# Fragile X Syndrome- Overview & Intervention- New Zealand March 2014

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## Why is FXS important ?

Most common inherited cause of DD
Prevalence ~ 1 / 3,600 (cf CF)
1 / 150 women carry premutation
Detection allows effective treatment and informed decisions for family planning
Portal condition – insight into genetic causes of behaviour

## Fragile X Alliance Clinic- DEMOGRAPHICS

| | |
|---|---|
| Sample size | n = 214 |
| Full / premutation | 134 (63%) / 80 (37%) |
| Gender | 130 M (60%), 74 F (40%) |
| Age range | 2mo- 78 years |
| IQ range | Normal to severe ID |

Neurodevelopmental vs behavioural

## Phenotype

Developmental- global delay, specific learning difficulties
Behavioural & emotional- ADHD, anxiety, OCD, autism spectrum
Physical - narrow face, high forehead, prominent ears, loose joints, macro-orchidism
NB- wide spectrum of involvement, typical features not always present

## Developmental Delay

Intellectual disability- 80% males, 50% females
Co-ordination, fine and gross motor difficulties- not always global
Specific learning difficulties – typically maths esp females
Strengths: Strong visual skills, gestalt learners, imitation, intense interests, functional life skills

## Behavioural & Emotional

ADHD
Anxiety- generalised, panic, social
Autism spectrum disorder- 30% (ADOS, ADI) social difficulties
Hyperarousal – difficulty modulating sensory input, aggression
Strengths: Friendly, strong sense of humour. NB approach-avoidance

## Physical Features

Typical physical features highly variable prepuberty, little value in females
Broad high forehead, protuberant ears, high-arched palate, loose connective tissues, macro-orchidism
Epilepsy 13% , 75% CPS.
EEG abnormalities common. NB Absence of EEG spikes not a contraindication to initiating medication

## Females FM – cognitive profile

IQ – 1 SD < N , 70% < 85, 50% < 70,
Lower arithmetic score, similarities, EF, spatial-visual
Higher verbal scores, picture completion, comprehension, symbol search
Striking EF deficit, spared verbal skills (Bennetto ’01 – N & IQ matched)

## Females FM- behavioural profile

ADHD- 35% (Hagerman 2000)
Shyness, social anxiety common ( Mazzocco 1998, Sobesky 1995)
Anxiety- 40% (Lachiewicz 1994)
Avoidant personality- majority (Freund 1993)
Selective mutism (Hagerman 2000)

## Premutation phenotype

Normal IQ (Mazzaco ’93, Reiss ’93, O’Brien ’98)
anxiety, shyness, social phobia, OCD, depression (Frank ’96, ’98, Sobesky ’95, ’98)
ID, LD, ASD
Executive function – response inhibition assoc with depression, anxiety, ADHD (Kraan et al)
FXPOI 20%- females ( c/w 1% in general popn)
FXTAS (Hagerman 2001) – males > females
( for recent review see: Kraan et al 2013 Neuroscience and Biobehavioral Reviews 37 (2013) 522–547)

Phenotype range
Male and female full mutation
Male and female premutation
Grey zone
Mosaicism – DNA, methylation, tissue type, X-inactivation ratio
Physical & cognitive features not obvious
Behavioural & emotional are main issues but rarely measured

Adults
Appropriate accommodation – home, CRU, cluster housing, forensic facility
Adequate workplace support
Day programs – supervisors
Behaviour management
Abuse
Carer training / up-skilling
Confusion between independence and dependence
'Collusion of anonymity'

Missed medical conditions
Neurol - Epilepsy- GM, TLE, CPS
Gastro - constipation, reflux oesophagitis
Uro/gen - Female: PCO, POF, VUR, kidney
- Male: undesc testes, hypospadius, VUR, kidney
Ortho - pes planus, hyperextensible joints, scoliosis, recurrent ear infections,
CT - strabismus, mitral valve prolapse, #.
Dental - caries, gingivitis, root abscess
Nutrition - obesity, undernutrition
Dermatol - dry skin, eczema, striae
CVS - heart valve, aortic root
Psych - 'dual disability'- anxiety, ADHD, self-esteem, schizophrenia, depression.

Diagnosis- Delayed Diagnosis
Average age diagnosis (Aus/NZ) 66 months (c/w 38 months in USA)
50% had a 2nd child prior to 1st child Dx
43% of these had a second affected child
75% "best time to test is before pregnancy"
General paeds unsure, so referred on to specialists, hence delay.
(Don Bailey MMWR Aug 02, Pediatrics; 2. Family Study FXAA 2009 )

Guidelines- DNA testing for FXS
Any male or female with ID / dev delay / ASD
ID w prev cytogenetic test / inconclusive DNA
Family history (inc pregnancy, foetuses)
LD and emotional / behavioural features FXS inc anxiety, ADHD, ASD
Prior to pregnancy with or without Fam Hx
Obstetric: antenatal, FXPOI, prem menopause (<40), IVF, amnio, CVS
FXTAS – males > 50yrs w tremour, ataxia, Parkn
NB Absent physical features or lack of family history are not a contraindication

Diagnosis
Allows search for and detection of likely associated issues
Allows implementation of targeted treatment and management strategies
Allows individuals to be aware of issues and lean to self-manage better
Allows identification of other family members with options for management and family planning
Intellectual disability / Developmental delay / ASD:

Microarray comparative genomic hybridisation ('Array CGH') – 2 x more diagnoses than karyotype
'DNA test for FXS'

Screening = testing a population
Four opportune times:
Preconception – eg with Pap smear
Prenatal – early pregnancy
Newborn – heel prick
Early childhood
Ethics, attitudes, acceptability, cost, how best to implement

Offering Fragile X Carrier Testing to Women: Comparing Prenatal and Preconception Screening
1/150 women carry the gene, any of whom may have an affected child.
NHMRC-funded study by MCRI & Uni Melbourne,
conducted in Melbourne & Perth, & compared:
Informed decision making
Uptake of testing
Psychological impact
Cost effectiveness

Population Carrier Testing
1237 women (702 non-pregnant 535 pregnant)
71% and 59% were tested, respectively
0.4% received a PM and 2.0% a GZ result
85% had good knowledge (≥7/10 correct)

Findings:
Good understanding of FXS
Minimal psychosocial impact (eg anxiety)
Most supported availability of testing
Pre-conception preferred

Interventions

Multidisciplinary team
Audiologist
Optometrist / ophthalmologist
Speech and language therapist
Occupational therapy / physiotherapy
Psychologist / psychiatrist
Specialist – paediatrician, neurologist, clinical geneticist, genetic counsellor
Teacher / Special education
General practitioner

Checklist
1. DNA testing to confirm FXS status
2. Genetic counselling for information and cascade testing of relevant family members
3. Grief and supportive counselling for family
4. Hearing assessment with audiologist
5. Vision assessment with optometrist / ophthalmologist
6. Assessment for orthotics with podiatrist
7. Speech & language therapist for help with communication
8. Educational psychologist- assess IQ, ADHD and ASD, behaviour management strategies
9. Occupational therapist including sensory issues
10. Developmental paediatrician for initial assessment and ongoing review
11. Trial medications for anxiety or ADHD if present under care of medical practitioner
12. Centrelink for Case Manager for help with funding, home support etc
13. Give information on FXS and advise to join Fragile X Alliance and Fragile X Association
14. Multidisciplinary assessment at FXS Clinic

Treatment
Medical- epilepsy, CT problems
Pharmacological- ADHD, anxiety, mood, urinary, sleep, aggression
Behavioural- ADHD, anxiety, depression
Educational- strengths and weaknesses
Specific treatment and management strategies are of great benefit to individuals and their families

Medications
Conditions treated in FXS:

| | |
|---|---|
| ADHD | I Stimulants, Clonidine |
| Anxiety | SSRIs, clonidine, antipsychotic, buspirone |
| Aggression, self-injury | SSRIs, clonidine, antipsychotics |
| Epilepsy | Carbemazepine, valproate |
| Sleep disorders | imipramine, melatonin, clonidine |

| | |
|---|---|
| Mood disorders | mood stabilisers |
| OCD | SSRIs, TCAs |
| Enuresis | imipramine, desmopressin |

Evidence for use of medications
Clinical experience internationally
Paediatric and adult indications
Body of literature
References:
Tranfaglia, M.- A Medication Guide for Fragile X Syndrome
Hagerman, RJ – FXS Diagnosis, Treatment & Research 3nd ed

Medication classes- 1
Antidepressants / anxiolytics
SSRI / SNRI- fluoxetine, sertraline, venlafaxine
block uptake of serotonin / NA from synapse,
inhibits the locus ceruleus, increases calm and contentment
SEs- paradoxical agitation, anxiety 20%, nausea

TCAs- Tricyclic antidepressants (eg imipramine)
SEs sedating, neuro & cardiovascular effects

Medication classes- 2
Stimulants- methylphenidate, dexamphetamine
enhance dopamine and noradrenalin
helps focus on task on hand ie attention, concentration, impulsivity, restlessness, motor and handwriting
> 5 years of age
60% respond (Hagerman 1988)
SEs- appetite, sleep, cardiovascular
NB SR tabs, newer agents

Medication classes- 3
Mood stabilisers / anti-epileptic
carbemazepine, valproate, lithium
Atypical antipsychotics
risperidone, olanzepine, quetiepine
Enuresis- imipramine, desmopressin nasal
Sleep - clonidine, melatonin, imipramine, antihistamines
Others - moclobemide, beta-blockers
Alternatives- St John's wort, valerian, vitamins

Zoloft (sertraline)
SSRI- anxiety, OCD, aggression, mood, attention
once daily dosing
relatively safe
low doses effective
4- 6 weeks for max effect
activation 20%, agitation, mania, nausea
combine with stimulant medication

Zoloft study
Zoloft is indicated for major depression, obsessive compulsive disorder, panic disorder
Clinically used to treat anxiety and disorders of mood, aggression, impulse control and attention in FXS
Studies confirm safety and efficacy in adults and children with these conditions

Attention
Inattention
Hyperactivity
Impulsivity
Treatment: - medication,- OT with sensory integration, behavioural and environment

Ritalin & Dexamphetamine
Stimulant medication for ADHD >5 yo
majority respond
improves attention, concentration, motor, handwriting, impulsivity, restlessness

short half life (effect lasts 2- 3 hours)
SEs- appetite, sleep, rebound, nausea, CVS, tic, psych
Addicition NOT a problem over last 50 years (RCH)
Impt for clinician to monitor height, weight, CVS
Monitor effect before & after with questionnaires

Environmental modifications
IQ and FMR in FXS vs non-carrier sibs (n=120)
Parent IQ best predictor of unaffected child IQ
Enriched home environment best predictor of IQ and freedom from distractibility in FXS
Strong case for home interventions & routines
Dyer-Friedman J et al J Am Acad Child Adolesc Psychiatry 2002;41:237-244

Medications plus behavioural approach are synergistic

New medications
mGluR5 inhibitors – AFQ056, arbaclofen
Memantine, an N-methyl-D-aspartic acid (NMDA) noncompetitive receptor antagonist blocks glutamate toxicity
Minocycline - lowers MMP9 levels
Abilify (Aripiprazole) – atypical antipsychotic, 1st line treatment for anxiety

10 top things for teachers to know about FXS
1. Don't force eye contact
2. Expect inconsistency
3. "Simultaneous" vs "sequential" learners
4. Allow and/or encourage frequent breaks
5. Verbal expression is cognitively taxingThink "indirect"
6. Prepare for transitions
7. Work with an OT to embed SI into the day
8. Notice environmental triggers
9. Know FXS strengths

NB Students prone to hyperarousal & anxiety
Also see Lesson Planning Guide
(Laurie Yankowitz, http://www.fragilex.org)

Research
Offering women FXS carrier screening pre-conception c/w prenatal- Metcalfe et al
Newborn screening (Field et al)
Premutation females – evidence for neurobehavioural effect- Kraan, Cornish et al
mGluR5 inhibitor drug trial (Novartis, Roche)
Genotype-phenotype studies PM (Cornish)
FXTAS (Cornish, Troller, Loesch)
Research database combined – MCRI
New blood and cheek swab / saliva tests

References
AAP medical guidelines 2011
http://pediatrics.aappublications.org/content/127/5/994.full.html
Management Guidelines- Developmental Disability Version 3, 2012. Pub Therapeutic Guidelines www.tg.org.au
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