Rett Syndrome: Characteristics, Causes, and Treatment

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Running head: Rett syndrome

The recognition of what would later be called Rett syndrome began around 1965 when an Austrian physician named Andreas Rett saw two girls sitting in the waiting room of his office demonstrating similar hand-wringing movements. After further investigation, he was able to find other patients in his practice with characteristics that resembled those of the two little girls. Rett published a study describing the syndrome, but it received very little attention (Harris, Glasberg, & Ricca, 1996; Perry, 1991; Skotko, Koppenhaver, & Erickson, 2004; Van Acker, 1991). In the early 1980s without knowledge of any earlier research, Bengt Hagberg began to speak about observations he had made of similar cases (Harris, et al., 1996; Perry, 1991; Skotko, et al., 2004; Van Acker, 1991). "Once made aware of Rett's earlier work, Hagberg termed the disorder 'Rett syndrome'" (Perry, 1991, p. 275). In 1983, Rett syndrome was recognized as a known condition and much more research was to follow including the determination and publication of a set of diagnostic criteria.

According to several studies, Rett syndrome (RS) affects approximately 1 in every 10,000- 15,000 girls (Bird, 2001; Katsiyannis, Ellenburg, Acton, & Torrey, 2001; Kerr, 2002; Pizzamiglio et al., 2008; Rapp, 2006; Skotko, et al., 2004; Van Acker, 1991; Webb & Latif, 2001). It is a pervasive neurodevelopmental disorder that is most commonly characterized by a marked decline in functional hand use and significant loss of language (Mazzocco et al., 1998; Pizzamiglio et al., 2008; Skotko et al., 2004). The severity and outcome of the disorder varies from person to person. It is possible, but not common, that persons with RS may die at an early age, usually due to complications related to symptoms of the syndrome. "However, there are a number of adult patients cited in the literature" (Perry, 1991, p. 285). The physical abilities of these adults may vary from ambulatory to dependence on a wheel chair for mobility. Cognitive ability, however, tends to be significantly delayed across the majority of affected individuals.

The purpose of this paper is to inform readers of what classic Rett syndrome is and what can be done to improve the lives of the people affected by it. This paper will address several aspects of Rett syndrome including its diagnostic criteria and stages, common characteristics, etiology, as well as possible treatment options.

Characteristics

Rett syndrome is characterized by a specific set of symptoms and behaviors, which constitute the diagnostic criteria. Generally the symptoms include "regression and loss of hand skills, apraxia, deceleration of head growth, and increasing spasticity and scoliosis" (Mount, Charman, Hastings, Reilly & Cass, 2003, p. 435). According to Pizzamiglio et al. (2008), children with Rett syndrome may also have other problems such as cognitive delays, stereotypical hand mannerisms, breathing difficulties, teeth grinding, trouble sleeping and seizures. These symptoms seem to follow a certain course; therefore the syndrome is usually divided into stages. In addition, the characteristics of Rett syndrome often overlap aspects of other disorders; therefore it is important to rule out possible other considerations through the use of differential diagnosis. These topics are discussed in further detail in the upcoming sections.

Diagnostic Criteria

According to Perry (1991), the first set of accepted diagnostic criteria was established in 1984 at a conference in Vienna. The measures that are used today were created by a 41-member team and are based upon the first set of criterion known as the "Vienna criteria".

> There are nine necessary criteria, all of which must be present to make the diagnosis; eight supportive criteria, many of which are usually present, but none of which is required to make the diagnosis; and seven exclusionary criteria, any

> one of which is sufficient to rule out Rett syndrome. The diagnosis is tentative until age two to five years. (Perry, 1991, p. 276).

The necessary criteria according to several research studies are as follows (Bird, 2001; Harris, et al., 1996; Kerr, 2002; Perry, 1991; Pizzamiglio et al., 2008; Van Acker, 1991). The first two necessary criteria are apparently normal prenatal and perinatal periods as well as normal psychomotor development until about six to eighteen months old. The onset of symptoms varies between each child. The third and fourth criteria are average head circumference at birth with a stop in the progress of head and brain growth between the ages of five months and 48 months. The next symptom occurs between the ages of six and 30 months, which is the loss of acquired purposeful hand skills. Another criterion is the development of stereotypic hand movements, which typically take the place of the productive hand usage the girls once had. According to Perry (1991, p. 277), "hand stereotypies of some kind appear in all reported cases." These hand mannerisms are usually movements such as hand wringing/squeezing or washing, clapping or tapping, and hand mouthing. The seventh necessary criterion is the regression and severe impairment of expressive and receptive language as well as significant cognitive delays. Most studies suggest that the majority of girls are at a functioning level below a mental age of eight months and they have not developed beyond the third sensorimotor stage of Piaget (Mount, Hastings, Reilly, Cass, & Charman, 2003; Perry, 1991). The final factor associated with Rett syndrome is the loss of the ability to walk and control other motor movements. Overall, the diagnosis is said to be flexible until the child is two to five years old.

Research also describes several supportive criteria that are typically present in persons with Rett syndrome (Bird, 2001; Harris, et al., 1996; Kerr, 2002; Perry, 1991; Pizzamiglio et al., 2008; Van Acker, 1991). The first supportive criteria is difficulty with breathing including, but not limited to, intermittent apnea while awake, periods of hyperventilation, holding of the breath, and intentional ejection of air or saliva. Two more symptoms of Rett syndrome are frequent seizure activity as well as abnormal echoencephalographs (EEG) even in people without seizures. Approximately 75% of the girls affected with Rett syndrome experience seizure activity (Perry, 1991). A fourth supportive criteria is the wasting away of muscles, increased spasticity, and involuntary muscle spasms. Cold and blue hands and feet are supportive criteria of Rett syndrome due to peripheral vasomotor disturbances. People with Rett syndrome are also likely to have small, thin feet. Progression of scoliosis as well as growth retardation are also supportive criteria and are often associated with Rett syndrome.

Finally, there are also criteria that diagnosticians will use to rule out the diagnosis of Rett syndrome. According to several research studies (Bird, 2001; Harris et al., 1996; Kerr, 2002; Perry, 1991; Pizzamiglio et al., 2008; Van Acker, 1991), there are seven exclusionary criteria which are as follows. The first two exclusionary criteria are evidence of preexisting growth retardation or acquired brain damage occurring before, during or immediately after birth. Another criterion that would exclude the diagnosis of RS is the presence of any signs of storage diseases such as those resulting in enlarged organs. Problems with the eyes such as retinopathy or optic atrophy would also rule out the diagnosis of Rett syndrome. The diagnosis of microcephaly at birth is also an exclusionary criterion. If a person has an identified metabolic or other progressive

neurological disorder then he or she will be excluded from the diagnosis of Rett syndrome. And finally, the last exclusionary criterion is existence of a neurological disorder resulting from an infection or head trauma.

The identification and assessment of the criteria listed above should lead to an accurate diagnosis of Rett syndrome in persons that are affected with the disorder. Due to a breakthrough in research pertaining to the etiology of the syndrome, which will be discussed further in a later section, there also is now a simple blood test that can be done to confirm a diagnosis of Rett syndrome in most cases (Bird, 2001; Kerr, 2002).

Stages

Through various observations and research studies, it was noted that the symptoms and characteristics of Rett syndrome seem to follow similar patterns of development and progression. After identification of these similarities, Hagberg and Witt-Engerstrom suggested in 1986 that Rett syndrome be divided into four clinical stages to assist clinicians in accurately diagnosing the disorder (Perry, 1991; Van Acker, 1991). The four-stage model that was proposed by Hagberg and Witt-Engerstrom continues to be used today with only a minor change in the names of the stages. The labels that were previously used were considered to be negative so the stages are now referred to by number only (Perry, 1991; Van Acker, 1991). Several studies describe the age of onset, duration and characteristics associated with each stage, which will summarized in this section (Harris et al., 1996; Kerr, 2002; Perry, 1991; Van Acker, 1991).

The first stage of Rett syndrome typically begins around the age of six to eighteen months and may last for several months. This stage is generally defined by developmental stagnation. The child will experience a slowed rate of motor development as well as head and

brain growth and seem to have a flaccid muscle tone. The child will also develop a lack of awareness and concern for her environment, especially play activities.

Stage two of Rett syndrome has an onset around one to three years of age and generally lasts from weeks to months. Regression or loss of previously acquired skills most commonly characterizes this stage. There are multiple areas of regression. The most predominant losses associated with Rett syndrome are the loss of purposeful hand use as well as speech. A decrease in social interaction and cognitive abilities also occurs during this period. Many parents state that their children seem very irritable. Some even begin to have self-abusive behaviors. The onset of stereotypic hand movements such as wringing, tapping, and mouthing begins during this stage and about 25% of them experience seizures. Insomnia is also a symptom that sometimes occurs during stage two (Harris et al., 1996; Kerr, 2002; Perry, 1991; Van Acker, 1991). The presence of autistic like behaviors also occurs during this stage. Although Rett syndrome is considered a disorder on the autism spectrum, it is often misdiagnosed as classical autism during this stage (Mazzocco et al., 1998).

The third stage of Rett syndrome may occur somewhere during the ages of two to ten years old and may last from several months to years. During this stage, the girls tend have much more difficulty with motor planning leading to progressive ataxia and apraxia, which is often caused by spasticity and scoliosis. The cognitive functioning of the girls typically regresses to the range of severe mental retardation. The hand stereotypies become even more prominent in this stage. However, the autistic tendencies are much less noticeable and social interaction seems to improve. Seizures typically increase in frequency during this time though (Harris et al., 1996; Kerr, 2002; Perry, 1991; Van Acker, 1991).

Finally, stage four of Rett syndrome usually occurs around age ten on and lasts for years. During this stage, persons affected typically lose much of their mobility due to increased spasticity, rigidity, scoliosis and progressive muscle wasting. Some may even require the use of a wheelchair. Positively, seizure activity typically decreases dramatically and social skills, especially eye contact improves greatly during this stage. Unfortunately, there is very little expressive and receptive language present at this stage of the disorder (Harris et al., 1996; Kerr, 2002; Perry, 1991; Van Acker, 1991).

The age of onset, duration and severity of symptoms vary among each person affected with Rett syndrome. However, the symptoms listed above continue to be relatively consistent across most of the cases of Rett syndrome.

Causation

When Andreas Rett first discovered the collection of symptoms that was later identified as a specified disorder that received his name, he was uncertain of the cause of the disorder. According to Kerr (2002), Rett's first thought was that the symptoms were associated with high levels of ammonia in the blood stream because he found this to be the case in some of the patients that he had seen. In the 1970s however, this theory was not proven (Perry, 1991). Many researchers believed from the beginning that the disorder was caused by a mutation on an X chromosome, but cases were so sporadic that it was almost impossible to perform linkage studies (Kerr, 2002).

After significant research, there was an advancement in 1999. Amir and his colleagues from Baylor University were able to find several mutations on the methyl CpG binding protein 2 (MECP2) gene at the Xq28, which is the tip of the long arm of the X chromosome (Kerr, 2002; Rapp, 2006). "A succession of papers has since confirmed the causative link with Rett syndrome

and identified more than 100 mutation sites on this gene" (Kerr, 2002, p. 277). Rett syndrome is now considered an X-linked dominant disorder.

According to several studies, in all of the females identified as having classical Rett syndrome, about 80% of them have been identified as having a mutation in this gene (Kerr, 2002; Mount, Charman et al., 2003; Rapp, 2006). Males may also have a mutation on the MECP2 gene, but it usually expressed through a diagnosis of Klinefelter syndrome, Angelman syndrome or possibly a somatic mosaic pattern (Mount, Hastings et al., 2003; Rapp, 2006).

Rett syndrome is said to be caused by impairment in the methylation of DNA. "DNA methylation provides a permanent mechanism to silence, or deactivate, genes by repressing transcription (the transfer of genetic code information from one kind of nucleic acid to another)" (Bird, 2001, p. 93). The MECP2 gene, which encodes the MECP2 protein that is responsible for deactivating specific genes from being read in the body and when there is a mutation on this gene, it is unable to correctly do its job (Rapp, 2006; Webb & Latif, 2001). According to Bird (2001) and Kerr (2002), it seems that there are genes that are being expressed in persons with Rett syndrome that should not be. Researchers continue to work to find exactly what genes those are and where they are located. Studies have also shown that the way that the X chromosome is inactive determines the severity of the disorder in each person (Kerr, 2002). The goal for researchers is to be able to identify what genes are being inaccurately expressed, where they are located and why it is occurring in specific cases of Rett syndrome.

Recent research of Rett syndrome has lead to several answers, but also raised many new questions, which opens the door for several possible research areas. Determining a common cause of Rett syndrome will likely lead to more successful treatment options and possibly the discovery of a cure for this disorder in the future.

Treatment Implications

At this time, there is no cure or precise treatment for Rett syndrome. There are however, several treatment options for the symptoms associated with the disorder. "Interventions are generally aimed at preserving physical and psychosocial functioning, enhancing quality of life, and providing education and support to families" (Pizzamiglio et al., 2008, p. 50). Because characteristics may occur at varying degrees for each person affected with RS, it is important that any intervention programs are highly individualized to meet her specific needs (Van Acker, 1991). Treatment options may take the form of medical as well as educational interventions.

Medical Interventions

Since the decline in physical abilities such as hand function and ambulation are such defining characteristics of Rett syndrome, it comes to no surprise that physical and occupational therapy are very important parts of a treatment plan. Thorough therapy in these areas will help people affected with Rett syndrome to preserve or even recover functional movement and mobility, avoid malformation, as well as maintain a connection to their surroundings (Van Acker, 1991). Occupational therapy can also include "assistive technology devices, such as pointers and switches that activate toys or a simple cause/effect computer activity" (Pizzamiglio et al., 2008, p.51).

Interventions such as the use of therapy balls, weight shifting activities, segmental rolling, balance-stimulating floor activities, swings, and merry-go-rounds have shown to be effective in the treatment of ataxia and apraxia (Katsiyannis et al., 2001; Van Acker, 1991). A continued focus on maintaining the ability to walk is vital as well. This can be done by doing gait training and weight-bearing exercises. It is also very important that "walking and stair

climbing should be a regular part of the daily routine to maximize these skills" (Van Acker, 1991, p. 395).

Hydrotherapy can be used to decrease discomfort and increase range of motion. Effects appear to last for a few weeks after each session. It is reported by Pizzamiglio et al. (2008) that there is very little research in this area, so in order to validate the positive results of hydrotherapy, more research studies need to be conducted. Physiotherapy is also a treatment that is used to improve difficulties with motor movements including range of motion, walking and flexibility (Perry, 1991). Horseback riding has also been used to increase balance as well as the emotional well being of the children, but its results have not been scientifically reported (Pizzamiglio et al., 2008).

Stereotypical hand movements are also a highly recognized feature associated with Rett syndrome. There has not been a great deal of progress in the area of intervention for this trait and it is often questioned whether such interventions are needed. Some research studies (Perry, 1991; Van Acker, 1991) show that hand splinting can be successful in stopping hand wringing and hand to mouth actions while the splints are on the hands. This does seem to help the person be more attentive to their environment at the time, but there seems to be no long term effects because once the splints are removed the behavior is likely to return. It is also reported that very few people are able to endure the use of the arm and hand splints, even for short periods of time.

Persons affected with Rett syndrome will likely have to deal with the effects of scoliosis or curvature of the spine. Spinal braces are sometimes used to slow the progression, but this does not always prove to be effective. In critical cases, surgery might be necessary to correct the alignment of the spine, which typically stops any further problems (Perry, 1991).

Medications and dietary control are other interventions that are sometimes used to treat the symptoms of Rett syndrome (Perry, 1991; Pizzamiglio et al., 2008). Doctors may prescribe medications to manage seizure activity, improve breathing problems, and reduce sleeping difficulties. Changes in diet have been explored in several studies to improve weight gain and alleviate seizures. This diet is high in fat and calories and low in carbohydrates and also includes various supplements.

Educational Interventions

It has been noted that even though there are varying degrees of cognitive delays in persons affected with Rett syndrome, most people affected appear to be in the range of moderate to severe mental retardation often around the mental age of eight months (Mount, Hastings et al., 2003; Perry, 1991). Educational assessment must be conducted to determine the individual needs of each person affected with Rett syndrome because there is the possibility of a wide range of abilities (Kerr, 2002). In most cases, children with Rett syndrome will receive special education services to learn or often relearn specific functional, adaptive and cognitive skills (Pizzamiglio et al., 2008).

Lack of expressive and receptive language is also a large part of Rett syndrome. Communication systems and augmentative and alternative communication devices are often used to increase communication skills. Some of these systems include "eye pointing, communication boards (pictures, facial expression, gestures, and the activation of switches" (Van Acker, 1991, p. 401). However, "little research has been done to cultivate communication and literacy in girls with this condition" (Skotko et al., 2004, p. 145). Some of the research that has been done showed the successful use of switch-activated augmentative communication devices, computers with graphics to make requests and eye pointing with picture communication symbols. Story

book reading was found to facilitate meaningful communication for girls affected with Rett syndrome as well (Skotko et al., 2004).

Music therapy is also often a common intervention used in Rett syndrome (Kerr, 2002; Perry, 1991; Pizzamiglio et al., 2008; Van Acker, 1991). It can encourage functional hand use through manipulation of the instruments as well as interaction through the alertness created by the music. It may also facilitate communication and is simply just an enjoyable activity for the child.

Occasionally, there is research that supports the effectiveness of a highly individualized and specialized treatment regimen. For example, a study conducted and reported by Pizzamiglio et al. (2008) took place over a period of three years and determined the effectiveness of a sensory-motor rehabilitation treatment program that was highly involved, which included intensive physical and cognitive therapy. The individual student that was involved in this study made dramatic progress in several areas. She regained the functional use of her hands, improved communication skills, became more attentive, more coordinated, and overall was in a much better emotional state (Pizzamiglio et al., 2008).

Discussion

Rett syndrome is a complex disorder that has seen much progress in the past few years. The characteristics and symptoms have been described above and it is obvious that Rett syndrome significantly alters the life of the people who are so diagnosed. However, having a greater understanding of what Rett syndrome is, what causes it and what can be done to improve the symptoms can help those affected lead more comfortable and enjoyable lives.

The accomplishments made in the determination of a genetic cause of Rett syndrome has opened the door for the need for even further research such as the specific location of the

mutations as well as why the mutations occur. Continued progress in this area will hopefully lead to an eventual cure for Rett syndrome.

It is important that educators and therapists are using research-validated interventions and approaches to treat and improve the symptoms associated with Rett syndrome. There are numerous strategies and techniques that have surfaced in the literature, many of which were mentioned in this paper. However, there is much more research that needs to be conducted to ensure that individuals are getting the most effective treatment possible.

It is always a constant battle when you are working with a specific disorder such as Rett syndrome because no matter how much progress you make there is always something more that can be done to improve the quality of life of those affected. We will continue to look ahead to even more effective treatments, early intervention, ways of prevention and in the long run maybe even a cure. A quote by Van Acker (1991, p.402), which is identified as one of the slogans of the International Rett Syndrome Association, sums up the overall message of this paper, "If we care today, we can cure tomorrow."

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