Fragile X syndrome: Part 1

This week’s Update is the first in a two-part series on fragile X syndrome. Part 1 focuses on clinical presentation and diagnosis.

Introduction

FRAGILE X syndrome (FXS) is the most common known inherited cause of developmental disability worldwide, the next most common overall cause after Down syndrome, and the most common single gene cause of autism spectrum disorder.

The genetic mutation associated with the FXS full mutation causes a range of serious, lifelong features including intellectual disabilities, learning difficulties, and behavioural and emotional problems such as anxiety, attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder. The characteristic physical features are often subtle or absent, especially before adolescence. They include a long, narrow face; prominent forehead; large, protruding ears; large testicles; and loose connective tissues.

FXS is a portal condition offering detailed insight into genetic causes of learning and behavioural difficulties. Diagnosis allows implementation of effective treatment and management strategies for individuals and their families, regardless of age, but these are more effective if started early.

As the behaviours associated with FXS have a neurological basis, medications can be very helpful in management and are synergistic with behaviour management strategies.

Because this is an inherited condition that will affect the extended family directly and indirectly, it is vital to identify all family members at risk. In particular, females of child-bearing age need to be counselled regarding testing for carrier status, so they can make informed decisions about family planning. Genetic counsellors can facilitate genetic testing and provide support for families. Current medical advances have made it possible for a woman carrying the gene to have the choice of having an affected or unaffected child.

Epidemiology

The estimated prevalence of individuals with the full mutation is about one in 3600 males and one in 4000–6000 females, which makes FXS as common as other more well-known genetic conditions like cystic fibrosis.

The pervasiveness of the pre-mutation is much more common occurring in males at one in 800, and even more common in females, with one in 150 in the general population being at risk of having a child with the full mutation.

Delayed diagnosis is common, with many individuals not being diagnosed until school age or later, if at all. It has been estimated that in 30% of families, by the time a child is diagnosed, the family already has a second affected child. Missed diagnosis may occur due to a combination of absent ‘textbook’ physical features, failure to consider and test for intellectual or developmental disability, and failure to consider a neurodevelopmental genetic cause for unusual behaviour. Even though the diagnostic DNA test is available on the Medicare schedule, it is often not requested by the treating physician.

It has been estimated that up to 100,000 people in Australia carry the gene change associated with FXS either as a full mutation or pre-mutation. Routine genetic testing for FXS carrier status is increasingly likely to occur along with other more common genetic conditions and is currently the subject of ongoing research.
Aetiology

The cause of FXS is a mutation in the long arm of the X chromosome, where the repeating trinucleotide sequence expands. At this length, the gene is unstable in female carriers when passed to the next generation, and so may expand further in their offspring to more than 200 repeats, thus resulting in an individual with the full mutation.

The repeat range between 44 and 55, known as the ‘grey zone’, is of current interest in that there has been no expansion to the full mutation. However, the pre-mutation range, it is not clear whether there is some clinical effect which is as yet undefined.

The condition is X-linked. Females who carry the pre-mutation or full mutation have only one X chromosome affected, so they have an overall risk of one in two of passing on their affected gene to their children. However, the greater the length of the pre-mutation, the higher the risk of their offspring’s gene expanding to the full mutation.

The pre-mutation tends not to expand when passed from father to child, therefore all daughters of male pre-mutation carriers will be obligate carriers.

It is worth noting that genetic testing of family members has occasionally identified a parent as not being the biological parent, and so this point needs to be mentioned before offering testing to family members. Because the condition is X-linked and males have only one X chromosome, they are more likely to be more severely affected. However, mosaicism can occur, with some individuals being relatively higher functioning.

It is also worth noting that there may be mosaicism between different tissues, so that the trinucleotide sequence ‘cytosine-guanine-guanine’ in the 5’t untranslated region of the ‘FMR1’ gene expansion in white blood cells (used for the DNA diagnostic blood test) may not always reflect central nervous system expansion and function.

Females carry two X chromosomes, so depending on the degree of X inactivation, they may be severely or less affected. All this goes some way to explaining the wide spectrum of severity seen in FXS.

Clinical features

The phenotype seen with both males and females with the full mutation consists of three core features: developmental disability; behaviour; and emotional and executive function defects.

Developmental disability

Developmental disability is the hallmark of FXS and typically includes intellectual disability. However, a normal intellectual quotient (IQ) can be measured with a formal assessment tool such as the Vineland Adaptive Behaviour Scales, or Wechsler Intelligence Scale for Children, which are not usually used until early primary school age.

However, developmental milestones are typically late, usually recognised by parents, and able to be readily assessed by a physi
can or psychologist. Parents should be reassured that affected individuals will, in general, continue to develop and improve functionally, although the gap between their abilities and that of their peers will widen. The term ‘delay’ is therefore more appropriately termed ‘disability’. FXS should be suspected and excluded in any individual with delayed milestones, regardless of the presence or absence of other typical features.

While adults retain most features many do progress to meaningful employment in areas such as hospitality, horticulture and cleaning. While some males will gain a driver’s licence and live relatively independently, typically males do not manage to form long-term relationships and will need to live under lifelong supervision.

Females who are not severely affected will form long-term relationships and live a relatively normal life, although they may have difficulty with academics, workplace situations and raising children.

Behavioural issues

The behavioural problems associated with FXS tend to be the main reason patients present to the physician. Marked anxiety, negative or oppositional behaviour, resist ance to change, outbursts or aggression are typical and are almost invariably the result of the core underlying emotional and psychiatric disorders. These include major anxiety disorder, panic disorder, social anxiety disorder, generalised anxiety disorder, ADHD (with or without hyperactivity) and autism spectrum disorder, including pervasive developmental delay not otherwise specified (PDD-NOS) and Asperger syndrome.

As many children are typically hyperactive and often anxious, this behaviour may be put down to a normal development stage at an earlier age, but the key differentiating factor is more often than not parental concern. Parents are often able to differentiate problems with communication, and are sensitive to differences from age-matched peers.

Physical

The physical characteristics include a long, narrow face; broad, high forehead; long, narrow face; broad, high forehead; prominent ears; and large testes. While this presentation is indeed typical and not to be missed, enlarged testes, if looked for, are rarely seen before puberty and are only present in 50% of adult males. Strabismus (eye turned in or out) may be intermittent, and recurrent ear infections due to Eustachian tubes dysfunction are common and thought to be due to the loose connective tissue abnormality similar to Ehlers-Danlos syndrome.

Other connective tissue features include loose, hyper-extensible joints; flat feet; and aortic root or valve rupture has been described.

A subset may present with a Prader-Willi phenotype with excessive weight gain, and the incidence of concomitant genetic conditions may be up to 5%.

Clinical presentation

Children

Children typically present with a number of unusual or odd behaviours. Gaze aver
ing is common and results from an over sensitivity to being looked at – the child perceives this as intrusive. This ‘sensory defensiveness’ commonly extends to a dislike of loud noises, bright lights, physi
cal touch or feel of some clothing, strong smells and lateral movement.

Poor oral motor sensation and coor dination result in poor speech echolalia. There is often difficulty with chewing and swallowing, and gastrointestinal reflux disease, bowel motility disorder and food aversion are common.

The skin is often dry and velvety, and it is common for individuals to scratch or bite themselves, and these present as self-harm ing.

Females

Females with the full mutation may appear typically less affected compared to males with a group, with a mean IQ one standard deviation lower than the norm. About 50–70% will have an IQ lower than 85, and even with a normal IQ, most will

Table 1: Full mutation phenotype

<table>
<thead>
<tr>
<th>PHYSICAL:</th>
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<tbody>
<tr>
<td>Narrow face; high forehead; prominent ears</td>
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<tr>
<td>Connective tissue laxity including hyper-extensible joints</td>
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<tr>
<td>Flat feet; low muscle tone</td>
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<td>Macroorchidism</td>
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<td>Epilepsy</td>
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<td>Recurrent ear infections</td>
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Table 1: Full mutation phenotype

<table>
<thead>
<tr>
<th>DEVELOPMENTAL:</th>
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<tr>
<td>Global delay including speech</td>
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<td>Language and communication difficulties</td>
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<td>Poor fine and gross coordination</td>
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<td>Specific learning difficulties</td>
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| BEHAVIOURAL: | EMOTIONAL: | |
|---|---|
| Gaze aversion | Anxiety | |
| Hand flapping, hand biting | ADHD, autism spectrum disorder | |
| Sensory defensiveness | Aggression, self-injury | |

NB: There is a wide spectrum of involvement and characteristic features are not always seen. Videos of some individuals showing a range of symptoms can be viewed at http://www.fxs.org.uk/camping

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<tr>
<th>综合征的检查和治疗</th>
<th>Clinical review</th>
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<tr>
<td>FXS and autism.</td>
<td>FXTAS, it is a neurodegenerative condi tion predominantly occurring only in male pre-mutation carriers. Tained the fragile X tremor ataxia syndrome (FXTAS), it is a neurodegenerative condi tion similar to Parkinson’s disease.</td>
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<tr>
<td>It is hoped that understanding the underlying epigenetics will open up the</td>
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<tr>
<td>neurobiological understanding of both FXS and autism.</td>
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<tr>
<td>Many individuals, both male and female, do not appear ‘syndrome-like’ and are physically unaffected. Compared to otherwise unaffected females with typical developmental and behavioural features appear ‘normal’ and so have never been offered the diagnostic DNA test.</td>
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Diagnosis

The presentation of a parent with a child with problematic behaviour should trigger a search for the difficulty: developmental or learning problems. The diagnosis should be considered when there is developmental delay and/or behavioural abnormality.

REFERRAL FOR DNA TESTING

Referral to a developmental paediatrician and/or clinical geneticist is usually the first step for both diagnosis and ongoing expert management. When adults have not previously been investigated with a DNA test, diagnosis usually rests on the GP.

The diagnosis of FXS is made with a DNA blood test, with the alternative of a cheek swab expected to become available soon. The pathology request should include ‘DNA for fragile X syndrome’ and, in addition, ‘Chromosome analysis by genomewide microarray’ for any individual with developmental disability who has not previously been fully assessed. The latter test detects chromosomal causes of developmental delay (microdeletions and microduplications), with the exception of FXS, hence the need to specifically request DNA for FXS.

Testing for carrier status in the absence of known family history costs about $200.

Indications for testing

The indications for testing for FXS include any individual, male or female, of any age with intellectual disability, developmental delay, or learning disability and features of FXS including anxiety, ADHD or autism spectrum disorder. FXPOI and FXTAS have recently been included.

Women with difficulty conceiving or entering early menopause should be tested for the FXS gene. Males and females older than 50 presenting with Parkinsonian-type tremor, movement or balance problems should also be tested.

Both FXPOI and FXTAS should especially be considered if there is a history of any extended family member with developmental delay, autism spectrum disorder, late-onset tremor or early menopause.

Relatives of individuals diagnosed as carrying an expansion in the fragile X gene need to be offered testing, and this especially applies to women of child-bearing age.

DEVELOPMENT AND IQ

Anxiety, ADHD and autism spectrum disorder are diagnosed on the basis of meeting DSM criteria.

Referral to a developmental paediatrician or appropriate psychologist may be helpful, as they will be able to more formally assess developmental delay, and be able to advise on appropriate educational and behavioural management strategies as well as psychopharmacological management.

An educational psychologist will be able to perform IQ testing, and educational and behavioural assessments for school. Accessing professionals for adults is more difficult, but can improve quality of life both in the short- and long-term.

SEIZURES

Seizures occur in 10–20% as either tonic-clonic or, more commonly, complex partial seizures. The latter can be more difficult to detect as they may present as petit mal (“absences”) or behavioural outbursts.

Epileptic seizures may be difficult to perform and are often abnormal, but they do not always demonstrate classical seizure activity. A normal EEG is not a contraindication to a trial of anti-epilepsy medication, which may also be useful as a mood stabiliser.

It is important to gain appropriate consent before ordering any test, but especially genetic tests. GPs who are unsure of this area should refer to a developmental paediatrician or clinical geneticist.

MBS CRITERIA FOR GENETIC TESTING IN DEVELOPMENTAL DISABILITY

Detection of FMR1 gene mutation where:

- the patient exhibits intellectual disability, ataxia, neurodegeneration, or premature ovarian failure consistent with an FMR1 mutation, or
- the patient has a relative with a FMR1 mutation

Prior to ordering these tests appropriate genetic counselling should be provided to the patient by the treating practitioner, a genetic counselling service or by a clinical geneticist and the patient should give informed consent. Further counselling may be necessary upon receipt of the test results.

Analysis of chromosomes by genomewide microarray including targeted assessment of specific regions for constitutional genetic abnormalities in diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities.

Table 2: Pre-mutation phenotype

Milder features similar to the full mutation may occur

- Fragile X primary ovarian insufficiency (FXPOI) – early menopause in 20%
- Fragile X tremor ataxia syndrome (FXTAS) – at least 40% of males older than 50; 8%-16% of females

Table 3: Human Genetics Society of Australasia guidelines for testing for FXS

1. Any male or female with intellectual disability or global developmental delay
2. Any male or female with intellectual disability and a previously incontinent cytogenetic test (karyotype)
3. A family history of FXS (including pregnancy, fetuses)
4. Learning disability and emotional or behavioural features of FXS including autism spectrum disorder, PDD-NOS, Asperger syndrome and ADHD
5. Primary ovarian insufficiency or early menopause (younger than 40 years)
6. FXTAS – males or females older than 50 years

Figure 1: CGG repeat ranges in FMR1 gene

No. of repeats

6-44 Normal

45-54 Grey zone

55-200 Premutation

>200 Full mutation
DIAGNOSIS of fragile X syndrome (FXS) allows implementation of effective treat-
ment and management strategies for indi-
viduals and their families regardless of age,
but these are more effective if started early.
While there is currently no cure for the
underlying genetic mutation, specific treat-
ment and management strategies are of
great benefit to individuals and their fami-
lies. Management rests on implementation
of behavioural and educational strategies in
conjunction with appropriate pharma-
cotherapy.
Several medications have been shown
to be helpful in managing the associated
behavioural disorders commonly seen with
FXS, such as anxiety disorders, ADHD, epi-
lepsy, enuresis and encopresis, aggression
and self-injury.
Management is multidisciplinary, and it
is important to both involve and follow up
with the family on a regular basis to provide
support and ensure the appropriate strate-
gies are being implemented (see Table 1).

Table 1: Care plan summary

<table>
<thead>
<tr>
<th>Task</th>
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<tr>
<td>For DNA testing to confirm FXS status: genetic counselling for information and cascade testing of relevant family members; grief and supportive counselling for family</td>
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<tr>
<td>Hearing assessment with audiologist</td>
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<tr>
<td>Vision assessment with optometrist/ophthalmologist</td>
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<tr>
<td>Assessment for orthotics podiatrist</td>
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<tr>
<td>Trial SSRI for anxiety: start with a low dose and report back to GP in one week or earlier, if needed</td>
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<tr>
<td>Speech and language therapist</td>
</tr>
<tr>
<td>Educational psychologist: assess for IQ, ADHD and autism spectrum disorder, behaviour management strategies</td>
</tr>
<tr>
<td>Occupational therapist including sensory issues</td>
</tr>
<tr>
<td>Developmental paediatrician</td>
</tr>
<tr>
<td>Centrelink for help with funding, home support, etc</td>
</tr>
<tr>
<td>Information on FXS: to join Fragile X Alliance and Fragile X Association of Australia</td>
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<tr>
<td>Multidisciplinary assessment at Fragile X Association clinic</td>
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</table>

Genetic testing is important to identify those at risk.

As this is an inherited condition, it is likely
to impact multiple family members, so it is
important for the GP to identify all those
at risk with genetic testing. This especially
applies to females of child-bearing age, who
will need to know their carrier status if they
want to have any choice in whether or not
to have an affected child.
Knowledge of carrier status offers the
full spectrum of reproductive options,
including the choice of becoming preg-
nant, testing of the fetus for FXS, and
the option of termination. There is also a
range of assisted reproduction techniques
including egg or embryo donation and pre-
implantation genetic embryo testing using
DNA techniques before implantation into
the uterus.
Pharmacological treatment of clinical features

ANXIETY
SRIs such as sertraline, fluoxetine, citalopram, escitalopram or fluvoxamine can be extremely effective in managing the anxiety disorders that occur in most individuals with the full mutation and a subgroup with the pre-mutation. These medications help block the uptake of serotonin from synapses in the locus coeruleus, increasing the individual’s ability to remain calm when confronted by perceived threatening situations. It is axiomatic that medications are used to treat the disorder as defined by DSM-IV, not the behaviour per se.

Paradoxical arousal or activation occurs in up to 20% of those prescribed fluoxetine, so this medication should be avoided when there is hyperactivity, hyper-activation, restless-ness or agitation. However, it can be helpful for treatment of those who are extremely shy, socially avoidant, or diagnosed with social anxiety disorder or selective mutism. SNRs such as venlafaxine or desvenlafaxine are also helpful in ameliorating symptoms of anxiety, as well as concentra-
tion and attention. This tends to be a class effect, so a trial of one or two medications from this class is often worthwhile. If behav-
ioral worsening in the absence of an anteced-
ent cause, then another medication should be trialled.

Benzodiazepines such as diazepam are generally unhelpful in FXS as they can dis-
Inhibit and so worsen the underlying prob-
lem. Buspirone is an exception to this, and

Adult females are much more likely to live a relatively normal life; however, some will be severely affected. Counselling for sexuality issues needs to be offered, with the aim of ensuring females can manage their periods and are taught the skills to be able to decline unwanted advances and to be safe.

While some paediatricians continue to see affected individuals into adulthood, this is not common. Apart from a handful of special adult disability units, management generally falls to local GPs, most of whom are generally not trained in this area.

In addition, community resources, when present, are generally extremely poor. Many problems have been identified surrounding inappropriate accommodation for individ-
uals such as the existing community resi-
dential units, where a cluster of people with behavioural problems share a unit under guidance of well-meaning but often untrained carers. Preferred alternative hous-
ing such as cluster units are rarely available.

Seizures
Anticonvulsant medications are generally very effective in FXS, with carbamazepine and valproate being equally effective as monotherapy and well tolerated by most. If seizures are not controlled, most other currently available anticonvulsants can be trialled, bearing in mind their potential side-effects. Phenytion, phenobarbitone and gabapentin are generally avoided due to their potential for unwanted side-effects in this group.

MOOD INSTABILITY AND AGGRESSION
In addition to the anticonvulsants above, the atypical antipsychotics such as risperi-
done, olanzapine, quetiapine and aripipra-
zaole may be helpful in alleviating what can be very dramatic behavioural problems.

Many individuals with FXS will meet the criteria for either bipolar mood disor-
der or autism spectrum disorder, and so can be prescribed these medications on the PBS. Risperidone (starting with low-dose 1 mg bd and increasing as needed) is effec-
tive in both young children with autism spectrum disorder and also adults with severely challenging behaviour.

Olanzapine and aripiprazole have a wide range of action in managing many of the emotional and developmental delay problems seen in FXS including anxiety, agitation, aggression and mood stability; however, a supervised diet needs to be implemented to avoid significant weight gain.

SLEEP DISORDERS
Sleep disorders are common and will usu-
ally respond to behavioural management techniques, which have been shown to be effective. Clomipramide can be used at night, with the added benefit of helping manage anxiety and hyperactivity. Melatonin can be helpful in FXS and has no known or appar-
ent side-effects.

Initial Assessment

It is therapeutic for the family and carer that they be listened to carefully, as they may have been struggling with the many challenges associated with looking after an individual with FXS for a long time.

It is important to specifically look for the typical phenotypic features of FXS when taking medical and family history and initially examining the child. As it is common for the mother to be the carrier, it is important to ensure another family member attends the consultation.

Providing a clear explanation of the rea-
sons for behavioural presentations can be helpful for the family and/or carer, as this removes the fear of previously misunder-
stood behaviour, and provides a basis for the necessary educational management in the home, school and at work or day placement.

Educational Assessment

The main presenting concerns for families regarding their children centre on educa-
tional approaches, which are best man-
eged by a combination of a speech and language therapist, occupational ther-
pist, psychologist and a special education teacher.

While most younger children will be able to attend a mainstream school, if there is an understanding teacher and the appropriate support from the school, few mainstream secondary schools provide an optimal environment, necessitating transfer to a special develop-
mental school in most cases. Higher-functioning individuals with FXS may be able to transition into the various TAFE options on offer which include workplace experience in areas such as hospitality, horticulture, aged care and retail.

Physical Assessment

There is a high incidence of both hear-
ing and vision problems in FXS, which add to the difficulties experienced by peo-
ple with intellectual difficulties, so appro-
priate referral is critical. Referral to an optometrist and audiologist familiar with neurodevelopmental issues in developmen-
tal disability is often more helpful function-
ally, and they are able to refer directly to ophthalmologists and ENT surgeons for surgical intervention, if necessary.

Strabismus can often be managed with eye exercises and spectacles provided ther-
apy is implemented early enough, with the aim of achieving binocular vision.

Current laser or prismatic therapy responds well to goniotomy tube insertion and allows earlier restoration of normal hearing.

Management of adults

PREVENTIVE CARE
A number of medical conditions are often missed in the developmentally disabled popula-
tion and FXS is no exception (see Table 2).

ADULT ISSUES
Few adult males will be able to form rela-
tionships with females and, in general, their social contacts tend to be limited to their immediate family, carers and therapies. Many adults work in areas such as hospitality, horticulture, cleaning and occasionally retail, with some in sheltered workshops or taking part in supervised day programs.

In the absence of a caring family mem-
ber, many adults with FXS are completely dependent on the goodwill and abilities of the carers who supervise their activities on a daily basis.

Mood and anxiety disorders

Medication is generally effective in FXS, with SSRIs such as sertraline, fluoxetine, citalo-
pram, escitalopram or fluvoxamine having a good record in reducing anxiety and improving mood. As these medications may be especially helpful for children older than five years. It has been used effectively for the treatment of hyper-
activity and sleep disorders in FXS as well as in older individuals by itself or in conjunc-
tion with SNRs. Side-effects include hypo-
tension, so the lowest effective dose is used generally at night before bed, and ECGs are recommended to monitor for arrhythmias.

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Mental health

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Enuresis and encopresis

While management of these conditions is the same as in the general community, the problems may extend to a later age associ-
ated with developmental delay. Behaviour management techniques such as alarm blankets can be very help-
ful. Medications such as imipramine and desmopressin are also helpful, but require careful ongoing monitoring.

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ent side-effects.
New developments and future directions in research

| Table 2: Often missed medical conditions in fragile X patients |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Neurological** | Epilepsy — tonic-clonic seizures, complex-partial seizures |
| **Gastrointestinal** | Constipation, reflux oesophagitis |
| **Urogenital** | Female – polycystic ovaries, FXPOI, vesicoureteric reflux, renal abnormalities |
| | Male – undescended testes, hypospadias, vesicoureteric reflux, renal abnormalities |
| **Orthopaedic** | Pes planus, hyperextensible joints, scoliosis, asymmetrical leg length |
| **ENT** | Recurrent otitis media, hearing loss |
| **Dental** | Caries, gingivitis, root abscesses |
| **Ophthalmological** | Strabismus, visual perception defects |
| **Nutrition** | Obesity, under-nutrition |
| **Dermatological** | Dry skin, eczema, striae |
| **CVS** | Mitral valve prolapse, aortic root dissection/rupture |
| **Psychiatric** | Anxiety, low self-esteem, schizophrenia, depression, ADHD |

**NEW MEDICATIONS**
Animal knockout models have contributed to the understanding of the neurological abnormalities in FXS, and a number of promising medications targeting synaptic proteins involved with regulation of emotions and learning are currently in various stages of development.

FMRP is an mRNA-binding protein normally needed for synaptic protein inhibition. The lowered levels seen in FXS result in up-regulation of several synaptic proteins, including metabotropic glutamate receptor activated pathways (GluR1 and mGluR5).

Inhibition of mGluR5 would therefore, in theory, inhibit these pathways and contribute to alleviating many of the core symptoms seen in FXS including anxiety, arousal and aggression.

A stage II multicentre DIRRCT trial of an mGluR5 inhibitor in FXS AFQ056 is currently underway, with several other medications in various stages of development or at trial, including other mGluR5-negative modulators, arbaclofen, minocycline, lithium and ampakines.

The aim of developing these and newer medications is to reverse the synaptic modifications with repair of the pathways needed for normal emotional and intellectual function in individuals affected by FXS and other disorders such as autism.

**FUNDING**

The Better Start program under FaHCSIA offers funding for early intervention for children younger than six years. The Department of Education provides some funding for school-age children with intellectual disability or severe disabilities.

For children and adults, there is a number of Medicare item numbers that may act as an incentive to provide a care plan including annual health assessments, medication reviews, case conferences and care plans. Private health extras insurance covers some allied health services.

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**ADHD**

ADHD occurs more frequently in FXS and management is very much the same as with individuals with or without intellectual disability. Behaviour management strategies and educational modifications are synergetic with medications.

**Sleep Disorders**

Sleep disorders are common and will usually respond to behavioural management techniques, which have been shown to be effective. Clonidine can be used at night, with the added benefit of helping manage anxiety and hyperactivity. Melatonin can be helpful in FXS and has no known or apparent side-effects.

**Anxiety**

SSRIs such as sertraline, fluoxetine, citalopram, escitalopram or fluvoxamine can be extremely effective in managing the anxiety disorders that occur in most individuals with the full mutation and a subgroup with the pre-mutation. These medications help block the uptake of serotonin from synapses in the locus coeruleus, increasing the individual's ability to remain calm when confronted by perceived threatening situations. It is axiomatic that medications are used to treat the disorder as defined by DSM-IV-TR, not the behaviour per se.

Paradoxical arousal or activation occurs in up to 20% of those prescribed fluoxetine, so this medication should be avoided when there is hyperactivity, hyper- arousal, restlessness or agitation. However, it can be helpful for treatment of those who are extremely shy, socially avoidant, or diagnosed with social anxiety disorder or selective mutism.

SNRIs such as venlafaxine or desvenlafaxine are also helpful in ameliorating symptoms of anxiety, as well as concentration and attention. This tends to be a class effect, so a trial of one or two medications from this class is often worthwhile. If behaviour worsens in the absence of an antecedent cause, then another medication should be trialled.

Benzodiazepines such as diazepam are generally unhelpful in FXS as they can disillusion and so worsen the underlying problem. Buspirone is an exception to this, and midazolam can be helpful for procedures such as dental visits. Tricyclic antidepressants and the older antipsychotics are contraindicated due to their side-effect profiles, including a range of cardiovascular and neurological effects such as sedation, which worsens pre-existing cognitive problems.

**Seizures**

Anticonvulsant medications are generally very effective in FXS, with carbamazepine and valproate being equally effective as monotherapy and well tolerated by most. If seizures are not controlled, most other currently available anticonvulsants can be trialled, bearing in mind their potential undesirable side-effects and the potential for unwanted side-effects in this group.

**Mood Instability and Aggression**

In addition to the anticonvulsants above, the atypical antipsychotics such as risperidone, olanzapine, quetiapine and aripiprazole may be helpful in alleviating what can be very dramatic behavioural problems. Many individuals with FXS will meet the criteria for either bipolar mood disorder or autism spectrum disorder, and so can be prescribed these medications on the PBS. Risperidone (starting with low-dose 1 mg bd and increasing as needed) is effective in both young children with autism spectrum disorder and also adults with severely challenging behaviours.

Olanzapine and aripiprazole have a wide range of action in managing many of the emotional and developmental delay problems seen in FXS including anxiety, agitation, aggression and mood stability; however, a supervised diet needs to be implemented to avoid significant weight gain.

**Enuresis and Encopresis**

While management of these conditions is the same as in the general community, the problems may extend to a later age associated with developmental delay. Behaviour management techniques such as alarm blankets can be very helpful. Medications such as imipramine and desmopressin are also helpful, but require careful ongoing monitoring.

**Physical Assessment**

Counselling for individuals with FXS may have been struggling with the many neurodevelopmental issues in development, and may be able to attend a mainstream school, if there is an understanding teacher and the appropriate support from the school, few mainstream secondary schools provide the necessary educational management in the home, school and at work or day placement.

**Educational Assessment**

The main presenting concerns for families regarding their children centre on educational approaches, which are best managed by a combination of a speech and language therapist, occupational therapist, psychologist and a special education teacher.

While most younger children will be able to attend a mainstream school, if there is an understanding teacher and the appropriate support from the school, few mainstream secondary schools provide the necessary educational management in the home, school and at work or day placement. In the absence of an antecedent or precipitating event, so a trial of one or two medications has been used effectively for the treatment of hyperactivity and sleep disorders in FXS as well as in older individuals by itself or in conjunction with SSRIs. Side-effects include hypo-tension, so the lowest effective dose is used generally at night before bed, and ECGs are recommended to monitor for arrhythmias.

**Management of adults**

**Preventive Care**

A number of medical conditions are often missed in the developmentally disabled population and FXS is no exception (see Table 2).

**Adult Issues**

Few adult males will be able to form relationships with females and, in general, their social contacts tend to be limited to their immediate family, carers and therapists. Many are unable to work in areas such as hospitality, horticulture, cleaning and occasionally retail, with some in sheltered workshops or taking part in supervised work.

Adult females are much more likely to live a relatively normal life; however, some will be severely affected. Counselling for sexuality issues needs to be offered, with the aim of ensuring females can manage their periods and are taught the skills to be able to decline unwanted advances and to be safe.

While some paediatricians continue to see affected individuals into adulthood, this is not common. Apart from a handful of special adult disability units, management generally falls to local GPs, most of whom are generally not trained in this area.

In addition, community resources, when present, are generally extremely poor. Many problems have been identified surrounding inappropriate accommodation for individuals such as the existing community residential units, where a cluster of people with behavioural problems share a unit under guidance of well-meaning but often untrained carers. Preferred alternative housing such as cluster units are rarely available and consequent to behavioural outbreaks, some residents may be transferred to forensic facilities.

Appropriate support in the workplace and in day programs may be less than satisfactory, and numerous cases of all forms of abuse have been well documented. Well-mentioned social change in the past few decades has brought with it confusion about allowing an intellectually disabled individual independence, which includes allowing undesired activities and behaviours.

For example, it is questionable as to whether an individual with a chronologically age of 40 but a developmental age of four should be allowed to smoke cigarettes or eat whatever they like. Needless to say, much of this is completely out of the hands of the average GP.

A careful family member, many adults with FXS are completely dependent on the goodwill and abilities of the carers who supervise their activities on a daily basis.
Table 2: Often missed medical conditions in fragile X patients

| Neurological | Epilepsy – tonic-clonic seizures, complex-partial seizures |
| Gastrointestinal | Constipation, reflux oesophagitis |
| Urogenital | Female – polycystic ovaries, FXPOI, vesicoureteric reflux, renal abnormalities |
| Male – undescended testes, hypospadias, vesicoureteric reflux, renal abnormalities |
| Orthopaedic | Pes planus, hyperextendable joints, scoliosis, asymmetrical leg length |
| ENT | Recurrent otitis media, hearing loss |
| Dental | Caries, gingivitis, root abscesses |
| Ophthalmological | Strabismus, visual perception defects |
| Nutrition | Obesity, under-nutrition |
| Dermatological | Dry skin, eczema, crèpe |
| CVS | Mitral valve prolapse, aortic root dissection/rupture |
| Psychiatric | Anxiety, low self-esteem, schizophrenia, depression, ADHD |

Table 3: Multidisciplinary team

| Audioligist/ENT |
| Optimetrist/ophthalmologist |
| Speech and language therapist |
| Occupational therapy/physiotherapy |
| Psychologist/psychiatrist |
| GP |
| Specialist: developmental paediatrician, neurologist |
| Genetic counsellor/geneticist |
| Special education teacher |

New developments and future directions in research

NEW MEDICATIONS
Animal knockout models have contributed to the understanding of the neurological abnormalities in FXS, and a number of promising medications targeting synaptic involvement with regulation of emotions and learning are currently in various stages of development.

FMRP is an mRNA-binding protein normally needed for synaptic protein inhibition. The lowered levels seen in FXS result in up-regulation of several synaptic proteins, including metabotropic glutamate receptor activated pathways (GluR1 and mGluR5).

Inhibition of mGluR5 would therefore, in theory, inhibit these pathways and contribute to alleviating many of the core symptoms seen in FXS including anxiety, arousal and aggression.

A stage II multicentre DBRCT trial of an mGluR5 inhibitor in FXS AFQ056 is currently underway, with several other medications in various stages of development or at trial, including other mGluR5-negative modulators, arbaclofen, minocycline, lithium and ampakines.

The aim of developing these and newer medications is to reverse the synapse modifications with repair of the pathways needed for normal emotional and intellectual function in individuals affected by FXS and other disorders such as autism.

POPULATION SCREENING
FXS satisfies the WHO criteria for population screening and there are currently a number of trials underway exploring how best to offer this. Newborn screening is being investigated and enables access to early intervention.

Other screening options are to offer carrier testing to women either before conception or in early pregnancy. While research confirms that this type of screening is feasible and acceptable, reproductive options are greater if carrier screening occurs before pregnancy.

Once a child is identified with FXS, many women may be carriers yet unaware of their carrier status. While research confirms that this type of screening is feasible and acceptable, reproductive options are greater if carrier screening occurs before pregnancy.

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