Psychological Aspects of Fragile X Syndrome

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Developing Mental Health Services for Children and Adolescents with Learning Disabilities: a Toolkit for Clinicians

Sarah Bernard & Jeremy Turk
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Fragile X Syndrome: Prevalence

- **Full Mutation**
  - 1 PER 3600 Males
  - 1 PER 4000 Females

- **Premutation**
  - 1 per 700 Males
  - 1 per 259 Females

- Similar frequencies in all ethnic groups
- One of the most common single gene disorders
- The most common identifiable inherited cause of intellectual disability
DNA CGG Expansions

- Normal: 6-40
- Intermediate: 40-55
- Premutation: 50-200
- Full mutation: greater than 200
X fra(X) fra(X) Y
Physical aspects *(Turk & Patton 2000)*:

- Longish largish head
- Protruding ears
- Largish chin
- Longish flattened nasal bridge
- High arched palate
- Hypermobile joints, lax ligaments
- Unusual palmar & plantar creases
- Postpubertal testicular enlargement
- Cardiovascular issues
- Sensory issues
- Epilepsy
Fragile X Syndrome: Intellectual functioning

- usually mild to moderate intellectual disability
- verbal/performance discrepancy
- characteristic developmental trajectory
Fragile X Syndrome: Speech & language
(Cornish, Sudhalter & Turk, 2004)

- jocular litanic phraseology
- perseveration
- repetitiveness
- echolalia
- cluttering
- sounds more rapid “but isn’t”
Fragile X Syndrome: Social impairments (Turk & Graham, 1997)

- social anxiety
- aversion to eye contact
- self-injury, usually hand biting in response to anxiety or excitement
- delayed imitative and symbolic play
- stereotyped & repetitive behaviours
Fragile X Syndrome & Autism:
(Cornish, Turk & Levitas: 2007)

- 4-6% of people with autism have fragile X syndrome
- A substantial minority of people with fragile X syndrome have autism (29%)
- Many more people with fragile X syndrome have a characteristic profile of communicatory and stereotypic “autistic-like” behaviours
<table>
<thead>
<tr>
<th><strong>FRAGILE X SYNDROME</strong></th>
<th><strong>AUTISM</strong></th>
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<tbody>
<tr>
<td>Social anxiety</td>
<td>Social indifference</td>
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<td>Gaze aversion</td>
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<td>Self-injury usually in form of hand biting in response to anxiety &amp; excitement</td>
<td>Self injury variable in topography &amp; causation</td>
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<td>Delayed imitative &amp; symbolic play</td>
<td>Permanently distorted imitative &amp; symbolic play</td>
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<td>Hand flapping in response to anxiety &amp; excitement extremely common</td>
<td>Stereotypical &amp; manneristic behaviours highly variable in topography &amp; causation</td>
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<td>Language impairments characteristically comprise delayed echolalia with repetitive, rapid &amp; cluttered speech</td>
<td>Language impairments highly variable, usually affecting comprehension more than expressive language</td>
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<td>Good understanding of facial expression (Turk &amp; Cornish 1998)</td>
<td>Lack of understanding of facial expression</td>
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<td>Theory of mind may be distorted but is not absent (Cornish et al., 2005)</td>
<td>Absent theory of mind</td>
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<td>Characteristically friendly &amp; sociable, albeit often shy &amp; socially anxious with primarily communicatory &amp; stereotypic “autistic-like” disturbances (Kau et al., 2004)</td>
<td>“Aloof”, “passive”, “active &amp; odd” or “overpedantic &amp; pseudomature” with primarily social &amp; symbolic “autistic-like” disturbances (Wing, 2003)</td>
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Distinguishing Behaviours:

- delayed echolalia
- repetitive speech
- hand flapping
- gaze aversion
- good understanding of facial expression (Turk & Cornish, 1998)
- Theory of mind as expected for general levels of ability (Garner, Callias & Turk 1999)
- friendly and sociable but may be shy
Fragile X Syndrome: Attentional deficits *(Turk, 1998)*

- poor concentration
- restlessness
- fidgetiness
- impulsivity
- distractibility
- +/- overactivity
When you control for age and intellectual ability:

- Boys with fragile X syndrome show similar rates of Hyperkinetic Disorder to those with intellectual disability of unknown cause.
- And the same levels of overactivity.
- But they show greater inattentiveness, restlessness & fidgetiness.
- And these features don’t diminish with increasing developmental ability.
Boys with Fragile X Premutations:
(Aziz et al., 2003)

↑ rates of:

− Delayed development of adaptive behaviours
− Autistic spectrum disorders
− Attention deficit disorders
− Speech & language problems
  • Social use of language
  • Speech intelligibility
  • Expressive language
Men with Fragile X Premutations:
(Mills et al., 2002)

- Slow, polite & precise +++
- Overfriendly & over-compliant
- Poor at showing emotions and feelings
- Social perception & empathy problems
- Problems making & keeping close friendships
- Poor visuo-spatial skills
- Difficulties concentrating & sustaining attention
- Memory problems relating to accessing memory & forgetfulness
- Physical & psychological symptoms attributable to stress
Are Male Premutation Carriers of Fragile X Syndrome Clinically Affected?

Andrea Mills, Jeremy Turk – St. Georges’s, University of London

Kim Cornish – McGill University, Montreal

Nicole James, Chris Hollis - University of Nottingham

Ann Dalton (Senior Clinical Scientist), Andrew Rigby (medical statistician) - University of Sheffield

Wellcome Trust - Project Grant
Summary

In comparison to the Normal Population and Family Controls, Premutation males showed greater:
- memory problems relating to accessing memory and forgetfulness
- incidence of physical and mental symptoms symptomatic of stress
- problems with close friends

In comparison to the Normal Population and Family Controls, Premutation males have shown no differences in:
- Self-Esteem
- Attention Deficit Disorder
- Schizotypal Personality
- Anxiety
- Depression
Summary

- Seems there may be genetic influences on personality and temperament in the premutation population
- Real, common & concerning issues
- Useful for individual and family to have a greater understanding of themselves - and reasons for being the way they are
- But not usually sufficient to come to clinical attention
Highly Provisional Findings

- performance on “eyes task” similar to that for high-functioning autism & Asperger
- poor at showing emotions and feelings
- poor at block design & object assembly - ? unusual strategies
- difficulties “getting the gist”, not understanding instructions, “getting it wrong”
- attentional deficits especially for memory
- mostly average IQ
Family Cosegregation Studies

- Exploration of extended families who have proband with premutation/intermediate allele & developmental difficulties
- Do premutations and intermediate alleles cosegregate with:
  - Intellectual disability (general or specific)
  - Other important neurodevelopmental/ neuropsychiatric disorders?
- Biswas et al., 2003
  - Yes they do
Females with Fragile X Syndrome:  
(Turk & Howlin, 2003)

-↓ intellectual functioning range
  - Mean = 60, no verbal/performance discrepancy
-↑ Autistic Spectrum Disorder

Irrespective of diagnostic label:
- shyness, social anxiety, self-conscious, easily embarrassed, social isolation
- obsessional including obsessive worrying
- problems socialising
- Social use of language & "semantic/pragmatic problems
Concentration Skills:

- Attention Deficit-Hyperactivity Disorder
- Irrespective of diagnostic label:
  - inattentive, restless, impulsive, distractible
- Low self-esteem
Other Emotional & Behavioural Difficulties:

- Clingy & dependent
- Fearful
- Executive Function Problems
  - planning & organising thoughts
  - shifting topic of thought
  - problem-solving
  - perseveration
  - difficulty focussing the mind
### Follow-up Study of Boys & Young Men: Social Aspects *(Das & Turk, 2002; Turk et al., 2003)*

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Results

- Increase in rate of diagnosable autistic spectrum disorder from 59.2% to 85.3%
- In the same cohort over time
- Using updated version of same diagnostic instrument
- Rate of ICD-10 Autism has doubled
Deconstructing the attention deficit *(Cornish et al., 2004)*

- Executive control component weaknesses rather than single static higher-level deficits

- Affects:
  - Development of more complex mental functions
  - Current psychological performance

- Explains:
  - Wide discrepancies in cognitive profile patterns
  - Semi-intact ability modules
Thus...

- Developmental disorders need to be studied alongside each other cognitively & behaviourally focussing on between-syndrome differences & similarities.

- Need to move from phenomenologically driven classification system towards multidimensional aetiologically driven classification of complex neurodevelopmental disability.
Hints of the Fragile X Endophenotype

- Memory access & retention (working) problems
- Impaired inhibitory control & cognitive switching abilities
- Impaired sequential information processing
- Impaired, repetitive & impulsive speech
- Impaired arousal modulation → ↑ anxiety
- ? executive control dysfunction
Clinical Consequences:

- Sensory integration difficulties
- Language dysfluencies
- Social anxiety
- General hyperarousal
- Non-autistic social impairments (NASI’s)
- Inattentiveness, impulsiveness, distractibility
- Memory, numeracy & spatial difficulties
- Sequential information processing difficulties
Symptom profile requiring treatment

- Inattentiveness, restlessness, overactivity, impulsiveness, distractibility
- Anxiety
- Disorganised thinking (can’t focus thoughts & switch to another agenda)
- Self-fuelling overexcitement
- Settling & Waking problems
Cognitive-behavioural psychotherapeutic approaches

- Cognitive-behavioural psychotherapy with children & young people with developmental disabilities & their parents (Turk, 2004)
- Post-traumatic stress disorder in young people with intellectual disability (Turk, Robbins & Woodhead, 2005)
Clonidine (Ingrassia & Turk, 2005)

- $\alpha_{2A}$ noradrenergic receptor agonist
- Good for anxiety, overactivity, impulsiveness, inattentiveness
- Mildly sedating, mildly hypnotic
- Good for tics & Tourette’s
- No effect on appetite
- Can drop your blood pressure
- 25-300 $\mu$g daily in divided doses
MELATONIN  (Turk, 2003)

- Pineal indole
- Diurnal secretion variation
- Widely available as food supplement in North America
- Unlicensed in U.K. - only prescribable on named patient basis
Conclusions:

- Beneficial, short-term, rapid-onset & safe treatment for intractable sleep disturbance
- Therapeutic dose not predicted by:
  - severity of sleep disturbance
  - severity of intellectual disability
  - presence/absence of autism
- Habituation common but not universal.
- Concomitant psychological, behavioural, educational, family & social interventions essential
- No obvious short-term adverse effects but long-term safety has not been confirmed
- No adverse effects other than habituation up to 3 years after commencement
Premutation Effects

- Developmental & behavioural phenotypes
- Premature ovarian insufficiency
- Tremor-ataxia syndrome
Fragile X tremor-ataxia syndrome

(Kogan et al., 2007; Cornish et al., 2008)

Molecular: CGG repeat 55 – 200

Clinical
- Major: intention tremor, gait ataxia
- Minor: Parkinsonism, short-term memory problems, executive function deficits

Radiological:
- Major: MRI white matter lesions involving middle cerebellar peduncles
- Minor: MRI white matter lesions involving cerebral white matter, generalised brain atrophy

Histological: intracellular inclusions
Conclusions: (Cornish, Turk & Hagerman 2008)

Fragile X syndrome
- demonstrates the importance of aetiology in determining nature as well as severity of developmental & psychological difficulties
- Emphasises need to explore syndrome-specific profiles of cognitive, social, language, attentional, sensory & motor impairment, their developmental trajectories & co-morbidities
- Facilitates development of syndrome-specific multidisciplinary early interventions & longer term multi-agency supports
The Importance of Diagnosis
(Turk, 2003)

- the right of the individual & family to know
- relief from uncertainty
- facilitation of grief resolution
- focusing on the future
- genetic counselling
- information on likely strengths & needs
- early instigation of appropriate interventions
- linking with appropriate support network