Ahlgren. Aspects of rehabilitation – with focus on women with trapezius myalgia. Umeå University Medical Dissertations, New Series no 715, 2001 (Department of Public Health and Clinical Medicine, Occupational Medicine)

Ann Öhman. Profession on the move - changing conditions and gendered development in physiotherapy. Umeå University Medical Dissertations, New series No 730, 2001 (Departments of Community Medicine and Rehabilitation, Physiotherapy and Public Health and Clinical Medicine, Epidemiology)

Kerstin Söderman. The female soccer player – Injury pattern, risk factors and intervention. Umeå University Medical Dissertations, New series no 735, 2001 (Departments of Surgical and Perioperative Sciences, Sports Medicine, and Community Medicine and Rehabilitation, Physiotherapy)

Lena Grönbom-Lundström. Rehabilitation in light of different theories of health. Outcome for patients with low-back complaints – a theoretical discussion. Umeå University Medical Dissertations, New series no 760, 2001 (Departments of Public Health and Clinical Medicine, Epidemiology, and Community Medicine and Rehabilitation, Social Medicine)

Kerstin Waling. Pain in women with work-related trapezius myalgia. Intervention effects and variability. Umeå University Medical Dissertations, New series no 762, 2001 (Departments of Public Health and Clinical Medicine, Occupational Medicine, and Community Medicine and Rehabilitation, Physiotherapy)

Eva-Britt Malmgren-Olsson. Health problems and treatment effects in patients with non-specific musculoskeletal disorders. A comparitson between Body Awareness Therapy, Feldenkrais and Individual Physiotherapy. Umeå University Medical Dissertations, New series no 774, 2002 (Department of Community Medicine and Rehabilitation, Physiotherapy and Department of Psychology)

Jane Jensen. Fall and injury prevention in older people living in residential care facilities. Umeå University Medical Dissertations, New series no 812, 2003 (Department of Community Medicine and Rehabilitation, Physiotherapy and Geriatric Medicine)

Anncristine Fjellman-Wiklund. Musicianship and teaching. Aspects of musculoskeletal disorders, physical and psychosocial work factors in musicians with focus on music teachers. Umeå University Medical Dissertations, New series no 825, 2003 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Börje Rehn. Musculoskeletal disorders and whole-body vibration exposure among professional drivers of all-terrain vehicles. Umeå University Medical Dissertations, New series no 852, 2004 (Department of Public Health and Clinical Medicine, Occupational Medicine)

Martin Björklund. Effects of repetitive work on proprioception and of stretching on sensory mechanisms. Implications for work-related neuromuscular disorders. Umeå University Medical Dissertations, New series no 877, 2004 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit, Umeå University, The Center for Musculoskeletal Reseach, University of Gävle, Umeå, and Alfta Forskningsstiftelse, Alfta)

Karin Wadell. Physical training in patients with chronic obstructive pulmonary disease – COPD. Umeå University Medical Dissertations, New series no 917, 2004 (Departments of Community Medicine and Rehabilitation, Physiotherapy; Public Health and Clinical Medicine, Respiratory Medicine and Allergy, Surgical and Perioperative Sciences, Sports Medicine)

Peter Michaelson. Sensorimotor characteristics in chronic neck pain. Possible pathophysiological mechanisms and implications for rehabilitation. Umeå University Medical Dissertations, New series no 924, 2004 (Departments of Surgical and Perioperative Sciences, Sports Medicine Unit, University of Umeå, Southern Lappland Research Department, Vilhelmina, Centre for Musculoskeletal Research, University of Gävle, Umeå)

Ulrika Aasa. Ambulance work. Relationships between occupational demands, individual characteristics and health related outcomes. Umeå University Medical Dissertations, New series no 943, 2005 (Department of Surgical and Perioperative Sciences, Sports Medicine and Surgery, University of Umeå and Centre for Musculoskeletal Research, University of Gävle)

Dissertations

Ann-Katrin Stensdotter. Motor Control of the knee. Kinematic and EMG studies of healthy individuals and people with patellofemoral pain. Umeå University Medical Dissertations, New series no 987, 2005 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Tania Janaudis Ferreira. Aspects of muscle function and training with oxygen in patients with chronic obstructive pulmonary disease – COPD. Umeå University Licentiate Thesis, 2005 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Erik Rosendahl. Fall prediction and a high-intensity functional exercise programme to improve physical functions and to prevent falls among older people living in residential care facilities. Umeå University Medical Dissertations, New Series no 1024, 2006 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)

Michael Stenvall. Hip fractures among old people. Their prevalence, consequences and complications and the evaluation of a multi-factorial intervention program designed to prevent falls and injuries and enhance performance of activities of daily living. Umeå University Medical Dissertations, New Series no 1040, 2006 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)

Petra von Heideken Wägert. Health, physical ability, falls and morale in very old people: the Umeå 85+ Study. Umeå University Medical Dissertations, New Series no 1038, 2006 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)

Karl Gisslén. The patellar tendon in junior elite volleyball players and an Olympic elite weightlifter. Umeå University Medical Dissertations, New Series no 1073, 2006 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit)

Gerd Flodgren. Effect of low-load repetitive work and mental load on sensitising substances and metabolism in the trapezius muscle. Umeå University Medical Dissertations, New series no 1130, 2007 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit, Centre of Musculoskeletal Research, University of Gävle, Umeå, and the Department of Community Medicine and Rehabilitation, Rehabilitation Medicine)

Staffan Eriksson. Falls in people with dementia. Umeå University Medical Dissertations, New series no 1135, 2007 (Department of Community Medicine and Rehabilitation, Physiotherapy and Geriatric Medicine)

Jonas Sandlund. Position-matching and goal-directed reaching acuity of the upper limb in chronic neck pain: Associations to self-rated characteristics. Umeå University Medical Dissertations, New series no 1182, 2008 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit, Umeå University, Centre of Musculoskeletal Research, University of Gävle, Umeå)

Gunilla Larsson. Motor function over time in Rett syndrome-loss, difficulties and possibilities. Umeå University Licentiate Thesis, 2008 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Charlotte Åström. Effects of vibration on muscles in the neck and upper limbs. With focus on occupational terrain vehicle drivers. Umeå University Medical Dissertations, New series no 1135, 2008 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Ellinor Nordin. Assessment of balance control in relation to fall risk among older people. Umeå University Medical Dissertations, New series no 1198, 2008 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Bertil Jonsson. Interaction between humans and car seat. Studies of occupant seat adjustment, posture, position and real world neck injuries in rear-end impacts. Umeå University Medical Dissertations, New Series no 1163, 2008 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit)

Jenny Röding. Stroke in the younger . Self- reported impact on work situation, cognitive function, physical function and life satisfaction. A national survey. Umeå University Medical Dissertations, New series no 1241, 2009 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Therese Stenlund. Rehabilitation for patients with burn out. Umeå University Medical Dissertations, New series no 1237, 2009 (Department of Public Health and Clinical Medicine, Occupational and Environmental Medicine)

Elisabeth Svensson. Hand function in children and persons with neurological disorders. Aspects of movement control and evaluation of measurements. Umeå University Medical Dissertations, New series no 1261, 2009 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Helena Nordvall. Factors in secondary prevention subsequent to distal radius fracture. Focus on physical function, co-morbidity, bone mineral density and health-related quality of life. Umeå University Medical Dissertations, New series no 1252, 2009 (Department of Community Medicine and Rehabilitation Physiotherapy and Department of Surgical and Perioperative Sciences, Orthopaedics)

Ingela Marklund. Intensivträning av nedre extremitet för personer med stroke– effekter och upplevelser. Umeå University Licentiate Thesis, 2009 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Ulrik Røijezon. Sensorimotor function in chronic neck pain. Objective assessments and a novel method for neck coordination exercise. Umeå University Medical Dissertations, New series no 1273, 2009 (Department of Community Medicine and Rehabilitation, Physiotherapy , Centre of Musculoskeletal Research, University of Gävle, Umeå)

Birgit Enberg. Work experiences among healthcare professionals in the beginning of their professional careers. A gender perspective. Umeå University Medical Dissertations, New series no 1276, 2009 (Department of Community Medicine and Rehabilitation, Physiotherapy and Department of Public Health and Clinical Medicine, Epidemiology and Public Health Sciences)

Per Jonsson. Eccentric training in the treatment of tendinopathy. Umeå University Medical Dissertations, New series no 1279, 2009 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit)

Taru Tervo. Physical activity, bone gain and sustainment of peak bone mass. Umeå University Medical Dissertations, New series no 1282, 2009 (Department of Surgical and Perioperative Sciences, Sports Medicine, Department of Community Medicine and Rehabilitation, Geriatric Medicine, Department of Community Medicine and Rehabilitation, Rehabilitation Medicine)

Kajsa Gilenstam. Gender and physiology in ice hockey: a multidimensional study. Umeå University Medical Dissertations, New series no 1309, 2010 (Department of Surgical and Perioperative Sciences, Sports Medicine Unit)

Margareta Eriksson. A 3-year lifestyle intervention in primary health care. Effects on physical activity, cardiovascular risk factors, quality of life and costeffectiveness. Umeå University Medical Dissertations, New series no 1333, 2010 (Department of Community Medicine and Rehabilitation, Physiotherapy and Department of Public Health and Clinical Medicine, Epidemiology and Public Health Sciences)

Eva Holmgren. Getting up when falling down. Reducing fall risk factors after stroke through an exercise program. Umeå University Medical Dissertations, New series no 1357, 2010 (Department of Community Medicine and Rehabilitation, Physiotherapy and Department of Public Health and Clinical Medicine, Medicine)

Tania Janaudis Ferreira. Strategies for exercise assessment and training in patients with chronic obstructive pulmonary disease. Umeå University Medical Dissertations, New series no 1360, 2010 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Dissertations

Sólveig Ása Árnadóttir. Physical Activity, Participation and Self-Rated Health Among Older Community-Dwelling Icelanders. A Population-Based Study. Umeå University Medical Dissertations, New series no 1361, 2010 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Maria Wiklund. Close to the edge. Discursive, embodied and gendered stress in modern youth. Umeå University Medical Dissertations, New series no 1377, 2010 (Department of Public Health and Clinical Medicine, Epidemiology and Global Health and Department of Community Medicine and Rehabilitation, Physiotherapy)

Catharina Bäcklund. Promoting physical activity among overweight and obese children: Effects of a family-based lifestyle intervention on physical activity and metabolic markers. Umeå University 2010 (Department of Food and Nutrition)

Helene Johansson. En mer hälsofrämjande hälso- och sjukvård: hinder och möjligheter utifrån professionernas perspektiv. Umeå University Medical Dissertations, New series no 1388, 2010 (Department of Public Health and Clinical Medicine, Epidemiology and Global Health)

Håkan Littbrand. Physical exercise for older people: focusing on people living in residential care facilities and people with dementia. Umeå University Medical Dissertations, New series no 1396, 2011 (Department of Community Medicine and Rehabilitation, Geriatric Medicine and Physiotherapy)

Marlene Sandlund, Motion interactive games for children with motor disorders. Umeå University Medical Dissertations, New series no 1419, 2011 (Department of Community Medicine and Rehabilitation, Physiotherapy)

Ann Sörlin, Health and the Elusive Gender Equality. Can the impact of gender equality on health be measured? Umeå University Medical Dissertations, New series no 1420, 2011 (Department of Public Health and Clinical Medicine, Epidemiology and Global Health)

Björn Sundström, On diet in ankylosing spondylitis. Umeå University Medical Dissertations, New series no 1440, 2011 (Department of Public Health and Clinical Medicine, Rheumatology)

Gunilla Stenberg, Genusperspektiv på rehabilitering för patienter med rygg- och nackbesvär i primärvård. Umeå University Medical Dissertations, New series no 1482, 2012 (Department of Community Medicine and Rehabilitation, Physiotherapy and Umeå centre for Gender Studies).

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