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Normal reactions to orthostatic stress in Rett syndrome

Gunilla Larsson [a,b,*], Peter O.O. Julu [b,c], Ingegerd Witt Engerström [b], Marlene Sandlund [a], Britta Lindström [a]

[a] Department of Community Medicine and Rehabilitation, Physiotherapy, Umeå University, Sweden
[b] Swedish Rett Center, Jämtland County Council, Östersund, Sweden
[c] Breakspear Medical Group, Hertfordshire, United Kingdom

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ABSTRACT

The aim of this study was to investigate orthostatic reactions in females with Rett syndrome (RTT), and also whether the severity of the syndrome had an impact on autonomic reactions. Based on signs of impaired function of the central autonomic system found in RTT, it could be suspected that orthostatic reactions were affected. The orthostatic reactions in 21 females with RTT and 14 normally developed females matched by age were investigated when they rose from a sitting position, and during standing for 3 min. Reactions of the heart, the blood pressure and the time for recovery of systolic blood pressure, were studied in real time, heartbeat by heartbeat, simultaneously. There was no difference between participants with RTT and the normally developed controls regarding general orthostatic reactions (heart rate, systolic and diastolic blood pressure, and mean arterial pressure) when getting up from a sitting position, and when standing erect for 3 min. In the specific immediate response by the heart to standing up, the 30:15 ratio, significantly lower values were found for females with RTT. In the RTT group, the maximum fall of systolic blood pressure showed a tendency to a larger decrease, and the initial decrease in systolic blood pressure was significantly faster. The time for recovery of systolic blood pressure from standing erect did not differ between groups. At baseline the females with RTT had significantly lower systolic blood pressure and a tendency to a higher heart rate. The results do not indicate any autonomic limitations for people with RTT in getting up from a sitting position and standing. The participants with RTT had normal orthostatic reactions indicated by the heart and blood pressure responses when standing erect for 3 min. A faster initial drop in systolic blood pressure in people with RTT was notable.

1. Introduction

Rett syndrome (RTT) is a complex, X-linked dominant neurodevelopmental disorder with great individual variation that almost exclusively affects girls: 1 in 10,000 (Kerr & Witt-Engerström, 2001; Leonard et al., 2001). For diagnosis, clinical criteria have been confirmed internationally, both for classic RTT and variants of RTT (Hagberg, Hanefeld, Percy, & Skjeldal,

Abbreviations: RTT, Rett syndrome; HR, heart rate; POTS, postural orthostatic tachycardia syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; BP, blood pressure; OH, orthostatic hypotension; ECG, electrocardiogram; EEG, electroencephalogram; pO_2, partial pressures of oxygen; pCO_2, partial pressure of carbon dioxide; VT, vibroacoustic stimulation; ISS, International Severity Score; CP, cerebral palsy; WHO, World Health Organization.

* Corresponding author at: Department of Community Medicine and Rehabilitation, Physiotherapy, Building 15, Umeå University, S-901 87 Umeå, Sweden. Tel.: +46 63 15 48 10/910 392 41; fax: +46 63 15 45 00; mobile: +46 70 658 70 42.
E-mail addresses: gunilla.e.larsson@jll.se, gl@reago.se (G. Larsson).

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2002; Kerr & Witt-Engerström, 2001). The children are born after a normal pregnancy and seem to develop normally until approximately 6–18 months of age. After a period of developmental stagnation they lose abilities such as communication, and fine and gross motor skills. The point in time when different symptoms first appear varies, as does the severity of the symptoms, but after the regression, all of the children suffer from severe motor and communicative disabilities, with a degree of intellectual disability that is difficult to define. Diagnosis is based on clinical criteria, but since 1999, an association with mutations in the methyl-CpG-binding protein2-gene (MECP2) has been confirmed in 95% of those with classic RTT, mainly as de novo mutations (Amir et al., 1999; Hagberg et al., 2002; Percy, 2008). Correlation between mutation and disability, that is genotype-phenotype, is being studied and has been discussed as a prognostic predictor of severity of disability. So far this has been of limited value, since there is extensive variability (Ager et al., 2006; Bebbington et al., 2008; Charman et al., 2005; Halbach et al., 2012; Kerr & Prescott, 2005; Leonard et al., 2003). Deficient growth as well as immaturity of the central nervous system is apparent in RTT (Armstrong & Kinney, 2001; Julu, 2001; Tarquinio et al., 2012). The immaturity of the central autonomic control is particularly disabling, manifested as breathing dysrhythmia, abnormal variation in heart rate and blood pressures, peripheral vasomotor disturbance and gastrointestinal problems. The immaturity causes imbalance, where the parasympathetic function appears more affected than the sympathetic. A steady and well-adapted autonomic system is essential to adjust to physiological needs and activities. In people with RTT, the deficient adaptation of the autonomic nervous system frequently causes a state of stress (Bieber Nielsen, Friberg, Lou, Lassen, & Sam, 1990; Julu, 2001; Julu et al., 2001; Kerr & Witt-Engerström, 2001; Low & Benarroch, 2008; Nomura, Kimura, Arai, & Segawa, 1997; Weese-Mayer et al., 2006; Weese-Mayer et al., 2008; Witt-Engerström, 1990). Opinions have been presented that people with RTT may improve with physical activity (i.e. the effects of stress may be reduced), but knowledge is limited. The effect on heart rhythm and blood pressures when people with RTT perform activities such as standing up and standing for 3 min has not been studied (Guideri, Acampa, Hayek, Zappella, & Di Perri, 1999; Julu, Kerr, Hansen, Apartopoulos, & Jamal, 1997b; Madan, Levine, Pourmoghadam, & Sokoloski, 2004; Rohdin et al., 2007; Sekul et al., 1994).

Since 1998, studies have been in progress at the Rett Center in Frösön, Sweden, to examine how the central control of the autonomic nervous system functions in people with RTT. Respiratory dysrythmia has been investigated during sitting, as well as abnormal variations in blood pressures, blood gases and heart rhythm (Julu et al., 2001; Julu & Witt-Engerström, 2005). Autonomic responses to music and to vibroacoustic stimulation have also been studied, but so far not orthostatic reactions (Bergström-Isacsson, 2011; Bergström-Isacsson, Julu, & Witt-Engerström, 2007; Julu, 2001; Julu et al., 2001; Julu, Kerr, Hansen, Apartopoulos, & Jamal, 1997a; Julu et al., 1997b; Julu & Witt-Engerström, 2005).

Normal values for orthostatic reaction may vary somewhat (O'Brien, O'Hare, & Corrall, 1986; Wieling & van Lieshout, 2008). Wieling and van Lieshout (1993) stated that using standing up to assess cardiovascular autonomic function is easy, useful and clinically relevant, and the standing-up test can be used from 5 years of age (Hynninen, 2006; Wieling & van Lieshout, 1993). When standing up, the autonomic nervous system accommodates to supply the brain with blood/oxygen when the force of gravity transfers the blood to lower parts of the body, such as the abdomen and legs. The body compensates the change in blood pressure in a very finely tuned and complex way. In RTT, deviant orthostatic reactions could be suspected due to deficient autonomic function (Agelink et al., 2001; Borst, Van Brederode, Wieling, Van Montfrans, & Dunning, 1984; Borst et al., 1982; Hynninen, 2006; O'Brien et al., 1986; Schatz et al., 1996; Smith, Porth, & Erickson, 1994; Sprangers, Wesseling, Imholz, Imholz, & Wieling, 1991; Wieling & van Lieshout, 2008). With our equipment, it is possible to study the reactions of the heart, blood pressures and time for recovery in real time, heartbeat by heartbeat, and thus investigate how central autonomic reactions in people with RTT are affected by a physical task such as standing up from a sitting position. This may provide indications of whether exercise and activity are advisable and not dangerous for people with RTT, who have a weak parasympathetic nervous system.

Therefore, the main aim of this study was to investigate orthostatic reactions in females with RTT, compared with those of normally developed females, when getting up from a sitting position and during standing. Due to the heterogeneity within the group with RTT, the International Severity Score (ISS) for RTT was used to study whether the severity of the syndrome had an impact on the autonomic reaction (Kerr et al., 2001).

2. Methods

2.1. Participants

The participants were a consecutive selection of females with RTT, referred to the Rett Center for assessment of the central control of the autonomic nervous system. They had been diagnosed earlier by co-author IWE or by their local physician or paediatrician, and the diagnosis was confirmed at a medical examination before autonomic assessment at the Swedish Rett Center by IWE. They were diagnosed according to clinical criteria for RTT (Hagberg et al., 2002; Kerr & Witt-Engerström, 2001). To be included in this study the females had to be able to get up from sitting to standing, by themselves or with some support, and be able to sustain standing for 3 min. In Table 1 individual characteristics are given. Age-matched females as controls were recruited through friends and colleagues in the Östersund area. The control participants were recruited on the basis that they did not suffer from any medical complaints, and they were not on any medication.

Informed consent was received from all participants and all could opt out at any time. Ethical approval was granted by the Regional Ethical Review Board in Umeå 2010-03-02, Dry 09-192M.