Rett Syndrome

An Overview

October 4, 2011

Objectives

- Medical expert:
  - Understanding of neuropathology and genetics of Rett Syndrome
  - Understanding of the clinical features and co-morbidities
  - Understanding of the work up and differential
- Collaborator:
  - Importance of the interdisciplinary team in the management of Rett Syndrome
- Scholar:
  - Review of recent research and RCT on folate treatment

Pervasive Developmental Disorders

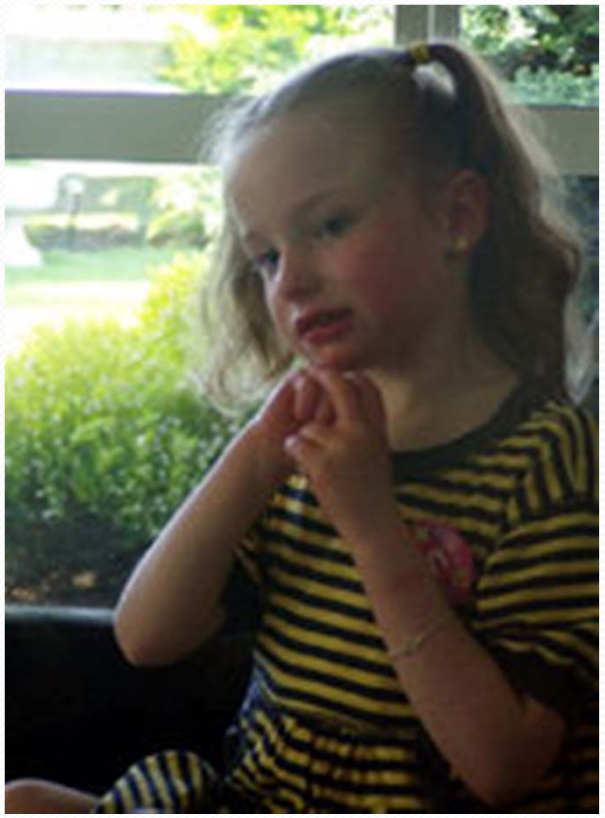
The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)

Autistic Disorder
Childhood disintegrative disorder
Rett Syndrome
Asperger disorder
Pervasive Developmental disorder Not Otherwise specified

http://www.medifitgroup.com/Rett%20Syndrome.htm

Rett Syndrome

- Neuro-developmental disorder
- Female predominance
- Characterized by:
  - Loss of speech
  - Stereotypical hand movements
  - Gait abnormalities
  - Autism features



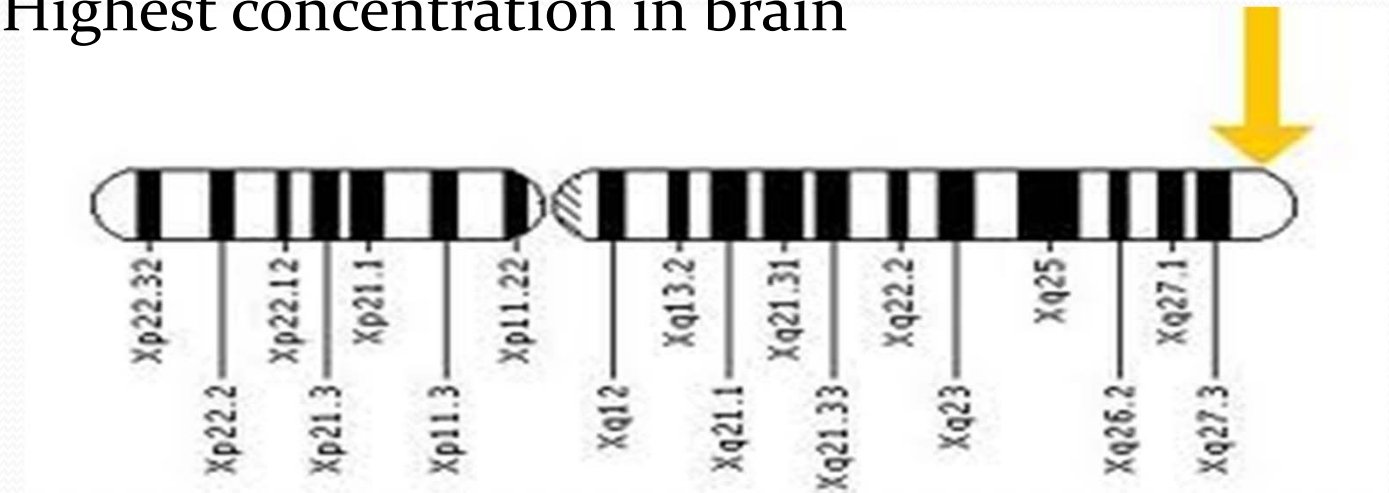
http://www.symptomsofirritablebowelsyndrome.com/rett-syndrome-symptoms.html

Epidemiology

- Prevalence 1: 22,800 between age of 2-18 years
- North American data base
  - Typical 1648
  - Atypical 259
- All racial/ ethnic groups affected equally
- No pregnancy risk factors
- Life expectancy age 45

The Genetics

- The Gene: MECP2 gene
- The Chromosome: xq28
- The protein: methyl-CpG- binding protein 2
  - Distributed throughout all tissues
  - Highest concentration in brain



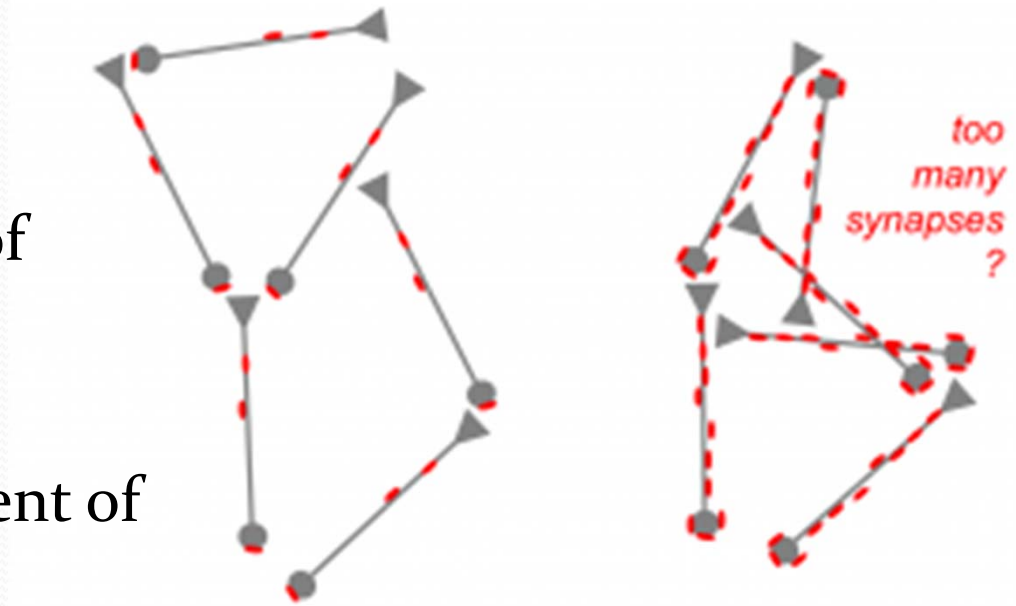
http://ghr.nlm.nih.gov/gene/MECP2

Neuro-pathophysiology

- http://www.youtube.com/watch?feature=player_embedded&v=eYrQoEhVCYA#!

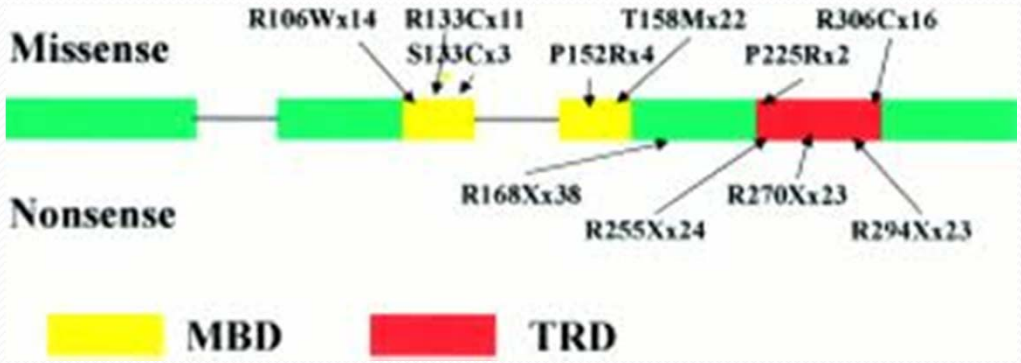
Outcome

- Gene dysregulation (over-expression)
- Decreased length of dendirite growth into cortex
- Defective expression of proteins that initiate expansion
- Possible defect of cytoskeleton component of cortex
- Deficiency of substance P
  - Autonomic dysfunction



More on genetics

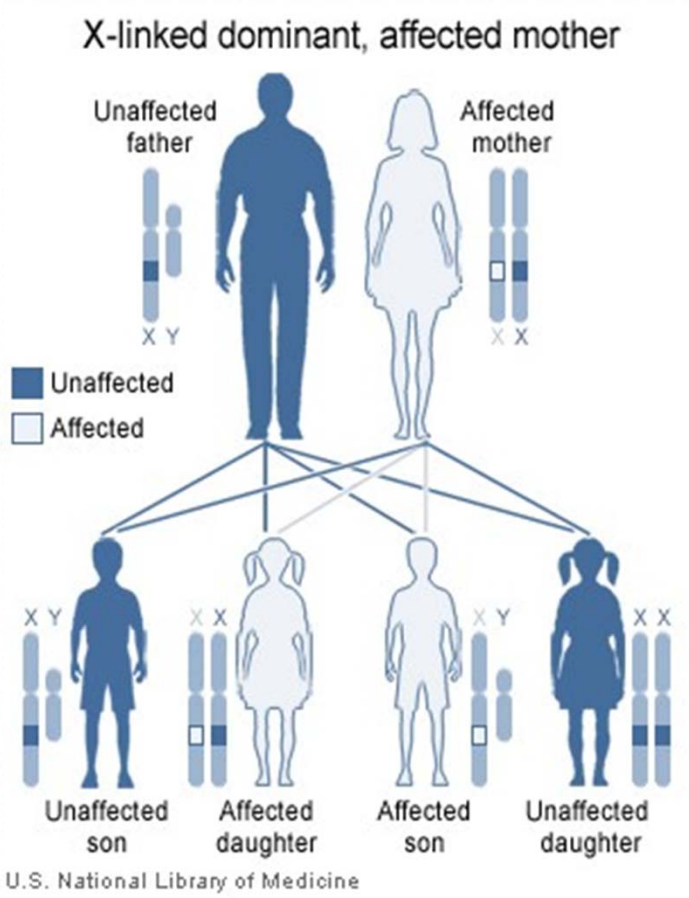
- Autosomal Dominant
- 99% de novo mutation
- X- inactivation random within all cells
  - Normal expression of protein in some cells
  - Genotype-phenotype variability
- Other genes: FOXG1, CDLK5
- MECP2 also related to:
  - Autism
  - X-linked MR
  - MECP2- related disorder



http://jmg.bmj.com/content/38/4/217.extract

What about the boys??

- MECP2 mutation in Rett Syndrome almost exclusively from paternal origin
- If boys do have MECP2 mutation is considered lethal
- Born with severe neonatal encephalopathy



The mutations:

Mutation	Phenotype
R106W	
R133C	Milder
T158M	More Severe
R168X	More Severe
R255X	More Severe
R270X	More Severe
R294X	Milder
R306c	
C-terminal mutation	Milder

The Features

- Stereotypical Hand Movements
  - Unique to each child!
  - Constant during day
  - Finger kneading
  - Clapping
  - Writhing

  - http://www.youtube.com/watch?v=53k1EsP5D8k

The Features

- Microcephaly
  - Brain growth stops at age 4
  - Deceleration of growth after birth
  - EARLIEST WARNING SIGN
  - Falls from 50%ile to <2%ile by age 4
  - Heart, kidney, liver, spleen arrest growth at 8-12 years
- Gait disturbance
  - Broad based
  - Clumsy, ataxic
  - Rock back and forth
- Extrapyramidal
  - Brusxism- 97%
  - Dystonia 59%
  - Excessive drooling 75%
  - Rigidity 44%

Stages

Stage 1

- Uneventful pregnancy
- Normal development up to 6 months
- Developmental arrest 6-18 month
- Can last months
- Less eye contact, less play
- Not as cuddly
- Decelerating head growth
- Unprovoked screaming episodes- TT

Stage 2

- Rapid deterioration and regression
- 1-4 years of age
- Can be acute or insidious
- Lose purposeful hand movements
- Develop hand stereotypes
- Develop breathing irregularities, sleep dysfunction
- Autistic behaviours

Stages

Stage 3

- Age 2-10
- Behaviours improve
- Can have less hand movements
- Improved communication – non verbal
- Seizures
- Gross motor changes

Stage 4

- Over age 10 usually
- Late motor deterioration
- Rigidity, bradykinesia, worsened mobility
- Stable communication
- Improved seizures

Co-morbidities

- Autonomic Dysfunction
  - Increased sympathetic tone: cold extremities
  - Apnea and hyperventilation during day
  - CARDIAC: electrical instability
    - Prolonged QTc (>0.45msec)
    - Increased rate of sudden death
- Sleep disturbances- 80%
  - Prolonged wakefulness, irregular sleep times

Co-morbidities

- Respiratory
  - Central apnea/ hyperventilation
  - 20-120 sec
  - Associated with hypoxemia/ cyanosis
  - Triggered by excitement/ agitation
  - Not present in sleep
- Scoliosis: 50-85%
- Feeding impairment
  - Oropharyngeal dysfunction
  - Upper GI dysmotility
  - GERD
- Growth failure: height and weight <5%ile by age 4-7

Co-morbidities

- Epilepsy
  - Between age 5-10: 60% will experience seizures
  - No new cases after 30
  - All seizure types: complex partial, tonic clonic
  - “breath-holding” spells- ?absence
  - Twitching/ falling/ trembling often mistaken for seizures
  - Abnormal EEG at age 2
    - Focal/multifocal epileptiform discharges
    - Theta activity in fronto-central regions

Diagnosis

Typical

- Meet all diagnostic criteria
  - A period of regression followed by recovery or stabilization
- The main criteria:
  - Partial or complete loss of acquired purposeful hand skills
  - Partial or complete loss of acquired spoken language
  - Gait abnormalities: impaired (dyspraxic) or absence of ability
  - Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms
- Exclusionary criteria for typical RTT are as follows
  - Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurologic problems
  - Grossly abnormal psychomotor development in first six months of life

Diagnosis

Atypical

- A period of regression followed by recovery or stabilization
  - Meet at least two of the four main criteria above
  - Meet at least 5 of the 11 supportive criteria below
- Supportive criteria for atypical RTT are the following
  - Breathing disturbances when awake
  - Bruxism when awake
  - Impaired sleep pattern
  - Abnormal muscle tone
  - Peripheral vasomotor disturbances
  - Scoliosis/kyphosis
  - Growth retardation
  - Small cold hands and feet
  - Inappropriate laughing/screaming spells
  - Diminished response to pain
  - Intense eye communication - “eye pointing”

Diagnosis

- Always do DNA MECP2
  - Consider FOXG1/ CDKL5
- If no MECP2 mutation
  - Brain MRI
  - Serum aa
  - Urine organic acids
  - cGH chromosome 15
  - Hearing tests
  - Vision testing
- Differential
  - ASD
  - Hearing impairment
  - PKU
  - Urea cycle disorder
  - Encephalitis
  - Leukodystrophies
  - Lennox-Gastaut
  - Angelman Syndrome

Management

- The team:
  - Neurology
  - Development
  - Orthopedics
  - GI
  - OT
  - PT
  - Swallowing team
  - Dietitian
  - Cardiologist
  - Pediatrician
- Nutrition:
  - High calorie supplements
  - Oral/G tube fed
  - OT: utensils, consistencies, positioning
- GI:
  - GERD treatment
  - Constipation: polyethylene glycol 3350 17g daily
  - Swallowing dysfunction

Management

- Neurology
  - Video EEG
  - Anti-epileptic medications
  - Education
- Breathing dysfunction
  - No improvement with oxygen
  - Some improvement with Naltrexone and Magnesium citrate

Management

- Cardiac
  - All need EEG
  - May require annual follow up
  - Avoid medications: tCA, erythromycin
- Sleep
  - Routines are crucial
  - Medication options: trazedone, melatonin, clonidine
- Parental Education
  - CPR
  - Fracture risk
  - Daytime routines
    - Avoid daytime sleep
    - No caffeine
    - Evening slow down
  - Reproductive Health

Management

- Motor:
  - Spasticity clinic
  - OT/ PT involvement
  - Goal to continue ambulation
  - ?hand elbow restraints – mixed study results
  - Music, horseback riding therapy

- Scoliosis:
  - 2009 guidelines: assess spine every 6 months
  - No improvement with bracing
  - Fusion if Cobb angle between 40-50 degrees

Study of the treatment of Rett Syndrome with Folate and Betaine

- P: 73 MECP2 mutation diagnosed with Typical Rett Syndrome
  - Split into groups age <5 and age >5
- I: Treated with Folate and Betaine for 12 months
  - Double blind, placebo controlled RCT
- C: clinical assessments at 3, 6 and 12 months
  - Assessed breathing, hand movements, growth, motor skills, EEG and parent questionnaires
- O: No significant improvements found

Questions????

Thank you!

References:

Pervasive Developmental Disorders. In: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision (DSM-IV-TR®). American Psychiatric Association, Washington, DC 2000. p.70

Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. Ann Neurol 2010; 68:944.

Rett A. [On a unusual brain atrophy syndrome in hyperammonemia in childhood]. Wien Med Wochenschr 1966; 116:723.

Schultz R, Glaze D, Patterson M, Firth H et al. Rett Syndrome. UpToDate. May 2011.

Amir RE, Van den Veyver IB, Wan M, et al. Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2. Nat Genet 1999; 23:185.

Allen RC, Zoghbi HY, Moseley AB, et al. Methylation of HpaII and HhaI sites near the polymorphic CAG repeat in the human androgen-receptor gene correlates with X chromosome inactivation. Am J Hum Genet 1992; 51:1229.

Percy AK, Lane JB, Childers J, et al. Rett syndrome: North American database. J Child Neurol 2007; 22:1338.

Percy AK, Neul JL, Glaze DG, et al. Rett syndrome diagnostic criteria: lessons from the Natural History Study. Ann Neurol 2010; 68:951.

Trappe R, Laccone F, Cobilanschi J, et al. MECP2 mutations in sporadic cases of Rett syndrome are almost exclusively of paternal origin. Am J Hum Genet 2001; 68:1093.

Wan M, Lee SS, Zhang X, et al. Rett syndrome and beyond: recurrent spontaneous and familial MECP2 mutations at CpG hotspots. Am J Hum Genet 1999; 65:1520.

Orrico A, Lam C, Galli L, et al. MECP2 mutation in male patients with non-specific X-linked mental retardation. FEBS Lett 2000; 481:285.

Meloni I, Bruttini M, Longo I, et al. A mutation in the rett syndrome gene, MECP2, causes X-linked mental retardation and progressive spasticity in males. Am J Hum Genet 2000; 67:982.

Villard L, Kpebe A, Cardoso C, et al. Two affected boys in a Rett syndrome family: clinical and molecular findings. Neurology 2000; 55:1188.

Clayton-Smith J, Watson P, Ramsden S, Black GC. Somatic mutation in MECP2 as a non-fatal neurodevelopmental disorder in males. Lancet 2000; 356:830.

Moog U, Van Roozendaal K, Smeets E, et al. MECP2 mutations are an infrequent cause of mental retardation associated with neurological problems in male patients. Brain Dev 2006; 28:305.

Ohki I, Shimotake N, Fujita N, et al. Solution structure of the methyl-CpG binding domain of human MBD1 in complex with methylated DNA. Cell 2001; 105:487.

References

Traynor J, Agarwal P, Lazzeroni L, Francke U. Gene expression patterns vary in clonal cell cultures from Rett syndrome females with eight different MECP2 mutations. BMC Med Genet 2002; 3:12.

Christodoulou J, Grimm A, Maher T, Bennetts B. RettBASE: The IRSA MECP2 variation database-a new mutation database in evolution. Hum Mutat 2003; 21:466.

Colvin L, Leonard H, de Klerk N, et al. Refining the phenotype of common mutations in Rett syndrome. J Med Genet 2004; 41:25.

Bebbington A, Anderson A, Ravine D, et al. Investigating genotype-phenotype relationships in Rett syndrome using an international data set. Neurology 2008; 70:868.

Neul JL, Fang P, Barrish J, et al. Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome. Neurology 2008; 70:1313.

Archer H, Evans J, Leonard H, et al. Correlation between clinical severity in patients with Rett syndrome with a p.R168X or p.T158M MECP2 mutation, and the direction and degree of skewing of X-chromosome inactivation. J Med Genet 2007; 44:148.

Zhang Y, Minassian BA. Will my Rett syndrome patient walk, talk, and use her hands? Neurology 2008; 70:1302.

Armstrong DD, Dunn JK, Schultz RJ, et al. Organ growth in Rett syndrome: a postmortem examination analysis. Pediatr Neurol 1999; 20:125.

Kozinetz CA, Skender ML, MacNaughton N, et al. Epidemiology of Rett syndrome: a population-based registry. Pediatrics 1993; 91:445.

Hagberg B, Witt-Engerström I. Rett syndrome: epidemiology and nosology--progress in knowledge 1986--a conference communication. Brain Dev 1987; 9:451.

Einspieler C, Kerr AM, Prechtl HF. Is the early development of girls with Rett disorder really normal? Pediatr Res 2005; 57:696.

Hagberg G, Stenbom Y, Witt Engerström I. Head growth in Rett syndrome. Acta Paediatr 2000; 89:198.

Temudo T, Oliveira P, Santos M, et al. Stereotypies in Rett syndrome: analysis of 83 patients with and without detected MECP2 mutations. Neurology 2007; 68:1183.

FitzGerald PM, Jankovic J, Percy AK. Rett syndrome and associated movement disorders. Mov Disord 1990; 5:195.

Colvin L, Fyfe S, Leonard S, et al. Describing the phenotype in Rett syndrome using a population database. Arch Dis Child 2003; 88:38.

Ager S, Fyfe S, Christodoulou J, et al. Predictors of scoliosis in Rett syndrome. J Child Neurol 2006; 21:809.

References

Percy AK, Lee HS, Neul JL, et al. Profiling scoliosis in Rett syndrome. Pediatr Res 2010; 67:435.

Stokland, E, Lidström, J, Hagberg, B. Scoliosis in Rett syndrome. In: Clinical and Biological Aspects, Hagberg, B (Ed), MacKeith Press, London 1993. p.61.

Schultz RJ, Glaze DG, Motil KJ, et al. The pattern of growth failure in Rett syndrome. Am J Dis Child 1993; 147:633. 666Morton RE, Bonas R, Minford J, et al. Feeding ability in Rett syndrome. Dev Med Child Neurol 1997; 39:331.

Budden SS. Management of Rett syndrome: a ten year experience. Neuropediatrics 1995; 26:75.

Budden SS. Rett syndrome: studies of 13 affected girls. Am J Med Genet Suppl 1986; 1:99.

Rice MA, Haas RH. The nutritional aspects of Rett syndrome. J Child Neurol 1988; 3 Suppl:S35.

Thommessen M, Heiberg A, Kase BF, et al. Feeding problems, height and weight in different groups of disabled children. Acta Paediatr Scand 1991; 80:527.

Thommessen M, Kase BF, Heiberg A. Growth and nutrition in 10 girls with Rett syndrome. Acta Paediatr 1992; 81:686.

Motil KJ, Schultz RJ, Browning K, et al. Oropharyngeal dysfunction and gastroesophageal dysmotility are present in girls and women with Rett syndrome. J Pediatr Gastroenterol Nutr 1999; 29:31.

Glaze DG, Percy AK, Skinner S, et al. Epilepsy and the natural history of Rett syndrome. Neurology 2010; 74:909.

Steffenburg U, Hagberg G, Hagberg B. Epilepsy in a representative series of Rett syndrome. Acta Paediatr 2001; 90:34.

Guideri F, Acampa M, Hayek G, et al. Reduced heart rate variability in patients affected with Rett syndrome. A possible explanation for sudden deat. Neuropediatrics 1999; 30:146.

Glaze DG, Frost JD Jr, Zoghbi HY, Percy AK. Rett's syndrome: characterization of respiratory patterns and sleep. Ann Neurol 1987; 21:377.

Kerr AM. Early clinical signs in the Rett disorder. Neuropediatrics 1995; 26:67.

Glaze DG, Schultz RJ, Frost JD. Rett syndrome: characterization of seizures versus non-seizures. Electroencephalogr Clin Neurophysiol 1998; 106:79.

Haas RH, Dixon SD, Sartoris DJ, Hennessy MJ. Osteopenia in Rett syndrome. J Pediatr 1997; 131:771.

Kerr AM, Armstrong DD, Prescott RJ, et al. Rett syndrome: analysis of deaths in the British survey. Eur Child Adolesc Psychiatry 1997; 6 Suppl 1:71.

Glaze DG, Frost JD Jr, Zoghbi HY, Percy AK. Rett's syndrome. Correlation of electroencephalographic characteristics with clinical staging. Arch Neurol 1987; 44:1053.

References

Hiatt, PW, Glaze, DG, Frost, JD Jr. Air flow obstruction in children with Rett Syndrome. Ann Neurol 1989; 26:487 (abstract).

Young D, Nagarajan L, de Klerk N, et al. Sleep problems in Rett syndrome. Brain Dev 2007; 29:609.

Hagberg B, Hanefeld F, Percy A, Skjeldal O. An update on clinically applicable diagnostic criteria in Rett syndrome. Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001. Eur J Paediatr Neurol 2002; 6:293.

Hagberg B, Witt-Engerström I. Rett syndrome: a suggested staging system for describing impairment profile with increasing age towards adolescence. Am J Med Genet Suppl 1986; 1:47.

Noutel J, Hong YK, Leu B, et al. Experience-Dependent Retinogeniculate Synapse Remodeling Is Abnormal in MeCP2-Deficient Mice. Neuron 2011; 70:35.

Glaze DG, Percy AK, Motil KJ, et al. A study of the treatment of Rett syndrome with folate and betaine. J Child Neurol 2009; 24:551.

Downs J, Bergman A, Carter P, et al. Guidelines for management of scoliosis in Rett syndrome patients based on expert consensus and clinical evidence. Spine (Phila Pa 1976) 2009; 34:E607.

Piazza CC, Fisher W, Moser H. Behavioral treatment of sleep dysfunction in patients with the Rett syndrome. Brain Dev 1991; 13:232.

Ferber, R, Kryger, M. Principles and Practice of Sleep Medicine in the Child, 1st ed, WB Saunders, Philadelphia 1995.

Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. Lancet 1998; 351:1254.

Hanks SB. Motor disabilities in the Rett syndrome and physical therapy strategies. Brain Dev 1990; 12:157.

International Rett Syndrome Association, Educational and Therapeutic Intervention in Rett Syndrome, 2nd ed, 1995.

Sharpe PA. Comparative effects of bilateral hand splints and an elbow orthosis on stereotypic hand movements and toy play in two children with Rett syndrome. Am J Occup Ther 1992; 46:134.

Naganuma GM, Billingsley FF. Effect of hand splints on stereotypic hand behavior of three girls with Rett syndrome. Phys Ther 1988; 68:664.

Aron M. The use and effectiveness of elbow splints in the Rett syndrome. Brain Dev 1990; 12:162.

Kirby RS, Lane JB, Childers J, et al. Longevity in Rett syndrome: analysis of the North American Database. J Pediatr 2010; 156:135.

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