Short Literature Review 2007-2008

Rett Syndrome: Developmental –Behavioral Features and the role of therapies in motor and social Development of the Rett Syndrome children.

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Abstract

Rett syndrome (RS) is a progressive, usually sporadic and rarely familial disabling neurodevelopmental disorder. The clinical presentation occurs in early childhood with mental retardation behavioral changes, late movement disturbances, loss of speech and hand skills, ataxia, apraxia, irregular breathing and frequent seizures. RS is characterized by developmental arrest in parts of the brain. Is an X chromosome-linked condition, which affects females almost exclusively. Although many different mutations of this protein are being studied in humans and mice, the pathogenesis of this disorder is still unclear. Unfortunately, nowadays, there is no effective treatment that can cure RS and related disorders with MECP2 mutations. As it is well known, the life expectancy of a RS patient is up to 40 years, which indicates the importance of the therapy in the life of the Rett syndrome child. The aim of this current review was to identify the kinds of therapies that could benefit the RS patients to improve their quality of life and social interaction with the outside environment. Today, the available therapies are only capable of derogating the symptoms. Some of the basic treatments are the physical therapy, occupational therapy, speech therapy and alternatives therapies like music therapy, hydrotherapy, and etc.

The current review revealed that there is still a lot of research to be done based on the therapies that can reduce the RS symptoms and benefit the quality of life and social environment of RS children. Some of the described treatments in this current review have no research background and mostly adopt a single rehabilitative technique, providing the researchers and the parents, which treatment is more effective for the RS patients. This review pointed that further research should be done in the field of the physical therapies.

1. Introduction

In 1966 a new syndrome was identified and described by the Austrian pediatrician Andreas Rett. It took more than 30 years to determine the genetic basis of, what is today known as, the Rett syndrome (RS). This syndrome is in fact a progressive disorder, which continues to worsen and can present a wide scope of disability ranging from mild to severe. The basic cause of this syndrome is to be found on the X chromosome, due to sporadic mutations in the gene MECP2. The course and harshness of the Rett syndrome is determined by the location, type, and severity of the child's mutation and X-inactivation.

In 1986, Hagberg and Engerstrom presented four stages of the Rett syndrome.

- *Stage I, early onset*: The first stage generally begins between 6 months and 1/½ years. The patients are symptomatic but there is no apparent regression. In this stage, the symptoms are often overlooked due to a relatively normal appearance and some developmental progress.
- *Stage II, rapid destructive*: The second stage begins around one year old and lasts until the age of three or four. It is a period of regression and it is labeled by a gradual inability of speech and purposeful use of the hands.
- *Stage III or* ***plateau*** *or* ***pseudo-stationary (3-10 years old)*** *&*
- *Stage IV or* ***late motor deterioration (10+years)***: The last two stages, the third and fourth can last for years, from early childhood to adult ages. These stages are characterized as periods of stabilization as the motor symptoms show a slow progression and the child begins to associate with the environment, using for example, eye pointing. The cognitive and motor impairments are still apparent and the seizures become less frequent (Shahbazian, 2002, Nomura et al, 2005).

RS is a rare disease which affects 1 in every 12,500 females by the age of twelve and seeming strikes at random (Shahbazian, 2002). The fact that the above mentioned mutation is located only on the X chromosome is part of the reason for RS's prevalence in girls. Most boys born with RS die so soon after birth that statistics on such cases are hard to obtain. Although the gene responsible for the disorder has been identified, the pathogenesis of RS

remains a puzzle. The majority of the research papers published, deals with the investigation of the mechanisms that explain how abnormalities of this DNA methylating protein selectively interrupt brain maturation (Percy, 2002). Reviews mainly cover the physical and biological aspects of the Rett syndrome (Shahbazian, 2002, Chahrour et al 2007).

Unfortunately, there is no effective treatment that can cure Rett syndrome and related disorders with MECP2 mutations. Advances from clinical tests that aim to relieve symptoms have been small, with only three trials completed since 1999 (Amstrong 2000, Harberg 2000). These trials focused on medications to improve sleep, energy levels, and communication skills. Alternative treatments have used music therapy in efforts to improve hand use, eye contact, and communication, but with little success. Although people with Rett syndrome can live into their forties, the lack of stimulation of both mind and body can lead to secondary disabilities and there is, therefore, a vital need for therapeutic input (Van Acker, 1991).

The current review is an effort not only to define and describe the developmental and behavioral features of the RS but also to discuss and illustrate commonly accepted therapies. The main goal of this review is to identify the type of treatment that benefit these children by improving their quality of life (i.e. everyday activities, independence etc.) and social interaction with the outside environment.

2. Clinical Features of Rett Syndrome

As mentioned in the introduction, infants with Rett syndrome predominantly exhibit developmental irregularities in four stages as they grow up. These abnormalities are related not only with (fine) motor development of the patients but also with the behavioral and emotional features. A brief description of these symptoms associated with the four stage of clinical manifestation of the RS will be presented.

2.1 Early Infancy (First 6 Months)

It is often pointed out that RS children display a rather normal development in the first 6 to 18 months (Namura et al, 2005). However, recent research shows that symptoms are already visible in the first months of the baby's life (Segawa et al 2004, Einspieler et al 2005).

2.1.1 Early motor disturbances

Segawa et al., (2004) reviewing his previous studies pointed at the existence of early motor disturbances in RS children. In his paper, Segawa et al did an evaluation of the motor milestones (head control, rolling, crawling, seating position etc) of 38 infants with RS. The infants showed a delay in motor function and development in this early stage of early infancy. Head control was delayed in 5 patients (13.1%), and this delay in motor function became more evident in mid infancy with a delay in rolling over in 13 (34.2%) and in adoption of the sitting position in 10 patients (30.3%). The delay in motor development became even more obvious with regard to crawling. Only 4 patients (10.4%) could crawl before 10 months. The researchers reported that the main early symptoms in Rett syndrome are postural hypotonia, failure in locomotion and disturbance in fine finger movements. The first two are considered to be caused by dysfunction of the serotonin (5HT) and the noradrenalin (NA) neuron, which modulate the postural augmentation system and locomotion. Hypotonia and failure in crawling are not due to abnormalities of the skeletal muscles nor motor neurons. In Rett syndrome tendon reflexes are preserved and muscle atrophy or muscle weakness is not observed. Instead hypotonia is due to hypo function of the aminergic neurons of the brainstem (Segawa 2004, Normura et al., 2005).

Also Einspieler et al (2005) tried to demonstrate that the features of the Rett syndrome can be observed in the first months of the baby's life. Einspieler et al (2005) analyzed homevideos of 26 girls with classical RS, born between 1964 and 1997; fourteen girls were recorded during their first 4 months of life and were thus available for the assessment of general movements (GM). The recordings were performed by the families as part of their family archive without the knowledge that the child had RS disorder. For the assessment of GMs, video sequences with a median duration of 3 min (range 1–22 min) with the infant lying in supine or semi-upright in a relaxing chair were used. The duration of the video clip and the infant's position were in accordance with the guidelines for the GM assessment. The results of this study showed that infants with Rett disorder had no normal fidgety movement.

Another case study by Tremudo et al (2007), confirmed that the movement abnormalities are present before the regression stage of RS including washing-like, twirling, clapping, or twisting hand movements, as well as repetitive closure of the eyes, grimacing, and tongue protrusion. This study also demonstrates the occurrence of dystonic movements preceding exuberant stereotypies. Dystonia is a common symptom in RS but, usually, it presents as a fixed posture and appears after some years of the evolution of the disease. For the patient of this study some of the repetitive dystonic limb movements were also resembles dystonic tics. The research of Tremudo et al was done in one girl of 19-months old, who was noticed 5 months earlier with an arrest of psychomotor development without any change in sleep pattern, behavior or social communication. A one-hour videotape observation was held to study the stereotypic movements of the face and hands. Overall, the video observation may contribute to the early recognition of movement disorders in RS and potentially allow an earlier diagnosis of this disease.

2.1.2 Other developmental problems

From other studies (Segawa 2004, Kenneth et al., 1991) it was also obvious that the sleeping pattern was disrupted in early infancy. The disturbances of the aminergic function have an age of appearance around 38 gestational weeks to 4 to 6 months of age. However, the cholinergic and the dopamine (DA) neurons modulating sleep parameters, which normally develop before 36 gestational weeks, are preserved. The Rett individuals have difficulties in falling asleep at night, have frequent waking during the night and awake early in the mornings and have frequent day-time naps. The characteristic of sleep indicate that Rett

syndrome children get less total sleep during the night than healthy subjects, but have more overall (24 hour) total sleep than healthy subjects. The amount of day time sleep is positively correlated with age and the amount of night time sleep was negatively correlated with age (Mount et al., 2001).

The problems in sleeping are associated with difficulties in breathing. The abnormal breathing is occurring in periods of excessively rapid and shallow breathing and the apnea periods last for 60-120 seconds. This pattern of alternate hyperventilation and breath holding is mostly apparent in younger girls and is being coupled with the mild to moderate and occasionally severe drop in blood oxygen saturation levels. Air swallowing (aerophagia) may accompany these irregular breathing patterns and may produce striking abdominal distension. Abdominal distension does subside spontaneously, specially, during sleep or periods of normal breathing patterns. These abnormal breathing may influence much more the walking activities (Percy et al 2003).

2.2 End of Infancy to Beginning of Early Childhood (1 to 3 years)

Often the end of infancy and early beginning of childhood is the period that typical symptoms of the Rett syndrome are being revealed. The brain morphology is characterized by a reduction in brain weight, a reduction in volume of specific brain areas, melanin pigmentation, neuron size and dendritic branching (Deidrick et al., 2005, Armstrong 2001).. In this stage, the babies start to show autistic like characteristics resulting from an inability to communicate with their environment. The most frequent behaviors that are observed include: loss of verbal expression, difficulty in copying movements made by other people (87%), auto stimulation behavior (73%) and sudden laughing and crying (73%) (Mount et al 2001, Nomura et al 2005). Hyperactivity and mental retardation are common occurrences, although the degree of each varies (Jellnger 2003).

Although, the Rett syndrome children may exhibit a number of autistic-like behaviors; they do so in a qualitatively different way. The features that are more often seen in cases of the Rett syndrome than in cases of autism are ataxia/apraxia, hand stereotypies with hands together, clumsiness of the hands and slow movements and lack of hand function, hyperventilation, breath-holding, air-saliva, and expulsion (Mount et al 2001).

2.2.1 Motor development

In this period, the motor development is further delayed. In the study of Segawa et al (2004), an evaluation of 130 cases demonstrated a delay in the ability to sit in 41.2% (40 children of 97 whose ages were known when they began to sit), to crawl in 63.6% (28 children of 44 whose ages were known when they began to crawl; 71 never crawled) and to walk in 83.3% (55 children of 66 whose ages were known when they began to walk). The loss of hand movement was observed at 12 to 18 months, which was followed by pathognomonic hand sterotypies. Generally, motor ability varies, ranging from clumsiness to spastic quadriplegia.

Another characteristic of this stage is speech delay. Bashina et al. (2000) showed that the Rett Syndrome children present a distraction in speech and motor development. The study was a clinical observation of 50 girls aged from 12 months to 14 years with classical Rett syndrome mostly at stages II-III. The results of this study demonstrated that the Rett syndrome children showed besides the appearance of autistic withdrawal followed by a rapid loss of the habit to produce words, a loss of voluntary movements and acquired motor acts, elementary sounds and syllables without any paralysis of the tongue, lips larynx, soft palate or pharynx.

2.2.2 Other disorders

Another feature, which is often seen in the Rett syndrome children in this stage, is self-abusive behaviour (Percy et al., 2002). The self-abusive behaviour can be a significant problem in some girls or women with Rett syndrome, usually in the form of hair pulling; biting of the fingers, hands, or other parts of the upper extremities; and hitting themselves about the face. This abusive or aggressive behaviour may result from pain or discomfort, in particular due to gastrointestinal dysfunction; hunger; medication-related effects; or other medical problems, which they are unable to communicate (Percy et al., 2002). Physiologically there is also an increased risk of gallbladder disease in Rett syndrome, which might also explain the pain crises seen in this population (Deidrick et al., 2005, Armstrong 2001).

2.3 Growing up (Stage III and Stage IV)

2.3.1 Early Childhood (3 to 10 years Stage III) to late Adulthood (10+years Stage IV).

The symptoms in these two periods seem to stabilize. Particularly, in stage III the autistic-like symptoms start to vanish and patients have a better ability to associate with their environment. The motor symptoms show a delay in their regression. However, the dystonia and hypotonia in the muscles start to increase, which results in joint contracture. Scoliosis begins slowly to promote (Percy et al., 2002). The progression of the scoliosis may be modest or, in some, may advance rather quickly. In such cases, scoliosis can be clinically significant and require medical or surgical mediation. Progression is much more likely in those girls who are not ambulant and whose seating arrangements do not provide proper lateral support in order to prevent leaning to one side. Most of the times, surgery is recommended strongly when curvature exceeds 40° degrees. In general, this procedure is tolerated well with minimal post-operative difficulties (Kenneth et al., 1991).
The diagnosis of Rett in adulthood might be hindered by a lack of detailed information on symptoms that occurred during early childhood. In stage IV, the clinical condition of the patients becomes more stable. The muscle tone shows plastic rigidity and Parkinsonism seems to be apparent. A case study of Rose et al., (2007), described a 49 Rett syndrome woman, who was diagnosed as a Rett Syndrome case after 48 years. This study came to the conclusion that hand stereotypies in a woman with psychomotor retardation raise the possibility of Rett syndrome as they are an early and specific manifestation and often persist throughout the disease course. Although the hand stereotypies can be addressed in other conditions, they are highly suggestive of the Rett syndrome in adults with psychomotor retardation, especially, when Parkinsonism and dystonic features are also present.

2.3.2 Summary

The features of the RS disorder are complex and varied and it is not surprising that there are wide variations in the symptoms displayed by individuals, and, consequently, coupled with the fact that the disorder has only recently been described, diagnosis is difficult. Even, nowadays scientists present a lack of knowledge in the spectrum of Rett Syndrome disorder, while sometimes questioning themselves when parents explain the problems that they have

with their children. In Rett Syndrome, because of the wide range of the symptoms, is advisable to categorize the symptoms avoiding any kind of misunderstanding and also providing the family with futher information for the future (Hill, 1997).The following table (Naidu, 1997) presents the characteristics of the Rett Syndrome being categorized in four regression stages and their relation with other syndromes.

Table 1. The categorization of the symptoms relating with the regression stage of Rett Syndrome (Naidu 1997)

Stage	Clinical Characteristics	Differential Diagnosis
I. Early onset Development stagnation/arrest Onset: 6-18 months	Development stagnation/arrest Stagnation stage Declaration of the head/brain growth Disinterest in play activity Hypotonia Nonspecific personality changes	Benign congetial hypotonia Prader-Willi syndrome Cerebral Palsy Autism
II. Rapid Destructive Onset: 1-3 years	Hand waving- nonspecific episodic Rapid developmental regression with irritability. Poor hand use Seizures Hand stereotypies:wringing Autistic manifestations	Psychosis Hearing or visual disturbances Encephalitis Infantile spasms (West Syndrome) Tuberous sclerosis Ornithine carbamoyl transferase

	Loss of expressive language Insomnia and irritability Self-abusive behaviour(e.g., chewing figers) Mental deterioration Clumsy mobility/apraxia/ataxia Better preservation of gross motor functions Irregular breathing-hypervention.	Deficiency Phenylketonuiria Infatile neuronal ceroid lipofuscionosis
III. Pseudostationary Stage Onset: 3-10 years	Severe mental retardation/apparent dementic Amelioration of autistic features Seizures and epileptic signs Typical hand sterotypies Prominent gait ataxia and apraxia Jerky truncal ataxia Spasticity; gross motor dysfunction Hyperventilation, breath holding, aerophagia Apnea during	Spastic ataxic cerebral palsy Spinocerebellar degeneration Leukodystrophies or other Storage disorders Neuroaxonal dystrophy Lenox-Gastaut syndrome Angelmann Syndrome

	wakefulness Weight loss with excellent appatite Early scoliosis, Bruxism	
IV. Late motor Detoration stage Onset:10+years	Combined upper and lower motor neurons signs Progressive scoliosis, muscle wasting and rigity Severe multihandling syndrome Paraparesis or tetraparesis Descreasing mobility, wheelchair-bound Growth retardation, but normal puberty Impaired social interaction Starting unfathomable gaze Emotional and eye contact “improving” Reduce seizure frequency Virtual absence of expressive and Receptive language Trophic disturbance of feet Cachexia Respiratory abnormality	Neurodegenerative Disorders of unknown Cause

3. Therapies for RETT Syndrome

Most research on RS focuses on understanding the cause of the disorder. The discovery of the gene, accountable for the RS, in 1999 provided a basis for further genetic studies and encouraged the use of animal models such as transgenic mice. Today, even though scientists are aware that improper function of MeCP2 protein disturbs normal development, they are unable to describe the exact mechanisms by which this happens. Researchers are trying to associate other genetic mutations with RS along with other genetic switches that operate in a similar way as the MeCP2 protein. Once they discover how the protein works and locate similar switches, they may be able to devise gene therapies that can substitute the malfunctioning switch or be able to manipulate other biochemical pathways to compensate for the malfunctioning genes, thus preventing progression of the disorder (Segawa & Nomura 2005).

At present there is no cure for the RS. Treatment for the disorder is symptomatic and supportive, requiring a multidisciplinary approach. The treatment approach is highly individualized because the specific symptoms vary from patient to patient; there is a diversity of ways to help minimize the effects of RS. Although the RS as a whole presents a variety of symptoms, most treatments, such as medication or surgery, try to reduce specific symptoms, for instance, surgery can correct scoliosis with a strong curvature. Similarly, anti-seizure medications can effectively control the seizures experienced by some RS patients and even more improve their movement skills and communications abilities. The study of Ellaway et al., 2001, aimed to determine the effects medium-term L-carnitine in 21 RS females.The results demonstrate that treatment could lead to major improvements in sleep efficiency, especially in subjects with sleep efficiency less than 90%, also in energy level and communication skills.

On the other hand, Corbachevskaya et al. (2001), investigate the influence of Celebrolysin (a brain derived peptidergic drug) on motor and higher cortical functions in RS girls. This study was performed in nine RS girls aged from 2 years and 2 months to 7 years and 6 months, who were in the stage 3 of the illness. The celebrolysin treatment, showed an increase in the behavioural activity, attention level, motor functions and non-verbal social communication. The EEG parameters after the treatment have change towards to normal values, which indicates an improvement of the brain functional state.

Regarding the fact that the medication treatment or surgery might contribute to the cure of the RS disorder, rehabilitation therapy displays the major role in improving the RS quality of life. Rehabilitation, generally aims to decelerate the loss of abilities, improve or preserve movement, and encourage communication and social contact. In many cases, it has been recorded that people with RS benefit from a care team approach, in which various health care providers collaborate with family members. Members of this care team include: physiotherapist, occupational therapist, developmental specialists, developmental paediatricians, orthopaedic surgeons, gastroenterologists, pulmonologists, special education providers, and nurses ("Autism Research at NICHD", NIH Publ. April 2006). Today, the available treatments that are provided to a child with Rett syndrome based upon the economical state and beliefs of the family but most of all to the physical and emotional condition of the child. A scientific overview of therapies will be presented in this thesis, trying to provide a more evidence-based picture of the therapies that can be profitable for patients with RTT syndrome. Evidence-based therapy states that clinical decision-making should be based on three components: research, clinical expertise, and patient values. Subsequently, in order to determine the optimal intervention we have to take into account not only the research studies, but also clinical expertise and the wishes of the patient and family. Therefore, in this review, I will evaluate therapies based on the spectrum of scientific research available, but also reported statements and observations of therapists. The main focus will be on treating communication skills and motor functioning since these are the essential fields of treatment in RS girls. Functional communication skills are important to accomplish practical participation in social activities which, along with motor functioning, impacts the children's daily living skills i.e playing, dressing, and eating.

3.1 Music and communication therapy

Though it is not possible to alter the course of the disorder, its effects can be reduced by maintaining or improving functional movement mobility, by preventing deformities and by keeping the girls in contact with their environment. The girls with RS might differ from other children in the way they develop their communicational and speech skills. One of the main problems is "dyspraxia" and "movement function", which proscribe them from making movements including those required for speech. Simple "communication strategies" can be applied like "eye gaze", "picture" "cards", "visual symbols", or the even "body language" to help them communicate better with their environment (Hanks, 1986). A second problem is a

delay in processing information and reacting. For a RS girl it might take some time to respond to a question which drives the other participant to repeat the question or assume that the person did not understand (Garret et al., 2004). Despite these difficulties RS patients can learn to communicate more effectively for example with the help of music therapy.

Music therapy is an applied and selected use of music to attain non-musical goals. The ability to appreciate and to respond to music is inborn in human beings; it remains unmoved by disability, injury or illness, and doesn't dependent on musical training. The advantage of the music therapy is that not only gives the opportunity to the child to express his/her feelings but also to pronounce words and contribute to social communication. (Freeman, 1994). After a period of music therapy, there is evidence to suggest that a child's confidence and self-esteem is improved; in addition improvements in physical abilities, such as holding a beater and using the body and voice to make musical sounds, may occur (Hill 1997).

Yasuhara et al. (2001) did a study to examine the effects of music therapy in Rett syndrome children. In this study three children 4, 5 and 6 years participated and performed active music therapy in individual session of 30 minutes/week for two months. The music therapy program was specific to each patient and designed based on the degree of mental and physical development with the main activity to capture their interest to be instrument playing. Each session was recorded by a written description and by videotape and was assessed according to an evaluation standard. This evaluation standard was established with reference to the Denver Developmental Screening Test. The instrument playing appeared to improve their purposive hand use. In addition, development of language comprehension was also observed in the children that did not speak but did utter sounds. The study tentatively suggests that these children possessed an ability to comprehend music, and that music therapy provoked them to become physically active and communicational.

Another case study of Wigram et al. (2005), suggested that music therapy is possible to reveal indicators of latent communicative responsiveness and intentionality. The assessment was a 30-min music session conducted by the authors, observed by the parents, and the rest of the team through a video link. Particular in this case study was the fact that the child demonstrated a sense of humor, understanding and participation in turn of taking, sharing, and a range of vocal skills that can be developed and more clearly understood. Also the child was attentive to what was happening, even if she was not looking directly at it. These studies

show that “girls with RS are receptive and discriminating towards musical sounds and music therapy itself can be successful in capturing their interest” (Rett Syndrome Association UK, Wigram 2005). Music appears to be able to work as an effective motivator and provide means of communication. In addition, the cause and effect relationships (the basis of music therapy) may allow these children to gain an understanding of their ability to impact on their environment.

A case study of Sullivant et al. (1995) showed that a RTT girl was able to learn to communicate by using switch-activated toys. With the help of music therapy she was taught how to use the toys and she developed independence in activating these toys in her classroom. A systematic exposure to opportunities for contingent control of audiovisual stimuli were positively motivating experiences for the child and appeared to promote attention to toys and objects in the environment, skills that apparently generalized to the larger classroom environment and ultimately to a new classroom.

Furthermore, the study of Elefant et al. (2005) demonstrated that music can be a strong motivational factor. The study assessed the learning ability of songs in seven Rett syndrome girls age from 4 to 10 years. The intervention trials incorporated choice-making of 18 familiar and unfamiliar children’s songs. The 18 songs were divided into three ‘sets’ with total of six songs in each set (four familiar and two unfamiliar songs in a set). Once the participants had made their choice during the trials (according to the pre-structured intervention procedure) the songs were sung by the investigator (a music therapist) accompanied by a guitar. The sessions were held individually three mornings per week and each lasted between 20 and 30 minutes. The duration of the study was 5 months and included baseline, innervations and maintenance trials followed by an additional 3 months with an additional 3 months with an additional 3 maintenance trials. The results of this study showed that all the girls produced an ability to learn and maintain the knowledge of songs over time.

As it was proposed from the above studies music therapy can be assessed to improve movement and communication skills in RS children. The music intervention should be planned through all the stages of the RS disorder and meet the needs of the individuals as they grow. Regarding the communication, music therapy should also provide appropriate vocabulary to reflect the chronological age interests. The communication skills might be improved by simply providing opportunities to the person to interact effectively in his or her

environment. It is also important to encourage the child to hold and manipulate toys or instruments and if it cannot interact directly with the play materials the carer or the parent should help the child to develop concepts and vocabulary by demonstration and verbal explanation of the activities (Garret 2004).

3.2 Sensory-motor rehabilitation

Until now hardly any research has been done on the effectiveness of physiotherapy in the daily living of the RS child. The basic principles of physical therapy are to prevent and treat movement disorder, and going further to enrich the physical and functional capabilities of people with disabilities. This indicates that physical therapy can help an individual to improve "gross motor abilities" (moving on their own) and provide the possibility of reducing any discomfort, leading to a long lasting independence. The main focus in the physical therapy of a girl with RS is associated with "apraxia" (Lotan et al 2006). RS girls show decreased coordination, changes in posture and skeletal alignment. Additionally, the reduced range of motion often results in a loss of balance and a decline in independent mobility such as walking. In the following section I will present a variety of therapies that aim to improve motor functioning and sensory-motor integration.

3.2.1 Physical Fitness

It is well known that the RS population has a tendency for developing a sedentary life associated with diseases such as elevated risk for coronary artery disease and stroke. Some research scientist proposed walking as an activity that might hold back or diminish secondary damage or even to prevent old age health problems. (Percy et al 2005, Shanbazian et al 2002).

Knowing the importance of working out, Lotan et al (2004) investigated the effect of physical exercise in functional ability and physical fitness in RTT children. Until now no other research has been done on the influence of physical fitness on the health of this population. In this study a daily training program on the treadmill was assessed in four females for two months. The participants were four RS girls aged between 8.5-11 (mean 10 years) with independent mobility and typical characteristics of Rett Syndrome stage III. The initial exercise sessions lasted 5 min, but were gradually lengthened over the first 3 weeks of training to 30 min each. The average session duration was later determined at 19.9 min.

“Each participant had 36–50 training sessions over a 2-month period with an average of 41 practice days for each child (the number of sessions depended on general health, and presence at school during the research period)”.

“The load of each training session” (calculated by: treadmill speed x session duration x weight of the child x the sinus of the angle of treadmil inclination) ranged between 117 kc (Kilo Calories) and 245.7 kc (average 213.5 kc). The overall work load taken by the participants during the course of the training period ranged from 3377 kc to 7243 kc (differences mainly because of weight differences between participants), averaging at 4599 kc, for each participant during a 2-month period. The training was performed on a treadmill with very long side rails and capable of very low speeds <0.5 k/h. The cardio-pulse was recorded constantly during training by an A3 polar pulse belt. The measurements that were monitored at the time of rest were evaluated as the aerobic physical condition of the participants. “Functional measurement was based on a scale specially established for this study. The scale was 31-item motor-functioning tool that measured the ability of the participants to knee walk and knee stand, to get up to a standing position, duration of walking different paths and go up and down stairs and slopes”. The pulse measured results showed that the physical fitness of the children at the end of the training program had improved significantly. Tests showed that general functional abilities had improved. Although all items of the functional ability measure showed positive change, some of the 31 items on it showed significant improvement (knee walking, going up and down stairs and speed of walking for 25m). The findings of this study proposed that a physical fitness program executed on a daily basis is capable of improving functional ability of children with Rett Syndrome (Lotan et al 2004).

3.2.2Hydrotherapy

"Aquatic therapy, also known as hydrotherapy, is a form of physical therapy that is typically enjoyed by children with Rett Syndrome. Water provides a non-weight bearing medium with hydrostatic pressure to give sensory input. It is an ideal environment for passive range of motion and sensory regulation. The warm temperature prompts muscle relaxation, facilitates stretching and generally reduces stress". The general aims of hydrotherapy are to improve circulation, and restore mobility by strengthening muscles and improving co-ordination (Rett Syndrome Association UK, Kerr 2002).

Bumin et al (2003) examined the effects of hydrotherapy on a girl in stage III of the RS. The exercise training was appealed in a swimming pool two times a week for a period of 8 weeks. The training was performed as a "one-on-one project" with the assistance of physiotherapist. The physical abilities were evaluated 3 times: "before and 5 minutes after a single hydrotherapy session and after 8 weeks of hydrotherapy". The tests included "stereotypical movement analysis, functional hand usage, hand skills, gait and balance, hyperactive behaviour, communication and social interaction". The evaluation of "stereotypical movements" was recorded from a 5-minute video camera. Hand movements like "grasping", "holding", "transferring small and large objects from one point to another", "finger feeding" and "drinking abilities" were tested. The "functional hand" use was accomplished based on the ability of the girl to eat crackers, which were placed on the table.

After the hydrotherapy session the hand to mouth and hand squeezing disappeared. The "amount of stereotypical movements reduced after the hydrotherapy and continued to reduce after 8 weeks". Moreover, after 8 weeks of hydrotherapy training balance control in walking got better, her social communication with the outside environment improved and "hyperactive behavior" and "anxiety" reduced.

The outcome of this study demonstrate that Hydrotherapy promotes balance and helps develop protective responses, as well as giving relief and pleasure to the RS patients. Although, many different therapeutic therapeutic techniques, which can be effective in facilitating communication, maintaining hand function, preventing deformities and reducing stereotypical hand movements, however, some children with RS react with anxiety during the application. On the other hand Hydrotherapy is the only therapy that provide a relax

environment at the time of the therapy. Especially, in this study the girl was calm in the pool and had no stereotypical movements (Bumin et al 2003). Although, the results from this study were remarkable, it must be noted that further research is required with a wider range of participants.

3.2.3 Moving with animals

In 1960 Dr John Lilly was the first physician and psychoanalyst that studied the dolphin-human communication. He was the first to suggest that dolphins can help people to communicate. In 1970, Smith marked the therapeutic effects of dolphins on her disable brother. After that Lilly and other researchers began to study the effects of interacting with dolphins on children with neurological impairments. There are many kinds of dolphin therapies, but all involve interacting with the mammals by swimming, touching or just looking at them.

Unfortunately, only few researchers have published their studies. Most of this research work was applied to children with autism. Nevertheless, there are some anecdotal reports, which appeared on websites and seem to be encouraging for the RS population.

Lukina (1999) and Servais (1999) stated that dolphin therapy can improve language behaviour, cognitive processing, attention and motivation to learn. Nathanson et al. (1997), claim that the dolphin therapy has the potential to increase gross and fine motor skills, attention, speech and language. They also suggest that a two weeks programme of dolphin therapy can provide equal results with a six month programme of physical or speech therapy. However, review papers of Marino et al. (2007) evaluated five published studies from 1999 to 2005 and discovered that all studies were "methodologically flawed and plagued by several threats to both internal and construct validity". Marino et al., noted that the studies contained a basic failure, which was to control other factors of the treatment i.e. like being in the water swimming outdoors, interacting with therapists etc, resulting to misconceptions. In general it can be noted that interacting with dolphins provides the RS children with an activity and promotes cooperation not only with the animal but also with the helpers.

Easier and more popular to apply is perhaps horse riding. This training allows the child to experience the freedom of moving with the animal. "The horse stride encourages alternating back movements in the rider in response to its own movement. The width of the horses back

offers stability by fixing the pelvis whilst providing a good range of hip abduction (depending on how fat the horse is!). If the horse is skinny the legs of the child will not be far apart when riding, whereas if the horse has eaten too much grass, the legs will be very far apart. The neigh produced by the horse, the smell and the feel of the coat give sensory feedback to the child". Sensory feedback is very important for RTT children, therefore several therapies are specifically developed to improve the dysfunctional sensory system ("An introduction to the Rett Syndrome", Wisbeach 2005).

Based on anecdotal reports both horse and dolphin therapies are beneficial in promoting movement and communication skills, and improving strength as well as providing enjoyment for the RS girls. Although, these therapies might be popular and pleasant for the RS children unfortunately, currently, there is no published research, which indicates their effectiveness. Both practitioners of hippo and dolphin therapy and parents, who are considering these therapies for their children should, made aware that "these treatments have yet to be subjected to an adequate empirical test, so to be considered as therapies, which degenerate the symptoms of RS". (Anthrozoos, 1998).

3.2.4 Sensory integration therapy

Sensory integration is the ability to collect information using one's senses, integrate and organize this information in the brain so that a meaningful response is acquired. "Children with RS may have a dysfunctional sensory system in which one or more senses overreact or underreact to stimulation from the environment. Sensory integration therapy focuses primarily on three basic senses; tactile (touch), vestibular (sense of movement), and proprioceptive (body position)" (Rett Syndrome Foundation 2008).

Pizzamiglio et al (2008) performed a study on sensory-motor integration in RS children. The disadvantage of this study was that it only involved one child. This child underwent a rehabilitation treatment modeled on Piaget's theory of sensory-motor intelligence development. The initial goals of this study were to improve postural control, avoid contractures and teach the subject to swallow her saliva and chew the food. "A computerized visual-motor coordination training and sensory-motor rehabilitation" programme were carried out to facilitate the progressive acquisition of the following skills in accordance with the stages of the infant intelligence development of Piaget 1937. Based on

Piaget (1937), child development involves the integration of new abilities with those previously acquired along lines of reorganization of the individual's entire network of abilities. The results, which were demonstrated after three years of therapy, showed that the subject partially regained the ability to apply the hands as an instrument of objective knowledge and as a tool of communication with other people.

An example of a typical Dutch therapy solely related to sensory integration is *snoezelen* (a combination of two Dutch words: *snuffelen*, which means to sniff and *doezelen*, which means to doze). The therapy involves immersion in a "snoezelroom". The multi-sensory snoezelroom is a room in which the nature, quantity, arrangement and intensity of the sensory stimulation is being controlled by the patient. "Snoezelrooms may have water mattresses, alternative lighting, visual image projection and auditory stimulation". (Lotan et al., 2005). The snoezel therapy is mostly applied to children entering stage II of the disorder, which is the period that dysfunctional neural developmental processes occur (Lotan, 2005). A snoezelroom is a calm place that might reduce the brain's excitability and furthermore it might activate the patient's interest which may result in an active exploration of the environment. This exploration should act as a forward step to their learning ability. At this point, it should be in aware that no article has been published investigating snoezel therapy in Rett syndrome children.

It is difficult to draw a conclusion regarding with the effectiveness of these two kinds of interventions. Without any comparison data, it is not possible to conclusively state that the changes in RS children behaviour are due to the current interventions. The same re-education paradigm should be applied to other children with RS and compared to interventions provided to adequate control. The only that it could be pointed out, is that sensory-motor integration and snoezelen are two promising therapies, which further research, could established them as basic therapies for the RS treatment.

4. Coclusion

Rett syndrome is a severe neurodevelopmental disorder which is described by motor, cognitive and social inabilities. The main reason which deprives the researchers from the answer to this problem is in fact the multi-differential symptoms of RS that remain a puzzle. However, a major step towards the solution appears to be the clinical staging of the syndrome by Hagberg and his colleagues (Hagberg et al., 1985). Hagberg et al., manage to categorize the RS symptoms in four stage based on the regression of the syndrome during the living years of the RS children.

In connection to the above, therapeutic initiatives must take the clinical staging of the syndrome into consideration in terms of developing right research criteria and establishing logical outcome variables. In addition, for the evaluation of the efficacy of each treatment, outcome variables must be considered carefully. These outcome variables should be relevant to the clinical features of RS and should be quantifiable.

Research is in progress to find specific ways to cure and relieve the problems associated with the Rett disorder (Chahrour et al 2007). Although, there is no apparent cure, a wide range of treatments is being used so to reduce the presence of the symptoms. The treatment of the RS requires an integral, multidisciplinary approach including symptomatic and supportive management based on the clinical progression of the syndrome.

Currently, there are no research based treatments that would dramatically change the nature and progression of the Rett Syndrome (Pizamiglio et al 2008). Interventions generally aim to preserve motor and psychosocial development, enriching quality of life and providing important information and support to the families. Efficacy of the adopted therapies is not well documented; “most of the outcome measures are based on single case studies and individual experiences rather than controlled experimental studies” (Zwaigenbaum & Szatmari, 1999). In these therapies children with RS are frequently placed in special educational programs and receive assistance, like drug therapy or other kind of treatments in order to gain or regain basic adaptive skills. Although the occurrence of the RS is rare, it is difficult to establish a therapy, which is based on case studies or worse to individual’s experiences and reports. As it was mentioned above the RS is a multi-symptom syndrome that’s why the therapies that are followed should base on scientific evidence.

In the past few years, there has been an increasing interest in the "clinical and rehabilitative aspects of this syndrome, especially in the cognitive, behavioral and emotional development of these children" (Ellaway et al., 2001). At the moment some therapeutic approaches are still under investigation. On the other hand, efforts are being made to develop pharmacological therapies directed at controlling seizures, sleep disorders and improving attention, eye contact and motor skills (Corbachevskaya et al. 2001).

On the other side different educational approaches including music therapy, hydrotherapy, hippo therapy or sensory –motor therapies are being proposed. The main objective of the music therapy is to recreate movement and communication skills in RS children. To motivate and promote purposeful hand movements and communication abilities. Case studies or small groups have shown improvements in physical abilities, such as holding things and using the body and voice to make musical sounds due to the comfort ness that music creates (Yashura et al., 2001, Wigram et al., 2005, Sullivant et al., 1995). The only disadvantage of this therapy is that the existing research does not establish long-lasting and generalize effect in daily life.

Another therapeutic approach in RS individuals is hydrotherapy. Hydrotherapy seems to promote balance and helps develop protective responses, as well as giving relief and pleasure to the RS patients. Moreover the use of the warm water facilitates to muscle relaxation and decreases the body tension. Nevertheless, these positive effects seem to last up to 8 weeks and after the therapeutic session (Bruin 2003). The existence of only one study for the hydrotherapy reveals the importance of further investigation with a larger sample of RTT syndrome participants. Other studies proposed that the use of animal therapy like dolphin and horse riding therapy can improve balance and children's social –emotional states (Wisbeach 2005, Nathanson 2007). Though these therapies might be beneficial for the RS life, further scientific studies have yet to investigate the effectiveness of this approach.

Physiotherapy and occupational therapy are used to develop in full potential, the physical abilities of the RS children. Physiotherapists and Occupational therapists create a special treatment program based on the needs of each child promoting balance, strength and coordination. These therapies employ assistive technology devices, such pointers and switches that activate toys or simple cause computer activity (Hanks 1986, Physiotherapy Treatment 2008). Although, many of the teaching skills in physiotherapy and occupational

therapy are important for making better quality of life in RS children, few studies have been published on the effectiveness of the physiotherapy and occupational therapy with individuals with RS.

Lastly, a new therapy was proposed by Pizzamiglio (2008) and it was based on sensory-motor integration approach. The sensory integration is the ability to collect information in the brain so that a meaningful response is required. The case study of Pizzamiglio et al., 2008, used a rehabilitation treatment conceived in line with the stages of Piaget's (1937) theory of cognitive development. The results of this study showed that the child regained the use of hands and improved the social interaction with the other people. The disadvantage of this study was that the results were demonstrated after a long period of time (3 years) and with a small sample of participants (one child).

The purpose of the current thesis was to introduce and evaluate different kinds of therapies that might help the RTT children to improve their functional ability and social communication with the outside environment. In the end it revealed that more research is required on the efficacy of the interventions for individuals with Rett Syndrome. It should be noted that some of the above described treatments have no research background and mostly adopt a single rehabilitative technique. According to statistics in order to create a pattern or estimate efficiency there must be a representative number of specimens which has not been collected yet.

The main goal of this review was to provide all the common rehabilitative therapies that are has been achieved for the RS. It should be pointed that there is still a huge gap and many questions are left unanswered regarding this disease. It is not accidental that none of the above mentioned therapies is considered as dominant among the scientific community. Further research should be encouraged in the physical therapies and an inspiring method to proceed would be to compare different treatments and demonstrate real results on a significant population of RS children.

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