Shropshire Community Health NHS Trust

Policies, Procedures, Guidelines and Protocols

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Local Ref (optional)	
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Who is the document aimed at?	Community Paediatricians, Community Children's Nurses, School Nurses, Health Visitors
Original Author	Dr I Mahabeer,Dr S Brown Dr G Minnaar , Dr P Raveendran
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Method	Electronically fragile x syndrome via managers/Datix, available to all staff by the Trust website
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Amendments History		
No	Date	Amendment
1	V1 April 14	New guideline
2	November 18	Updated
3	V3 March21	Review and guideline updated
4		
5		

Contents

1 Introduction

Fragile X syndrome is one of the most common form of inherited learning disability; it may also cause associated physical conditions. Prevalence estimates from UK screening study in 2003, estimated an overall prevalence of 1 in 4,000 boys and 1 in 8000 girls,this might be an underestimation. As the gene for the fragile X is located on X chromosome the prevalence is less in females.

Fragile X syndrome is inherited from a mother who has a premutation on one of her X chromosomes (a premutation is unstable and can alter to a full mutation in oocyte formation; this alteration does not happen in sperm formation). If it is inherited by a boy (who has one X chromosome and one Y chromosome) he will be affected, if it is inherited by a girl (who has two X chromosomes) she may be affected.

Fragile X syndrome will affect the child, however, as well as medical and management issues for the child, there are also genetic implications for the wider family.

2 Purpose

To provide guidelines on who should be tested for Fragile X syndrome and how to manage those children who have Fragile X syndrome.

3 Definitions / Glossary

Child Development Centre	CDC
Chromosomal Microarray Analysis	CMA
Cytosine-guanine-guanine trinucleotide	CGG
Disability Living Allowance	DLA
Echocardiogram	ECHO
Fragile X Mental Retardation 1 gene	FMR1 gene
Fragile X Mental Retardation 1 Protein	FMRP
Fragile X-associated Tremor/Ataxia	FXTAS
Intelligence Quotient	IQ
Multi-disciplinary team	MDT
Obsessive Compulsive Disorder	OCD
Primary Ovarian Insufficiency	POI
UK Genetic Testing Network	UKGTN

4 Duties

This guideline is for clinicians (community paediatric staff), supported by Services for Children and Young People, Shropshire Community Health NHS Trust.

4.1 Chief Executive

The Chief Executive has ultimate accountability for the strategic and operational management of the Trust, including ensuring there are effective and appropriate processes are in place for the diagnosis, medical management and investigation of children with Fragile X Syndrome.

4.2 Director of Nursing & Medical Director

The Director of Nursing & Medical Director have responsibility for ensuring that appropriate processes are in place for diagnosis, medical management and investigation of children with Fragile X Syndrome.

4.3 Service Managers

Service Managers are responsible for the day to day operational management and coordination of the medical management, health surveillance investigation and diagnosis of children with Fragile X Syndrome.

4.4 All Clinical Staff

Clinical staff are key essential members of the Multi-disciplinary team (MDT), in ensuring that children with Fragile X Syndrome are medically managed appropriately as per national / local guidelines and are offered regular health surveillance checks.[1,2] All clinical staff are required to comply with this guideline and to report any adverse care related issues to their line manager and to complete a Datix incident report in line with the Trust's Incident reporting policy.

5 Fragile X Syndrome, Investigations & Diagnosis

5.1 Molecular Basis

Fragile X syndrome has been termed as such due to the presence of a mutation at the rare fragile CGG triplet repeat site at the genetic locus Xq27.3 causing an abnormality in the FMR1 gene (the fragile X mental retardation 1 gene, which is a widely expressed RNA binding protein).This leads to an abnormal expansion of the triplet repeat area. The *FMR1* gene provides instructions for making a protein called FMRP. This protein helps regulate the production of other proteins and plays a role in the development of synapses. The abnormally expanded CGG segment turns off (silences) the *FMR1* gene, which prevents the gene from producing FMRP. Loss or a shortage (deficiency) of this protein disrupts nervous system functions and leads to the signs and symptoms of fragile X syndrome.

Unstable expansion of cytosine-guanine-guanine (CGG) trinucleotide repeat to more than 200 repeats is the reason in up to 99% of the cases. In the normal population there are 5 to around 44 repeats (likely to be stable), in the full mutation there are over 200 repeats while in the premutation (likely to show instability) there are 55 to 200 repeats (which are likely to increase in number in meiosis in females but not significantly so in males). Repeats of approximately 45 to 54 are intermediate and may show instability. In rare cases the Fragile X syndrome is not caused by CGG repeats but by a point mutation or deletion in FMR1 which leads to an abnormally functioning FMRP (fragile X mental retardation 1 protein).

5.2 Clinical Picture

Fragile X syndrome is seen in affected boys and in some heterozygous girls. The clinical pattern of fragile X syndrome is complicated due to the characteristics of the unstable repeat sequence mutation.

Physical features in older boys include large head, large forehead, long nose, prominent chin and long ears, These are not usually apparent in younger children. Boys may be tall but growth velocity slows in adolescence, and adult males tend to

be short. Macro-orchidism is common in adolescents and adults; it is less common in pre-pubertal boys.

Some of the physical features may be due to the changes in the connective tissue. Many babies with Fragile X have hypotonia. Fragile X has a connective tissue dysplasia, giving a soft skin and joint hypermobility; there is a very slight increase in the frequency of mitral valve prolapse, aortic root dilation and hernias. Other features can include congenital hip dislocation, clubfoot, pes planus, scoliosis, gastro-oesophageal reflux in infants and chronic otitis media. Seizures occur in around 15% of males with the full mutation and 5% of females with the full mutation. Visual difficulties may include strabismus, refractive errors and occasionally nystagmus and ptosis. There may be high arched palate and dental malocclusion.

Behavioural issues include attention difficulties and impulsivity, gaze avoidance, sensory defensiveness, anxiety related behaviours including obsessive compulsive behaviours, emotional lability and autism spectrum disorder. Affected girls and women are known to have problems with shyness or social withdrawal. Often noted symptoms include hand flapping, repetitive actions and clumsiness. Sleep disturbance may be seen.

Learning difficulties may vary from mild to severe (frequently moderate to severe). The average IQ for an adult man with Fragile X is around 40. There may be particular difficulties with numeracy and visuo-spatial skills with relative strengths in vocabulary and speech and language, however perseveration is known to be present. Simultaneous processing of information is stronger than sequential processing.

Both males and females with a premutation (CGG repeats of 55 to 200) can present with clinical disorders including cognitive and/or behavioural difficulties (in females this may include anxiety, obsessional thinking and depression, in males this may include attention difficulties, executive difficulties, social difficulties and obsessive compulsive behaviour).

Females may present with primary ovarian insufficiency (POI) (with cessation of menses before 40 years of age) as well as subclinical ovarian dysfunction. Males (and more rarely females) over 50 years of age may develop FXTAS (fragile X-associated tremor/ataxia).

5.3 Investigation

It is advised that genetic implications should be discussed with parents before testing due to the implications of a diagnosis for other family members. As features of premutation are present across the generations, a detailed family history is essential.

- If there are no clearly significant findings, Fragile X testing will be carried out if it has been requested at the same time and the referral form indications clearly meet UK Genetic Testing Network (UKGTN) criteria (December 2008 renamed April 2017), Appendix 1.
- Referrals for Fragile X carrier or premutation testing in families with a positive family history should be made by the genetics or obstetrics team. Screening during pregnancy is not recommended by UK National screening committee.

5.4 Genetic Counselling / Support for Families

Following a positive diagnosis all family members should be provided information to about Fragile X syndrome, its mode of inheritance and implications for the wider family. Face to face consultation should be by lead paediatrician and referral of the family to clinical genetics should be offered. Genetic counselling should be offered to all family members who are affected or at risk of having pre-mutation or an offspring.

Families should be given information on support groups and services available to the child and family including The Fragile X Society who produce a range of leaflets about many aspects of Fragile X syndrome (www.fragilex.org.uk) [3], Disability Living Allowance (DLA) and the local council (Shropshire or Telford and Wrekin) children's services.
Depending on age at diagnosis and if the child has already been seen at a Child Development Centre, consider:

- If under 3 years of age - referring to pathways for Early Links Shropshire Child Development Centre / First Steps Telford Child Development Centre. If child is pre-nursery age a referral to Portage Services
- If over 2 years 3 months of age and under 5 years CDC multi-disciplinary assessment
- Referral to education services if over 5 years of age.

5.5 Annual Health Surveillance

At all ages health surveillance should include [4]:

- Check growth
- Assess for hypermobility/scoliosis
- Monitor development and behaviour
- Monitor educational progress
- Assess for possibility of seizures
- Check child is under dental follow-up

Refer for initial consultant ophthalmology check in infancy. Suggest yearly optician checks for over 5 year olds who have had an initial ophthalmology check.

Refer for initial audiology check in infancy. Once children are over 5 years of age and have had an initial hearing check, monitor for concerns and refer back to audiology if any concerns expressed.

At secondary school age, listen to the heart at each yearly review. If there are any cardiac symptoms, refer for an Echocardiogram (ECHO).

Before transition to adult services make sure fertility has been discussed (males with a non mosaic full mutation have reduced fertility, females with a full mutation are fertile).

Recommendations for Age –Appropriate Health Surveillance in Fragile X Syndrome

Birth

0-1 month of age

- Examine for orthopaedic abnormalities –congenital dysplasia of hip,club foot
- Record and monitor increase in head circumference ,length and weight at regular intervals

- Watch for any feeding difficulties or gastro-esophaeal reflux

1month to 1 year

- Monitor developmental milestones –esp hypotonia
- Occupational Therapy and Speech and Language Therapy Input
- Feeding difficulties to be addressed
- Growth parameters need to be monitored.

1year to 5 years

- Ophthalmology input for refractive errors,astigmatism.
- Orthotics for flat feet,hyper mobilejoints and gait
- Manage inguinal hernia
- Watch for seizures
- Refer to audiology if recurrent symptoms otitis media ,consider ENT
- SALT input for language delay
- Occupational therapy input for sensory concerns

5 Years to 12 Years

- Monitor for macro-orchidism usually noted at 9 years of age
- Precocious puberty in females with FXS
- Monitor for seizures and consider referral in epilepsy to team

13 years to early adulthood

- Consider cardiology referral if presence of heart murmur
- Consider genetic counselling in reproductive age

6 Consultation

In August 2015 the regional Genetics Department at Birmingham Women's NHS Foundation Trust sent out a revised pathway for the genetic testing of children with developmental disorders and learning difficulties. Current practice is, detection of the pathological expansion in FMR1 by PCR with 5 to 10 of blood in EDTA sample and reporting time of two weeks. For further information please refer to the linkhttps://bwc.nhs.uk/genetics-tests/fragile-x-syndrome-890/.

The following Shropshire Community Health NHS Trust community paediatric doctors were consulted about the Policy in January 2021 .The final recommendations are therefore consensus recommendations from the team.

7 Dissemination and Implementation

This policy will be disseminated and implemented by the following methods:

- Managers Informed via DATIX system who then confirm they have disseminated to staff as appropriate
- Staff via Team Brief
- Published to the staff zone of the trust website

8 Monitoring Compliance

The current cohort of children with a diagnosis of Fragile X Syndrome is small and audit is not currently required.

Compliance to this guideline cannot be monitored as there is no current coding system in place.

9 References

1. Advances in the treatment of fragile X syndrome, Hagerman R, Berry-Kravis E, Kaufmann W et al. Pediatrics. 2009;123(1):378-390
2. Children with Neurodevelopmental Disabilities Mac Keith Press 2013 Chapter 33 p461-464
3. Fragile X Society information www.**fragilex**.org.uk
4. Health Supervision for Children with Fragile X Syndrome, Hersh J, Saul R, and Committee on Genetics. Pediatrics. 2011;127:994-1006 hello
5. Gene reviews FMR1 Disorders Jessica Ezzell Hunter, PhD, Elizabeth Berry-Kravis, MD, PhD, Heather Hipp, MD, and Peter K Todd, MD, PhD.Initial Posting: June 16, 1998; Last Update: November 21, 2019.
6. Consensus Statement of the Indian Academy of Pediatrics on Diagnosis and Management of Fragile X Syndrome in India. Indian Pediatrics,2019 Mar 15;56(3):221-228
7. NHS evidence screening

   https://patient.info/doctor/fragile-x-syndrome#https://fragilex.org/

   https://legacyscreening.phe.org.uk/fragilex

10 Associated Documents

Shropshire Community Health NHS Trust Consent to Examination and Treatment 15th November 2015 Policy

Shropshire Community Health NHS Trust Records Management 2nd March 2017 Policy

11 Appendices

Appendix 1 UKGTN Testing Criteria
Appendix 2 Letter 05 08 15 (PDF document)

Appendix 1

UK Genetic Testing Network (UKGTN) Testing criteria

Males with full mutation

Minimum criteria:

- Male
- **AND** moderate to severe developmental delay/learning difficulty (IQ if measured would be 35-70 range)
- **AND** does not have profound psychomotor handicap necessitating total care
- **AND** Fragile X test specifically requested by referrer (i.e. not laboratory initiated)

Typically will have:

- Gaze avoidance
- Resists physical contact (tactile defensiveness)
- Repetitive speech/perseveration (delayed echolalia) and behaviours on autistic spectrum (hand flapping, hand biting)
- Inattentive and distractible; motor hyperactivity/restlessness
- Shy and socially anxious, but also sociably friendly
- Particular difficulty with numeracy and visuo-spatial skills
- Head circumference > 50^{th} centile
- Joint laxity

Also may have:

- Family history of learning difficulty
- Long ears – post 7 years
- Large testes – post puberty
- Epilepsy

Very unlikely to have:

- High functioning (normal intelligence) autism/Asperger's syndrome
- Classic 'aloof' severe autistic phenotype
- Microcephaly

Females as index case

Minimum criteria:

- Female
- **AND** learning difficulty (usually mild, IQ often 80-85, but can be moderate or severe)
- **AND** does not have profound psychomotor handicap necessitating total care
- **AND** Fragile X test specifically requested by referrer (i.e. not laboratory initiated)

Often will have:

- Attention difficulty
- Gaze avoidance
- Resists physical contact (tactile defensiveness)
- Communication problems, impulsive faux pas in speech
- Shy, self-conscious and socially anxious behaviour
- Obsessionality
- Passivity
- Particular difficulty with maths and visuo-spatial skills
- Poor adaptive skills/vulnerable

Also may have:

- Family history of learning difficulty

Very unlikely to have:

- High functioning (normal intelligence) autism/Asperger's syndrome
- Classic 'aloof' severe autistic phenotype
- Microcephaly

Fragile X Carrier or Premutation test in relatives with known family history

Criteria:

- Known family history of Fragile X, premutation Fragile X, or intermediate allele of uncertain stability and ≥ 56 repeats (but excluding generationally stable intermediate allele), **AND** potentially sharing same X chromosome
- **OR** female with close family history of male relative with severe learning difficulty without specific diagnosis, especially if he fits guidance notes for affected males (see above)

Appendix 2

Clinical Genetics Letter of testing pathway for fragile X - 05 08 15

Letter 05 08 2015.pdf