Todays talk

• General management recommendations once diagnosis made
  – Helpful local lead clinician (GP, Paed) essential
  – Team approach

• Focus on HSCR, seizures, communication, behaviour and sleep

• Gaps in knowledge, future research
Mowat-Wilson syndrome

D R Mowat, M J Wilson and M Goossens

*J. Med. Genet.* 2003;40;305-310
doi:10.1136/jmg.40.5.305

Updated information and services can be found at:
http://jmg.bmj.com/cgi/content/full/40/5/305

These include:

**References**
This article cites 25 articles, 6 of which can be accessed free at:
http://jmg.bmj.com/cgi/content/full/40/5/305#BIBL

7 online articles that cite this article can be accessed at:
http://jmg.bmj.com/cgi/content/full/40/5/305#otherarticles

**Rapid responses**
You can respond to this article at:
http://jmg.bmj.com/cgi/eletter-submit/40/5/305

**Email alerting service**
Receive free email alerts when new articles cite this article - sign up in the box at the top right corner of the article
Clinical Features and Management Issues in Mowat–Wilson Syndrome

Margaret P. Adam,1* Susan Schelley,2 Renata Gallagher,2 April N. Brady,1 Kimberly Barr,3 Bruce Blumberg,3 Joseph T.C. Shieh,2 John Graham,4 Anne Slavotinek,5 Madelena Martin,5 Kim Keppler-Noreuil,6 Andrea L. Storm,7 and Louanne Hudgens2

1Department of Human Genetics, Emory University School of Medicine, Atlanta, Georgia
2Department of Pediatrics, Division of Medical Genetics, Stanford University School of Medicine, Stanford, California
3Division of Medical Genetics, Kaiser Permanente, San Francisco, California
4Division of Medical Genetics, Cedars-Sinai Medical Center, Los Angeles, California
5Department of Pediatrics, Division of Genetics, University of California San Francisco, School of Medicine, San Francisco, California
6Department of Pediatrics, Division of Medical Genetics, University of Iowa Hospitals and Clinics, Iowa City, Iowa
7Genetic Medicine, Children’s Hospital Central California, Madera, California

Received 24 March 2006; Accepted 7 September 2006

2013 update Genereviews on MWS by Dr Margaret Adams
Mowat-Wilson syndrome is a recently delineated mental retardation/multiple congenital anomaly syndrome, characterized by typical facies, severe mental retardation, epilepsy, and variable congenital malformations including Hirschsprung disease, congenital heart defects, urogenital anomalies (hypoplasia), and agenesis of the corpus callosum. Mowat et al. (1998) first described the syndrome in a series of six children with mental retardation and strikingly similar facial features. In 2001, two groups independently identified the underlying cause of Mowat-Wilson syndrome as mutations or deletions in the zinc finger E-box-binding homeobox 2 gene, ZEB2 (previously called ZFHX1B or SIP1; MIM# 608851) located at chromosome 2q22. Early diagnosis, particularly in the absence of Hirschsprung disease, is important for early intervention and multidisciplinary management. Although the exact incidence of Mowat-Wilson syndrome is unknown, based on the authors’ experience and the medical literature, we believe that incidence is at least 1 in 70,000. Management is symptomatic, including surgical correction of Hirschsprung disease and hypoplasia, anticonvulsant therapy for epilepsy, and standard interventions for developmental disabilities with an emphasis on promoting communication.

INTRODUCTION

Mowat-Wilson syndrome (MIM# 235730) is a recently delineated mental retardation/multiple congenital anomaly syndrome, characterized by typical facies, severe mental retardation, epilepsy, and variable congenital malformations including Hirschsprung disease, congenital heart defects, urogenital anomalies (hypoplasia), and agenesis of the corpus callosum. Mowat et al. (1998) first described the syndrome in a series of six children with mental retardation and strikingly similar facial features. In 2001, two groups independently identified the underlying cause of Mowat-Wilson syndrome as mutations or deletions in the zinc finger E-box-binding homeobox 2 gene, ZEB2 (previously called ZFHX1B or SIP1; MIM# 608851) located at chromosome 2q22. Early diagnosis, particularly in the absence of Hirschsprung disease, is important for early intervention and multidisciplinary management. Although the exact incidence of Mowat-Wilson syndrome is unknown, based on the authors’ experience and the medical literature, we believe that incidence is at least 1 in 70,000. Management is symptomatic, including surgical correction of Hirschsprung disease and hypoplasia, anticonvulsant therapy for epilepsy, and standard interventions for developmental disabilities with an emphasis on promoting communication.

INTRODUCTION

Mowat-Wilson syndrome (MIM# 235730) is a recently delineated mental retardation/multiple congenital anomaly syndrome, characterized by typical facies, severe mental
MWS Clinic

• Dr David Mowat and A/Prof Meredith Wilson
• Associate Genetic Counsellor (Bec MacIntosh)
• Dr John Lawson (Paediatric Neurologist)
• Dr Susan Adams (Paediatric Surgeon)
• Dr Liz Evans (Clinical Psychologist)
• Jenny Woods (Speech Therapist)
• Physiotherapist/ Occupational therapist
• Sleep physician
Evaluation at initial diagnosis:
To establish the extent of disease

- Baseline echocardiogram
- Baseline dental evaluation in early childhood
- Baseline ophthalmology evaluation
- Baseline audiology evaluation
- History of chronic constipation
- History of seizures
- Renal ultrasound examination to assess for structural renal anomalies
- Genitourinary evaluation, particularly for hypospadias and undescended testes in males
- Physical examination for chest anomalies and foot/ankle malpositioning
Treatment of Manifestations

- **Neurologic.** Referral to a pediatric neurologist if signs or symptoms suggest seizures. An EEG and/or head MRI may be warranted for diagnostic purposes or refractory seizures. Standard anti-epileptic drugs (AEDs) should be used, as indicated.

- **Developmental.** Educational intervention and speech therapy beginning in infancy because of the high risk for motor, cognitive, speech, and language delay.

- **Ophthalmologic.** Treatment and/or following of ocular abnormalities by a pediatric ophthalmologist.

- **Cardiovascular.** Referral to a cardiologist or cardiothoracic surgeon for treatment of congenital heart defects.

- **Gastrointestinal.** Referral to a gastroenterologist for evaluation and treatment when chronic constipation is present; evaluation for HSCR and ultrashort HSCR.

- **Genitourinary.** Referral to a urologist or nephrologist as indicated.

- **Musculoskeletal.** Referral to an orthopedist for significant pectus anomalies of the chest and/or foot/ankle anomalies.

- **Dental.** Referral to an orthodontist if significant dental anomalies are present.
Surveillance

• Annual eye examination in childhood to monitor for strabismus and refractive errors
• Monitoring for the development of otitis media (OM); for those individuals with chronic OM, referral to an otolaryngologist
• Regular developmental behavioural assessments to plan and refine educational/communication needs
Hirschsprung in MWS

- Present in 40-60%
- Constipation common, needs investigation
- Other gut motility problems – reflux, dysphagia
- Only one study Bonnard et al 2009 J Ped Surg and two other case reports
- 5 patients with MWS/HSCR in a cohort of 110 HCSR cases
More data needed

- Some people with MWS have a stormy course from the gut problems
- Tube feeds
- Parenteral nutrition
- Long term ileostomy
- Manage of HSCR in the setting of MWS is more complex but a good outcome is possible
Incontinence and psychological problems in persons with Mowat-Wilson Syndrome
- study information for parents and caregivers -

J. Niemczyk, M. Equit, A. von Gontard
Department of Child and Adolescent Psychiatry, Saarland University Hospital, Homburg, Germany

L. Rice, S. Einfeld
Department of Medical Genetics, Sydney Children's Hospital, NSW, Australia

D. Mowat
Centre for Disability Research and Policy, Brain and Mind Research Institute, University of Sydney, Sydney, NSW, Australia

L. Evans
Department of Developmental Disability Neuropsychiatry, School of Psychiatry, University of New South Wales, Sydney, NSW, Australia
Introduction

• Children with intellectual and physical disabilities are more affected by psychological problems and incontinence than typically developing children

• These problems are often overlooked in children with special needs although they can be treated effectively with standard therapy methods
What do we know about incontinence in Mowat-Wilson Syndrome?

- Attaining of bladder and bowel training is generally delayed in children with intellectual disability (ID)
  - About 30-40% of 7-year-old children with severe ID have daytime or nighttime wetting and/or soiling (von Wendt et al., 1990)
- Children with Mowat-Wilson Syndrome (MWS) are often affected by anomalies of the gastrointestinal and urogenital tract
  - e.g. Hirschsprung disease, hypospadia, reflux, urinary retention
- No information on incontinence rates in children with MWS available yet
Methods

– Parental Questionnaire: Enuresis/Urinary Incontinence
  • Questions about incontinence, toileting behavior, eating, drinking

– Developmental Behavior Checklist
  • Questions about behavioral and emotional problems, e.g. anxiety, attention problems, stereotyped behavior

• Estimated time: 20 min
Preliminary data
of 6 families with a child affected by MWS

• 4 boys, 2 girls, 4-13 years (mean age 10.4 years)

• All 6 children were affected by at least one subtype of incontinence
  – 4 children had nighttime wetting (nocturnal enuresis)
  – 5 children had daytime wetting (daytime urinary incontinence)
  – 4 children had fecal incontinence

• No child showed an score in the clinical range for overall behavioral and psychological problems
  – 2 children had a clinically relevant score for “anxiety”

• Physical disabilities and anomalies of the gastrointestinal and the urogenital tract
  – Seizures (83.3%)
  – Congenital heart defects (50%)
  – Hirschsprung disease (83.3%)
  – Hypospadia (33.3%)
  – Vesicoureteral reflux (16.7%)
Contact

If you would like to participate in the presented study, please contact:

Justine Niemczyk  
Research psychologist  
Department of Child and Adolescent Psychiatry  
Saarland University Hospital  
Homburg, Germany  

Mail to: justine.niemczyk@uks.eu
Seizures in MWS – 70-75%

- No systematic review.
- “no particular seizure type is characteristic of the disorder”
- Age of onset: neonate – 9.5yrs
- Seizure types:
  - Absences
  - Generalised
  - Myoclonic
- Natural history and treatment not well described

Adam MP et al Am J Med Genetics 2006, 140A

Mowat et al J Med Genetics 2003, 40
Epilepsy in Mowat–Wilson Syndrome: Delineation of the Electroclinical Phenotype

Duccio Maria Cordelli,1* Livia Garavelli,2 Salvatore Savasta,3 Azzurra Guerra,4 Alessandro Pellicciari,1 Lucio Giordano,5 Silvia Bonetti,1 Ilaria Cecconi,1 Anita Wischmeijer,2,6 Marco Seri,6 Simonetta Rosato,2 Chiara Gelmini,2 Elvio Della Giustina,7 Anna Rita Ferrari,8 Nicoletta Zanotta,9 Roberta Epifanio,9 Daniele Grioni,10 Baris Malbora,11 Isabella Mammi,12 Francesca Mari,13 Sabrina Buoni,14 Rosa Mostardini,15 Salvatore Grosso,15 Chiara Pantaleoni,16 Morena Doz,16 Maria Luisa Poch-Olivé,17 Francesca Rivieri,18 Giovanni Sorge,19 Graziella Simonte,19 Francesca Licata,19 Luigi Tarani,20 Emanuela Terazzi,21 Laura Mazzanti,22 Paola Cerruti Mainardi,23 Antonella Boni,24 Francesca Faravelli,25 Marina Grasso,26 Paolo Bianchi,27 Marcella Zollino,28 and Emilio Franzoni1

1Child Neurology and Psychiatry Unit, S Orsola Malpighi Hospital, University of Bologna, Italy
2Clinical Genetics Unit, Istituto di Ricovero e Cura a Carattere Scientifico, Arcispedale, S. Maria Nuova, Reggio Emilia, Italy
Cordelli et al 2012

• 22 patients (retrospective)
• All had at least one seizure
• Mean age 9.8 yrs (2-22 yrs)
• seizure onset, seizure types, evolution of epilepsy, anti-epileptic therapy, and EEG features in 22 patients (9 males and 13 females)
• Serial EEGs
22 patients

- Mean onset 14 months (1-108)
- All except one by age 5 yrs
- First seizure focal in all
- 15/22 trigger fever
- Sporadic or frequent
- Mostly when drowsy or asleep
- 13 developed atypical absence seizures usually after 4 yrs of age
  - a brief alteration of consciousness and behavior variably associated with subtle motor or orobuccal automatisms.
• Range of anticonvulsants used
• No correlation with MRI findings or structural malformations
• EEG and natural history suggests a genetic basis of the epilepsy
• ZEB2 affects GABA interneurons
• Opens up possibility of targeted treatment for seizures
A Sip of GABA for the Cerebral Cortex

Giulio S. Tomassy,¹,² Simona Lodato,¹,² and Paola Arlotta¹,*
¹Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA 02138, USA
²These authors contributed equally to this work
*Correspondence: paola_arlotta@harvard.edu
http://dx.doi.org/10.1016/j.neuron.2012.12.026

Cortical and striatal interneurons are both generated within the ventral telencephalon, but their migratory journey takes them to very different destinations. Two articles in this issue (van den Berghe et al., 2013; McKinsey et al., 2013) add an important molecular component to our understanding of how, during development, interneurons reach the cerebral cortex.
Figure 1. Sip1 Is Required for Cortical Interneuron Differentiation and Migration to the Cerebral Cortex
Small Epilepsy Survey 2010/11

Dr Gabby Dabscheck (Neurology fellow)
Dr John Lawson (Paediatric Neurologist)

• Approval from research ethics committee
• Thirteen unselected MWS cases known to Drs Mowat and Wilson
• Family/ carer contacted directly by telephone
• A consent form and participant letter was sent to the family
• Telephone interview and questionnaire
Results (1)

- Of 13 eligible patients one refused consent.
- The age range of the patients was 3 to 30 years of age with a median age of 17 years.
- Seizures affected 11 out of 12 patients (one unaffected patient was three years old.)
- Ten out of 12 patients had epilepsy onset before four years, with none less than three months.
Results (2)

• Epilepsy was at its most severe between one and four years.

• Six patients had at least one prolonged seizure (status epilepticus)

• Four reported generalised seizures, eight had complex partial seizures.

• Seven patients had atypical absences
Results (3)

- Seven patients had multiple seizure types.
- Five of the 11 patients were not currently taking anti-epileptic medication.
- Seven of 11 patients were seizure free.
- Two patients last seizures were at three to four years of age and three patients were at the age of 15 – 16.
- The most commonly prescribed medications were Valproate and Carbamazepine. The majority of carers reported that these medications provided little benefit.
Conclusion

• Clinicians should be aware that patients with MWS have a broad range of epilepsy
• More research needs to be done to see whether specific anti-epileptic medications are effective in patients with MWS
• Sleep and awake serial EEGs may be helpful
Development and Cognition in Mowat Wilson syndrome

Dr Liz Evans (PhD)
University of New South Wales
Development and Behaviour

• Case reports suggest:
  – least moderate but usually severe ID
  – Receptive language > Expressive language
  – Delayed motor milestones
  – Placid, affectionate, happy nature, smiling

• First systematic study of this topic
The Behavioral Phenotype of Mowat–Wilson Syndrome

Elizabeth Evans,1,2* Stewart Einfeld,2,3 David Mowat,4 John Taffe,5 Bruce Tonge,5 and Meredith Wilson6

1Department of Developmental Disability Neuropsychiatry, School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia
2Faculty of Health Sciences, University of Sydney, Sydney, New South Wales, Australia
3Brain and Mind Research Institute, University of Sydney, Sydney, New South Wales, Australia
4Department of Medical Genetics, Sydney Children’s Hospital and the School of Women’s and Children’s Health, University of New South Wales, Sydney, New South Wales, Australia
5Centre for Developmental Psychology and Psychiatry, Monash Medical Centre, Monash University, Monash, Victoria, Australia
6Department of Clinical Genetics, The Children’s Hospital at Westmead and Disciplines of Medical Genetics and Paediatrics and Child Health, University of Sydney, Sydney, New South Wales, Australia

Received 25 February 2011; Accepted 29 October 2011

Mowat–Wilson syndrome (MWS) is caused by a heterozygous mutation or deletion of the ZEB2 gene. It is characterized by a distinctive facial appearance in association with intellectual disability (ID) and variable other features including agenesis of the corpus callosum, seizures, congenital heart defects, microcephaly, short stature, hypotonia, and Hirschsprung disease. The current study investigated the behavioral phenotype of MWS.

How to Cite this Article:
Why research behaviour?

- Gene-brain-behaviour pathways
- Develop appropriate interventions and care
- Better understanding of a child’s behaviour alleviates anxiety and helps parents and teachers.
Aims of the MWS study

• To investigate the behavioural phenotype of MWS.
  – How do people with MWS develop?
    • What can they do for themselves?
    • Are there specific strengths and weaknesses?
  – Compared to those with ID from other causes, is there a difference in terms of:
    • Social behaviours
    • Mood, well being
    • Any other specific behaviours?
Participants

• Age range: 15 months – 51 years
• From Australia, USA, UK, Germany, Italy, France, Japan, Canada, UAE, Belgium, Netherlands.
• Controls:
  – N = 122
  – Matched for age and ID level
Measures & Methods

Questionnaires
N = 71
- MWS Questionnaire
- DBC *
- EAS *
- BIAS

Carer Interviews
N = 39
- VABS
- REEL3
- MESSIER
- GARS2
- Unstructured

Assessments
N = 30
- GMDS
- PPVT-III; K-BIT2
- Qualitative language assessment

Sleep Screen
N = 35
- SDSC
Results: Development & Language

• Range of Developmental/Intellectual Disability
  – At least moderate
  – Usually Severe – Profound

• Receptive language slightly better than expressive
  – Augmented communication can be successful

• Strength in Social Skills

• Weakness in Daily Living Skills

• Small increases in skills with increased age
Results: Behaviours

Developmental Behaviour Checklist:
• N = 61 MWS; N = 122 Controls
  – Affect
  – Sociability
  – Oral behaviours
  – Stereotyped behaviours
  – Under-reaction to pain

• Overall level of behaviour problems:
  – Similar to controls
  – 30% = clinically significant levels of behaviour and emotional problems

• ↓ on social relating subscale
Language skills in MWS


• The majority of people with Mowat-Wilson syndrome are non verbal.
• One third of the group (group=61 individuals) could speak at least one word. A small number (2) had at least 200 words.
• Average age of onset of speech was 4 years 4 months.
• Some people communicated using alternative communication, e.g. signing, pictures, communication device.
• Other non-verbal communication methods included body movements, eye gaze.
• Receptive language skills were slightly better than expressive language.
Results: Sleep

• Unstructured data:
  – Early waking
  – Night-time waking

• Sleep Disturbance Scale for Children, N=35
  – 43% in the “clinical disorder” range
  – 54% in the “borderline disorder” range
  – Sleep-wake transition disorders most common
Items more often in the MWS group than Contrast group

- Chews or mouths objects or body parts
- Eats non-food items (e.g., dirt, grass, soap)
- Flicks, taps, twirls objects
- Grinds teeth
- Switches lights on and off or other repetitive activity
- Stands too close to others
- Under-reacts to pain
- Unrealistically happy or elated
Items less often in the MWS group than Contrast group

- Appears depressed, downcast, or unhappy
- Cries easily for no reason, or over small upsets
- Doesn’t show affection
- Mood changes rapidly for no apparent reason
- Laughs or giggles for no obvious reason
- Prefers to do things on his or her own. Tends to be a loner
- Whines or complains a lot
Other Results: Unstructured data

- Page flipping
- Love of paper
- Feeding difficulties
- Drooling
- Strabismus
  - ? relationship to fine motor problems
- “Tactile defensive”
Implications for management of MWS from study

• Assess vision – correct strabismus
• Be aware of under-reaction to pain
  – Makes assessing medical emergencies harder
  – May mean further injury/worsening of illness possible
• Screen for, and treat, sleep disorders
• Oral behaviours:
  – Special safe “chewy” toy
  – Behaviour modification techniques
  – Teach to swallow or wipe drool
• Teach augmented communication:
  – and tailor it to person and their behaviours
• Awareness of potential for behaviour problems
Research

- Interventions for communication and mobility
- Milder forms of MWS with milder mutations
- More understanding of the gastrointestinal features of MWS
- More understanding on epilepsy
- Neuroimaging (MRI, other)
- Understanding the role of ZEB2 gene in neuronal development
Resources - HSCR

- [http://www.nationwidechildrens.org/colorectal-pelvic-reconstruction-center](http://www.nationwidechildrens.org/colorectal-pelvic-reconstruction-center)
- Cincinnati children's coelectoral centre - [www.cincinnatichildrens.org](http://www.cincinnatichildrens.org)
- [www.aboutkidsgi.org/](http://www.aboutkidsgi.org/)
MWS

- Website for families affected by MWS: [www.mowatwilson.org](http://www.mowatwilson.org)
- French forum for families: [http://smwf.forumactif.org/](http://smwf.forumactif.org/)
- Italian support group: [http://www.mowatwilson.it/](http://www.mowatwilson.it/)
Questions?
Consistent Clinical features 100%

- Facial gestalt
- *Developmental delay, usually severe.*
- No regression
- *Speech* impairment, none or minimal use words: receptive and nonverbal communication skills higher than verbal ones
Frequent clinical features (>80%)

- Microcephaly
- **Seizures** (70-75%)
- Constipation
- **Behaviour** distinct, happy demeanour, social orientated, Great observers
- Late walkers
Associated clinical features (20-80%)

- **Hirschsprung disease**, usually diagnosed shortly after birth, but late diagnosis of short segment HSCR possible
- Congenital Heart Disease, wide spectrum, pulmonary artery sling with or without tracheal stenosis
- Urogenital/renal anomalies/ hypospadius
- Short stature
- Hypoplasia or agenesis of Corpus callosum
- **Sleep disturbance**
Recognised but uncommon (<10%)

- Reflux oesophagitis/ dysphagia
- Pyloric stenosis
- Strabismus
- Structural Eye anomalies
- Cleft lip/palate/ choanal atresia
- Hypopigmented confetti-like skin
- Autonomic dysfunction
- Asplenia
- Duplicated hallux
- Neuronal migration disorder e.g. pachygyria
MWS Family day

- Opportunity for Australian families to meet
- Review web based information and support
- Medical/ Genetics/ Behavioural update
- Management Guidelines
- Speech and Communication
- Mobility and Epilepsy
- Gastrointestinal issues including feeding
- Adolescent and young adult with MWS
Hirschsprung in MWS

Normal sigmoid colon and rectum

Area affected by Hirschprung's disease