Emotion, behaviour and depression in Rett syndrome

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Rett syndrome is a neuro-developmental and behavioural disorder resulting from MECP-2 mutations. MECp2 mutations result in dysregulation of other gene expressions such as FXYD-1; and failure to curtail transcriptions of other genes. A direct effect is noted on neuromaturation resulting in poor brain growth and immaturity of brain stem function. These effects have been well documented showing neuroanatomical, physiological, biochemical and hormonal abnormalities which have a distinct effect on brain maturation resulting in cortical and autonomic disturbances. It is important that parents, physicians, therapists and teachers are well informed regarding these changes and the impact this has on emotions and behaviour in maturing people with Rett syndrome.

Emotion and behaviours change and evolve with in the growing child with Rett syndrome. From being a quiet, passive baby who sleeps more than other infants her age, sucks poorly and has a weak cry; parents report loss of acquired babbling or speech followed by decreased use of hand skills and onset of stereotypes such as rubbing and wringing their fingers and clapping their hands. Frequent and intermittent crossing of the eyes, irritability, agitation and screaming with hair pulling, biting or hitting occur with associated hyperactivity, rapid random pacing, and toe walking.

Sleep disturbances are accompanied by short periods of laughing or screaming and breathing problems become more obvious. Some people will breath hold and show significant bloating of their abdomen.

Older children demonstrate increasing intensity of gaze, loud moaning and screaming suggestive of distress. Adolescent Rett-people may present with moodiness, sleeplessness, poor appetite, loss of weight, lack of interest and unexplained crying; suggestive of possible depression.

Research in mutant mice reveals 25% reduction in total brain volume and in specific regions such as the amygdala, hippocampus, striatum and hypothalamus which are responsible for emotion, behaviour, attachment, anxiety and stress response. Norepinephrine, dopamine and more specifically serotonin play a major role in these regions and probably explain the emotional and behavioural changes. Younger children have transient elevation of lactates, pyruvates and alanine with low levels of carnitine suggesting metabolic stress which resolves but elevated levels of glutamine persist in the cerebrospinal fluid.

The biological underpinnings of emotional and behavioural disturbances probably result from dysfunctions in mono-aminergic systems secondary to genetic mutations and are age related. Neuropathological studies have shown high binding of serotonin type I and II receptors in the brainstem reflecting the immaturity of the neurons. Neurochemical changes in the synapses of cortical and subcortical regions of the brain and alterations in synaptic function further support possible mechanisms for behavioural disturbances.

Hypofunction of noradrenaline and serotonin are present as early as 36 weeks of gestational age and may explain placidity noted in infants and toddlers. Early behavioural changes are replaced by sleep disturbances, crying, irritability, followed by social withdrawal and loss of language and hand use. Subsequently, disruptive behaviours such as screaming, hair pulling, biting, hitting, pacing, anxiety, inattentiveness, and hyperactivity are reported in 5 to10-year-old Rett-people. This behaviour may also result from increased glutamate levels in early childhood.

It is well recognized that cortisol levels are elevated in anxiety and stress and elevated corticotrophin release factor (CRF) has also been documented in an RTT mouse model.

Other neurotransmitter abnormalities, such as elevated levels of B-endorphins and decreasing levels of biogenic amines with age, further support the biological basis for behaviour disorders in RTT.

Behaviours that may result from impaired autonomic nervous system include respiratory disturbances, agitation, panic-like attacks, disordered arousal and sleep, mood changes, intermittent strabismus, tremors, myoclonic jerks, abnormal motor activity, gastrointestinal dysfunction, vasomotor changes, cardiac irregularities, and fluctuating blood pressure.

Undesired behaviours may result from unrecognized medical conditions such as seizures, dental problems, ear infections, gastrointestinal reflux, constipation, gall stones, renal stones, fractures, dystonic spasms at night, menstrual discomfort, ovarian cysts, sleep apnea, and day-time sleepiness. Clinicians must remain alert in making a correct diagnosis before treating.

In maturing girls, depression is suspected based on history of sleeplessness, poor appetite, weight loss, and lack of interest in activities they previously enjoyed. Although other reasons for unexplained crying, sadness, and loneliness can result from changes in school, in care givers, loss of social contacts, and school peers, sometimes agitation and negative reaction can result from changes in daily routine and unrecognized abuse.

Some individuals using augmentative communication programs can assist providers in understanding their feelings and emotions. A knowledgeable team can assist in addressing these issues in the most effective way with the family, care provider, and staff at activity centres and make a major difference in the individual's life.

Management presents a challenge to the clinician who must consider not only the known neuro-physiological changes affecting emotion and behaviour but also determine whether there are underlying medical conditions aggravating these behaviours and treat them appropriately.

It is important to try nonmedical management and behaviour techniques before medications are instituted.

Experience has shown that non-invasive interventions may be effective. Small frequent snacks, soft music or a favourite video, deep pressure massage, warm baths or aquatic therapy, swings or sensory integration interventions using apple switches for people to make choices and use of elbow or hand splints can be beneficial. Often changing activity and giving the girls a break from routine such as a walk down the hall in school or taking a short stroll may be effective. Parents are wonderful resources in identifying activities that are effective. They are also excellent reporters and may be giving the clinician details that are important in leading them or the therapist to proper diagnosis and interventions. If a certain environment or activity triggers unwanted behaviours its simply managed, however, this information is not always available and may be difficult to identify.

In schools Applied Behaviour Analysis (ABA) is being used and its shown that it is effective in older Rett people in increasing communication and changing behaviour using eye gaze. It is time consuming and often used in schools. Some parents will adopt this approach if they are able to include it in their busy schedules.

When managing depression, the physician must remain cognizant in recognizing parental needs and possible depression in either or both parents which is more common and may remain unrecognized.

Hypothesis for using medications

It is well established that reduced Catecholamines in the brain are associated with abnormal synaptic function which is responsible for changes in mood and behaviour in Rett syndrome. This can be modified by medications that increase serotonin and norepinephrine at central synaptic sites.

Various medications are available for use, such as

1. Neuroleptics for self-injurious behaviour and may also help sleep:
   Risperdal, Seroquel, Geodon, Abilify, Orap, Zyprexa.

2. Anti-opioids e.g. naltrexone (Trexan or Revia)

3. Mood stabilizers e.g. Tegretol, Depakote

4. Antidepressants, e.g. SSRI (Selective Serotonin Reuptake Inhibitors): Celexa, Prozac
   SNRIs (Serotonin Norepinephrine Inhibitors) e.g. Effexor

5. Anxiolytics e.g. Serotonin 5-HT1 A agonist:Buspar (buspirone)
   Antihistamine: Atarax
   Benzodiazepines: Xanax, Tranxene, Valium (diazepam) Ativan (lorazepam)

6. For repetitive obsessive behaviours.
   Prozac (fluoxetine) Luvox (fluvoxamine), Celexa (citalopram), Zoloft (sertraline), Lexapro (escitalopram)

A team approach, including parents as team members is very effective in facilitating comprehensive treatment and management, and should be instituted as an optimal form of management as far as possible.