

# **PHAL 423**

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## **Epilepsy may not be the only cause of seizure activity in Rett Syndrome**

## **Epilepsy may not be the only cause of seizure activity in Rett Syndrome**

### **Rett syndrome**

Rett syndrome (RS) is a severe neurodevelopmental disorder that is believed to be one of the leading genetic causes of mental retardation in females affecting up to 1 in 10000 female births world wide (Asaka et al., 2006; Ferrer and Moral, 2007). In almost 80% of these patients', RS has been identified to result from a mutation in the Methyl-CpG binding protein 2 (MeCP2) gene located on the short arm of the X-chromosome (Mari et al., 2005; Huppke et al., 2007). Because of the random X-chromosome inactivation that occurs, there can be a large variability in the severity of the onset of RS (Ferrer and Moral, 2007; Kerr and Ravine, 2003). Despite the severity of RS, the progress of classical RS is common and can be characterised by four stages that were originally described by Hagberg and Witt-Engerstram in 1986 and later refined by Kerr and Stephenson, 1986 and Hagberg, 2002.

### **Stage I**

Stage one of RS signifies the onset of RS in individuals. This can occur anywhere after three months to 4 years of normal development. The most identifiable symptom that suggests the onset of RS is stereotypic hand wringing movements that includes twisting, wringing and clapping of hands. At this time there is also a stagnation of mental development. This stagnation includes a halt in learning new tasks, a decline in eye contact, decreased interactions with surroundings and a decreased ability to verbally communicate (Hagberg and Witt-Engerstram, 1986; Kerr and Stephenson, 1986; Hagberg, 2002).

### **Stage II**

The second stage refers to the decline in abilities that had been established before the onset of the disease. This usually follows a few months after the initial onset of the

disease and continues over several months. Here, there is a loss of fine motor control resulting in a very limited ability to use hands for goal-orientated tasks, and a clumsy gait. However, gross motor control remains intact. At this time breathing also becomes more irregular with periods of hyperventilation usually broken by breath holding for long periods of time, usually up to 40 seconds. At this time RS patients are often diagnosed with cerebral palsy and are described to have autistic like behaviours, which in many cases can lead to the misdiagnosis of RS in its early stages. At this time the first signs of epilepsy are sometimes observed as well (Hagberg and Witt-Engerstram, 1986; Kerr and Stephenson, 1986; Hagberg, 2002).

### **Stage III**

The third stage of RS is characterised by a clear mental retardation and a lack of emotional contact. However, communication through eye pointing and staring does seem to be apparent. There is also deterioration in motor control, apparent anxiety like behaviours, and a clear gait apraxia can be observed. At this point the onset of severe epilepsy is also a commonly observed. Patients often remain in stage three of RS for several years (Hagberg and Witt-Engerstram, 1986; Kerr and Stephenson, 1986; Hagberg, 2002).

### **Stage IV**

Finally the fourth stage of RS is where all affected girls will remain until they die. The life expectancy of girls affected with RS varies greatly depending on the severity, however, as medical interventions are becoming more successful girls can be expected to live into their 40s. By this stage there is a loss of mobility to the extent that individuals are wheelchair bound. There is also obvious growth retardation, anxiety like behaviours and development of severe scoliosis. However, interestingly the severity of epilepsy seems to decline in frequency and duration (Hagberg and Witt-Engerstram, 1986; Kerr and Stephenson, 1986; Hagberg, 2002).

### **Classical Rett syndrome MeCP2 mutation**

MeCP2 is an X-linked gene that is normally phosphorylated. Following phosphorylation MecP2 recruits co-repressors and histone deacetylase which then act to suppress gene transcription. MecP2 is therefore important for regulating transcription and gene expression. However, what genes MeCP2 regulates is unclear. Mutations of the MeCP2 gene result in the neurodevelopmental disorder Rett Syndrome (Miyake and Nagai, 2006).

### **Atypical Rett syndrome mutations.**

There are also other mutations that give the same clinical disorder as mutations to the MeCP2 gene. One such example is the cyclin-dependent kinase-like 5 gene located on the X-chromosome (Tao et al., 2004). The major difference with this mutation and the MeCP2 mutation appears to be that with the cyclin-dependent kinase-like 5 gene mutation there is an earlier onset of seizures.

### **Rett Syndrome in Males**

RS has been classically referred to as syndrome that affects only females. However, as the awareness of RS is increasing and the medical interventions are becoming more successful, there are more reports becoming available about RS in males. Males identified to have RS have presented at the most severe end of the spectrum of RS and do not have a very good life expectancy (Jan et al., 1999; Zeev et al., 2002).

### **Treatments used in Rett Syndrome**

The many symptoms of this multi disease disorder can each be individually treated to an extent. The loss of motor control can be delayed through intensive therapies including hydro-therapies (Bumin et al, 2003). Communication can also be established using eye communications and gestures through habilitation therapies (Hagberg, 2002). Scoliosis can be corrected through the surgical implantation of

metal rods to correct the curvature in the spine. While the treatments described so far have all been physical interventions, other symptoms can be controlled through drug therapies. Behavioural problems can often be alleviated with methylphenidate (Ritalin™), which is often used to treat attention deficit disorders (Martino et al., 2004), and epilepsy can be managed through the use of anti-epileptic drugs (AEDs).

Interestingly, epilepsy in RS is often overshadowed in favour of the more ‘unique’ neurodevelopmental deficits that are common in RS. However, in a survey by Bahi-Buisson et al. (2008) it was revealed that over half of the parents of RS children believe that seizures has the most impact on the quality of life in these girls. The generalisation and prolonged duration of seizures and its association with cyanosis was of great concern to the parents surveyed. Observations made following seizures in RS patients suggest that following seizures RS girls will become emotionally upset and may require several days for recovery, there is also a regression in social development and alertness, which greatly opposes the extensive therapies and impacts on the quality of life (Bahi-Buisson et al., 2008). As such, for the remainder of this essay I am going to discuss epilepsy in RS and what treatments have been employed to control this epilepsy. I will then discuss an alternative cause of seizures in RS that has been proposed.

### **Epilepsy in Rett Syndrome**

Epilepsy occurs in approximately 80% of individuals affected with RS by the age of 12, with an average age of onset of 4 years (Steffenburg et al., 2001; Hagburg, 2002). This is much later than the 0.8 years that the onset of seizures are normally observed in individuals with severe mental retardation (Steffenburg et al., 1996). In a retrospective study on 50 patients Steffenburg (2001) showed that the most common types of epilepsy identified in RS patients are partial complex, tonic-clonic, tonic, and myoclonic seizures. It was also shown that of the 50 RS subjects 44% exhibited more than one type of seizure (Steffenburg et al., 2001).

Complex partial seizures generally originate in the frontal or temporal lobes of the brain and spread out to areas of the brain associated with awareness. These seizures can last up to 15 minutes and during these seizures an individual may have the appearance of being aware, however, no information is being processed.

Tonic seizures often involve all of the brain and result in the rigidity of muscles while consciousness is maintained. These seizures often last for up to 20 seconds

Tonic-clonic seizures on the other hand can last for up to 5 minutes. Again these seizures involve the whole brain and start off with the rigidity of muscles, this is then followed by a loss of consciousness and rapid jerking movements.

Whereas myoclonic seizures last only for a few seconds and are very brief 'muscle-spasm' like movements.

In RS girls, however, irrespective of the type of seizure, seizures can often last over a period of hours to days, with only short intervals between each seizure. This is particularly noticeable during stage three of RS.

### **Diagnosis of Epilepsy**

Epilepsy is often diagnosed through a combination of comments from parents, observations made by the physician and results from an electroencephalography (EEG). EEG measures the electrical activity in the brain through electrodes that are placed on the scalp. Using EEGs it can be identified when there is abnormal activity going on in the brain, which could be an epileptic, behavioural, psychogenic, physiological seizure like event. From the EEG data the origin, spread, and duration of the seizure like activity can be obtained. This information is important for supporting the parent's observations and for identifying the type of seizure that is occurring. This information can help to identify what drug therapies should be used.

## **Treatments of Epilepsy**

In the retrospective study by Steffenburg et al. (2001) it was identified that the most common drug therapies used to treat epilepsy in RS patients were carbamazepine, lamotrigine and valproate. However, they did not identify the differential effects of these drugs in the control of seizures.

Briefly, carbamazepine acts to stabilise inactive voltage gated sodium channels making the cells less excitable. However, side effects often include a decrease in motor co-ordination, stomach aches, liver toxicity, headaches, and migrans.

Lamotrigine inhibits voltage gated sodium channels making the cells more stable and is often used to treat complex partial seizures. However, side effects include headaches, nightmares, insomnia, rash, night sweats, muscle aches, and memory and cognitive problems.

While valproate is a broad spectrum AED that acts on voltage gated sodium channels, calcium channels, and is believed to affect the GABA neurotransmitter. Side effects of its use include fatigue, dizziness, headaches, nausea, liver toxicity, and abdominal pain.

Steffenburg et al. (2001) also identified that 30% of RS patients were prescribed 2 AEDs while a further 10% were on a combination of 3 AEDs. However, they did not identify the types of treatments used for the different types of seizures therefore giving no indication if there were particular types of seizures that were more difficult to control. It also appeared that there was a higher incidence of partial seizures in RS, 32%, compared to the 13% in severely mentally retarded children.

Another retrospective study, this time with 110 patients, was carried out by Huppke et al. (2007). In this study types of seizures were not investigated, so, again there can be no comparison made between the type of seizure and the drug therapy. The average age of seizure onset was again 4 years, which was comparable to previous studies that looked at epilepsy in RS. In this study Huppke et al. (2007) identified that the drugs prescribed were influenced by the physicians personal experiences and the patients

response to the drug and the most common AEDs prescribed were sulthiame, carbamazepine and valproate.

Sulthiame is an inhibitor of the enzyme carbonic anhydrase and it is mainly used in the therapy for partial seizures. Side effects of sulthiame include, ataxia, nausea, rash, anorexia, hyperventilation, and shortness of breath.

In Huppke et al. (2007) it was identified that in AED monotherapies group (n=58) there was an over all 50% decrease in seizures in 54% of patients. However, in individual treatments there was a large variability. Patients treated with sulthiame (n=15) had a 50% decrease in seizures in 64% of patients, while carbamazepine (n=16) had a 50% decrease in seizures in 71% of patients. On the other hand, valproate (n=16) only had a 50% decrease in seizures in 38% of patients.

25 patients that were unresponsive to the first monotherapy were titrated off the AED and were then started on a second monotherapy. In these patients there was a 50% decrease in seizures in only 38% of individuals.

19 patients assessed were on polytherapy treatments with 2 or 3 AEDs. In these individuals seizures were decreased by 50% in only 43% of individuals. However, in patients that were taking a polytherapy with carbamazepine there was a 50% decrease in seizures in all patients.

In all drug treatments about 45% of patients reported adverse drug effects. However only 13% discontinued drug use as a result. These results were reported to be comparable to drug responses in other epilepsy groups as well.

Another interesting finding they made from this study was related to the average duration of drug therapies. Sulthiame was used for 36 months, while carbamazepine was used for 102 months, and valproate was used for only 29 months. However, there was no information provided as to why the average duration of treatment for carbamazepine was significantly greater than that of sulthiame and valproate.

Overall the paper by Huppke et al. (2007) suggests that carbamazepine may be the most effective AED in treating epilepsy in RS and should be recommended as the first drug of choice for treatment of epilepsy in RS. It was also suggested valproate may have been less effective in treating epilepsy in RS because of the MeCP2 mutation. There may instead have been a synergistic interaction between valproate mediated hyperacetylation of histones and the MeCP2 mutation mediated hyperacetylation of histones, thus possibly exasperating some of the RS symptoms in some instances.

What both of these studies do not show is whether there is a differential effect depending on the type of seizure that a patient is afflicted with. In 2007 Jian et al. showed that there was in fact a difference in the frequency of seizures between classical and atypical RS. Here they identified that there was a lower frequency of seizures in classical RS. However, within the classical and atypical RS groups the seizure rate was not affected by the type of mutation that resulted in RS. Unfortunately, yet again, there is no information provided on the type of seizures the patients were afflicted with and the efficacy of the treatments used for managing those seizures. They did, however, identify that the most commonly used AEDs were valproate, lamotrigine and carbamazepine. Also they do comment that seizures appear to be under control in only 38% of RS patients in this study. A further 11% of patients were reported to have no seizures during the assessment period.

This study was quite different to the previous studies as the families of 162 RS patients participated in a one-year study where the family or caregiver reported all events. As a consequence reported seizure frequencies may not be entirely accurate.

From these studies it has been identified that seizures in RS are often partial complex, tonic-clonic, tonic, and myoclonic seizures and the most effective and commonly used treatments appear to be carbamazepine and lamotrigine.

The suggestion that lamotrigine is beneficial for the treatment of epilepsy in RS is further supported in a pilot study carried out in 1998 by Stenbom et al. In this study the effects of lamotrigine on seizures and motor control was assessed. 12 RS patients were recruited and put on either a monotherapy with lamotrigine, or a polytherapy with lamotrigine and valproate or carbamazepine. Three participants withdrew from

the study due to adverse side effects from the drug; one was from the polytherapy AED motor group while the other two were from the monotherapy epilepsy group. The average dose of lamotrigine was 5.8 mg/kg/d in the monotherapy and 1.2 mg/kg/d in the polytherapy with a large variability in the patients' sensitivity to the drug. All doses appeared to be within the recommended maintenance doses for lamotrigine. Because RS is a multi disorder disease it must also be taken into account that the AEDs may not have been the only drugs that the patient was on. As a result, there may be some unknown drug interaction occurring with a non-AED drug.

Two of the three RS patients from the epilepsy group had a reduction in seizures of 50% and there was no difference between the mono or poly therapies. As well as this lamotrigine appears to be useful in the motor group patients. Here, four of the six patients showed increased alertness, better eye contact, better hand function and improved sleep patterns. Adverse effects that were experienced included tremors and poor gait.

Over all Stenbom et al. (1998) suggests that lamotrigine is an effective therapy for treating epilepsy and also motor functions in RS. Unfortunately, this was the only paper that I found that looked specifically at the role of an AED in epilepsy. Studies such as this one are very limited as it is often difficult to get enough subjects to participate in the study, this makes retrospective studies much more favourable.

So far we have looked at how epilepsy is managed with AEDs. However, we have also observed that there are significant therapeutic benefits in only approximately 55% patients, while the remaining patients show a resistance to drug therapies. This is a very high percentage of individuals that do not respond well to AEDs compared to the over all population of patients with epilepsy, where only 30% of individuals are resistant to AEDs.

This could mean that epilepsy in RS is different to classically described epilepsy in some way. This idea could be supported by the fact that epilepsy in RS develops at a much later age (4 years) compared to epilepsy in other mental retardation disorders (0.8 years). As such, alternative methods for managing epilepsy in RS must be investigated.

A new approach for managing seizures that are resistant to drug therapies is vagus nerve stimulation (Wilfong and Schultz, 2006). Vagus nerve stimulation has been shown to be successful in reducing the frequency of seizures in patients resistant to AEDs. Vagus nerve stimulation involves stimulation of the vagus nerve through electrical impulses delivered by a device that is similar to a pacemaker (Wilfong and Schultz, 2006).

Wilfong and Schultz (2006) were the first to look specifically at the effects of vagus nerve stimulation in RS patients resistant to AEDs. In this study five girls with classical RS and confirmed MecP2 mutation and two girls with atypical RS, confirmed to be negative for the MeCP2 mutation, were treated with vagus nerve stimulation for at least one year.

One year following the implantation of the vagus nerve stimulation device six of the seven patients showed a reduction in seizure frequency of at least 50%. Alertness was increased in all seven patients. In six of the seven patients there appeared to be no adverse side effects or exasperation of existing problems.

The advantage of this treatment is that there are no pharmacological side effects to contend with and there are also no drug interactions to worry about. It would be interesting to see the development of this therapy for RS patients who are not only resistant to AED therapies but also for those who have multiple disorders that are often treated through drug therapies.

### **Alternative Cause of Seizure Activity**

However, before vagus nerve stimulation becomes more widely used in RS it will be important to re-assess how epilepsy is diagnosed in RS. Another explanation for the high resistance to treatment with AEDs is that these individuals do not have epilepsy. For example, one of the symptoms described, but quite often overlooked, in RS is anxiety like behaviours. What if this was contributing to the brain activity and resulting in an EEG that resembled epilepsy but was not epilepsy.

Panic attack seizures are quite similar to partial epileptic seizures in that they both often originate from the frontal lobe (Bernik et al., 2002). However, while partial seizures induced by anxiety present with a different EEG pattern to those induced by an epileptic seizure, this can often be missed by less experienced or biased practitioners and diagnosed as epilepsy regardless of what it actually is (Bernik et al., 2002; Grenton et al., 1995). There have been many cases identified where panic attacks have been misdiagnosed as resistant epilepsy.

A case study by Sethi et al. in 1999 describes a woman who was diagnosed with frontal lobe epilepsy, yet she was resistant to drug treatments. After going for a video EEG evaluation of a history of night episodes of awakening and body and arm jerks she was diagnosed with nocturnal panic attacks. This enabled her to go onto a new drug therapy regimen that included her AED she was taking previously to continue to control general seizures with the addition of an anxiolytic and psychotherapy.

This story can be found in many situations. Bernik et al. 2002 looked at a series of case studies where panic attack partial seizures are misdiagnosed as epileptic seizures. One example is when a young woman suffering from tonic-clonic seizures began to develop anticipatory anxiety. These attacks began to increase in frequency and were unresponsive to her AEDs. Upon closer inspection her physician identified that she was having panic attacks and began her on clomipramine along with her AEDs and as a result she showed great improvement in her symptoms.

Again similar cases have been identified by Grenton et al. (1995) where apparent AED resistance was in fact due to panic attacks which required a different type of treatment to bring the non-epileptic seizures under control.

Although this concept of non-epileptic seizures has been around for a while there has been no 'push' for a higher quality investigation when diagnosing seizures in RS. Then in 2006 a paper by McGill et al. identified that anxiety may have a much larger role in RS than was originally identified.

## **Elevated Stress Hormone in Rett Syndrome**

Through the use of MeCP2<sup>308/Y</sup> mutant mice the cause of anxiety in RS has been identified. It is also possible that it may be one of the first symptoms where the molecular cause underlying the symptom has been identified (McGill et al., 2006).

MeCP2<sup>308/Y</sup> mice, like RS patients, show increased fear/anxiety behaviours (McGill et al., 2006). This led to investigations of the underlying cause of the observed anxiety. Since anxiety part of the stress response and stress is regulated by glucocorticoid release, plasma levels of corticosterone were analysed in MeCP2<sup>308/Y</sup> and wild type mice under normal and stressful situations. From this test McGill et al. (2006) identified that although basal levels of corticosterone were the same, under stressful conditions corticosterone concentrations in MeCP2<sup>308/Y</sup> mice peaked 1.5 times greater than the wild type response to the stressful situation. Suggesting that MeCP2<sup>308/Y</sup> mice have an increased response to stress. As such, the next logical step would be to look at the expression of the corticotropin-releasing hormone. Here they identified that there was an over-expression of the corticotropin-releasing hormone gene in MeCP2<sup>308/Y</sup> mice that may be the source of the elevated anxiety in these animals.

Finally, there needed to be a link between MeCP2<sup>308/Y</sup> mutation and the elevation of the corticotropin-releasing hormone gene. McGill et al. (2006) identified that MeCP2 normally suppresses the transcription of corticotropin-releasing hormone gene and that when MeCP2 is mutated the suppression of the corticotropin-releasing hormone gene is impaired resulting in an over production of corticotropin-releasing hormone in response to stress (McGill et al., 2006).

This study provided solid molecular evidence to support the idea that resistant epilepsy in RS may not be epilepsy but rather a non-epileptic stress induced seizure.

This new information provides strong support for the idea that some of the reported seizure activity in RS may not be epileptic. This could also explain why there is such a large percentage of individuals who appear to be resistant to AED therapy. It may also explain why there appears to be more patients with RS who have been diagnosed with partial seizures, 32%, compared with the general population, 13% (Steffenburg

et al., 2001). This further emphasised the information that the retrospective studies were lacking, as it would have been interesting to see if there was a particular type of seizure that appeared more resistant to treatment.

### **Diagnosis of Panic Attack**

As a result, before intense AED drug therapies are tried with patients that have been diagnosed with resistant epilepsy, there should be a more accurate diagnosis of what type of activity is occurring in the brain. As the community becomes more aware of panic attacks being a highly likely contributor to seizure like activities there is more demand for more specialised physicians and more sensitive methods of analysis of neuronal activity. One method that is becoming highly popular is the Video-EEG. This is a technique that not only takes EEG information, but also records the patient so that brain activity can be matched up with behavioural activity. In 2001 Thirumalai et al. carried out a study that looked at the diagnosis of epileptic and non-epileptic seizure like events in both normal and mentally retarded children. In this study 193 children, whose diagnosis was unsure based on EEG results alone, participated. The aim of this study was to clarify if the events recorded by EEG were epileptic seizures or not.

Overall, Thirumalai et al. (2001) identified that video-EEG enabled a more accurate diagnosis of the seizure like activity that was occurring. They also identified that there was no overall difference in the distribution of epileptic and non-epileptic activities in children with or without mental retardation. However, they did comment that it was easier to identify events in mentally retarded children as they had more frequent episodes of activity. Another observation they made was that sometimes results from a short out-patient study were inconclusive and the results differed from results from the long in-patient study. Although, this was also greatly influenced by the frequency of events that occurred. From this study Thirumalai et al. (2001) recommended the use of short out-patient video-EEG as this was successful in identifying the nature of activity in 62% of patients. They recommended that long video EEG was only necessary for those patients that showed inconclusive data.

Altogether, Video EEG shows more accuracy in identifying whether seizure-like activity in patients is epileptic or non-epileptic in nature.

This study further emphasised the importance of having a more accurate method of diagnosis as many of these patients ( $\approx 20\%$ ) may have been misdiagnosed with epilepsy if further investigations had not been carried out. This has significance for those patients as they can now undergo appropriate therapies that do not result in them being given unnecessary AEDs that may have adverse side effects and no therapeutic benefit.

## **Conclusion**

RS is a neurodevelopmental multi disease disorder that may be one of the leading genetic causes of mental retardation in females (Asaka et al., 2006; Ferrer and Moral, 2007). Despite this, there is very little that is truly understood about this disease. One particular aspect of interest in this disease is epilepsy. Epilepsy occurs in the RS with an estimated incidence of 80% (Steffenburg et al., 2001). With partial complex, tonic-clonic, tonic, and myoclonic seizures being the most common seizures occurring in RS girls. The most effective and commonly used drug therapies for these seizures appear to be carbamazepine and lamotrigine. While valproate is also a commonly used AED it does not appear to have as great a therapeutical value to RS patients compared to carbamazepine and lamotrigine.

However, the reported incidence of epilepsy may be a gross overestimation of epilepsy in RS. It has become increasingly obvious that there is something different about the data that is obtained on epilepsy in RS compared to the general population, this includes the over representation of partial seizures and drug resistant epilepsy (Steffenburg et al., 1996). These differences could be a characteristic feature of the RS disorder, however, recent information has been made available that suggests that misdiagnosis may be the main cause for the differences observed between RS and the general population. Still, there are some differences that cannot be attributed to misdiagnosis of epilepsy. For example, the late onset of epilepsy in RS. This onset

may represent a difference in the characteristics between epilepsy in RS compared to epilepsy in other disorders that has not yet been identified.

Since the identification of the possible panic attacks in the RS community individuals are becoming increasingly aware of the methods used to diagnose epilepsy in RS. There is currently an increasing demand for the use of video EEG in the assessment of epilepsy in RS as concerns have been raised about giving AEDs to RS girls where it may be not only ineffective but also detrimental to their health.

## References

- Asaka, Y., Jugloff, D., Zhang, L., Eubanks, J. and Fitzsimonds, R. (2006) Hippocampal synaptic plasticity is impaired in the Mecp2-null mouse model of Rett syndrome. *Neurobiology of Disease*. **21**, 217-227
- Bahi-Buisson, N., Guellec, I., Nabbout, R., Guet, A., Nguyen, G., Dulac, O. and Chiron, C. (2008) Parental view of epilepsy in Rett syndrome. *Brain and Development*. **30**, 126-130
- Bernik, M., Corregiari, F. and Braun, I. (2002) Panic attacks in the differential diagnosis and treatment of resistant epilepsy. *Depression and Anxiety*. **15**, 190-192
- Bumin, G., Uyanik, M., Yilmaz, I., Kayihan, H. and Topcu, M. (2003) Hydrotherapy for Rett syndrome. *Journal of Rehabilitation Medicine*. **35**, 44-45
- Ferrer, E. and Moral, A. (2007) Rett's syndrome. *Drugs of the Future*. **32**, 179-186
- Grenton, P., Bartolomei, F. and Guerrini, R. (1995) Panic attacks mistaken for relapse of epilepsy. *Epilepsia*. **36**, 48-51
- Hagberg, B. (2002) Clinical manifestations and stages of Rett syndrome. *Mental Retardation and Developmental Disabilities Research Reviews*. **8**, 61-65
- Hagberg, B. and Witt-Engerstram, I. (1986) Rett syndrome: a suggested staging system for describing impairment profile with increasing age towards adolescence. *American Journal of Medical Genetics*. **24**, 47-59
- Huppke, P., Kohler, K., Brockmann, K., Stettner, G. and Gartner, J. (2007) Treatment of epilepsy in Rett syndrome. *European Journal of Paediatric Neurology*. **11**, 10-16
- Jan, M., Dooley, J. and Gordon, K. (1999) Male Rett syndrome variant: Application of diagnostic criteria. *Pediatric Neurology*. **20**, 238-240
- Jian, L., Nagarajan, L., Klerk, N., Ravine, D., Christodoulou, J. and Leonard, H. (2007) Seizures in Rett syndrome: An overview from a one-year calendar study. *European Journal of Paediatric Neurology*. **11**, 310-317
- Kerr, A. and Ravine, D. (2003) Review article: Breaking new ground with Rett syndrome. *Journal of Intellectual Disability Research*. **47**, 580-587
- Kerr, A. and Stephenson, J. (1994) A study of the natural history of RS in 10 girls. *American Journal of Medical Genetics*. **1**, 77-83
- Mari, F., Azimonti, S., Bertani, I., Bolognese, F., Colombo, E., Caselli, R., Scala, E., Longo, I., Grosso, S., Pescucci, C., Ariani, F., Hayek, G., Balestri, P., Bergo, A., Badaracco, G., Zappella, M., Broccoli, V., Renieri, A., Kilstrup-Nielsen, C. and Landsberger, N. (2005) CDLK5 belongs to the same molecular pathway of MeCP2

- and it is responsible for the early-onset seizure variant of Rett syndrome. *Human Molecular Genetics*. **14**, 1935-1946
- Martino, A., Melis, G., Cianchetti, C. and Zuddas, A. (2004) Methylphenidate for pervasive developmental disorders: safety and efficacy of acute single dose test and ongoing therapy: an open-pilot study. *Journal of Child and Adolescent Psychopharmacology*. **14**, 207-218
- McGill, B., Bundle, S., Yaylaoglu, M., Carson, J. and Thaller, C. (2006) Enhanced anxiety and stress-induced corticosterone release are associated with increased Crh expression in a mouse model of Rett syndrome. *Proceedings of the National Academy of Sciences*. **103**, 18267-18272
- Miyake, K., Nagai, K. (2006). Phosphorylation of methyl-CpG binding protein 2 (MeCP2) regulates the intracellular localization during neuronal cell differentiation. *Neurochemistry International* **50**, 264 – 270
- Sethi, N., Torgovnick, J., Ebben, M., Assura, E and Sethi, P. (2007) Nocturnal panic attacks mistaken for frontal lobe epilepsy. *The Internet Journal of Neurobiology*. **7**, number 1
- Steffenburg, U., Hagberg, G. and Hagberg, B. (2001) Epilepsy in a representative series of Rett syndrome. *Acta Paediatrica*. **90**, 34-39
- Steffenburg, U., Hagberg, G. and Kyllerman, M. (1996) Characteristics of seizures in a population based series of mentally retarded children with active epilepsy. *Epilepsia*. **37**, 850-856
- Stenbom, Y., Tonnby, B. and Hagberg, B. (1998) Lamotrigine in Rett syndrome: Treatment experience from a pilot study. *European Child and Adolescent Psychiatry*. **7**, 49-52
- Tao, J., Esch, H., Hagedorn-Greiwe, M., Hoffmann, K., Maser, B., Raynaud, M., Sperner, J., Fryns, J., Schwinger, E., Gecz, J., Ropers, H. and Kalscheur, V. (2004) Mutations in the X-Linked Cyclin-Dependent Kinase Like 5 (CDLK5/STK9) Gene are Associated with Severe Neurodevelopmental Retardation. *American Journal of Human Genetics*. **75**, 1149-1154
- Thirumalai, S., Abou-Khalil, B., Fakhoury, T. and Suresh, G. (2001) Video-EEG in the diagnosis of paroxysmal events in children with mental retardation and in children with normal intelligence. *Development Medicine and Child Neurology*. **43**, 731-734
- Wilfong, A. and Schultz, R. (2006) Vagus nerve stimulation for treatment of epilepsy in Rett syndrome. *Developmental Medicine and Child Neurology*. **48**, 683-686
- Zeev, B., Yaron, Y., Schanen, C., Wolf, H., Brandt, N., Ginot, N., Shomrat, R. and Orr-Urtreger. (2002) Rett syndrome: clinical manifestations in males with MeCP2 mutations. *Journal of Child Neurology*. **17**, 20-24