PCP Handout

Caring for Persons with Fragile X

Fragile X is the most common inherited cause of intellectual disability, with x-linked dominant inheritance. Clinical features are variable. It occurs in ~1 in 4,000 males and 1 in 8,000 females. >99% caused by unstable expansion of CGG triplet repeat at 5' untranslated region of FMRI gene (fragile X mental retardation 1) on long arm of X chromosome (Xq27.3). The mutation causes gene hypermethylation and prevents production of the protein (FMRP), which regulates other proteins and plays role in synapse development. Connective tissue issues are related to lack of FMRP on elastin fibril structure in the skin, heart, vessels and organs.

Testing	▪ In typical persons, CGG triplet repeats 5 - 40 times. ▪ In carriers, premutations 55 - 200 repeats. Assoc w/ increased ovarian failure (12-28%), tremor-ataxia syndrome (FXTAS) associated with dementia, typically after age 50 (20-33%) ▪ In fragile X, CGG repeats > 200 times. Females less affected due to function of one X chromosome.

System	Information	Follow up
Cognition	▪ Adult male average IQ 41 (range 25-69), females 50% IQ 70–84, 60% males / 20% females have autism. ▪ Increased inattention. Speech impairment common	▪ Early intervention, special education ▪ Autism testing
Facial features	▪ Males-prominent ears (75-80%), long face, high forehead, high-arched palate, prominent jaw ▪ Dysmorphology in 50% females	
Vision	▪ Strabismus 7.5%, nystagmus, ptosis, refractive errors 25-50%	▪ Vision screening
Dental	▪ Dental crowding and malocclusion	▪ Routine dental care, accommodation as needed
Cardio-vascular	▪ Mitral valve prolapse 50% males, females 20% (most asymptomatic), increased hypertension ▪ Ascending aortic dilation 7.5% usual non-progress	▪ Screen cardiac exam, blood pressure ▪ Consider beta blocker for arrhythmia or dysautonomia
Endocrine	▪ Female precocious puberty occasional	▪ Evaluate for symptoms
Pulmonary/ ENT	▪ Recurrent sinus infections 25%, recurrent otitis media 60-80% (d/t long face, collapsible Eustachian tubes)	▪ May under-report pain.
GI	▪ Encopresis 49%, constipation	▪ Consider fiber supplement
GU	▪ Macro-orchidism begin age 9 - 80-90% ▪ Inguinal hernia - 15%, male, fertility may be reduced ▪ Enuresis	▪ Examine for hernias
Musculo-skeletal	▪ Soft velvet skin, hyperextensible fingers, subluxable thumbs, hyperextensible 70% as child, as adult 30% ▪ Scoliosis 20%, pes planus 60-80% ▪ Male adult short stature 26%, growth as child may accelerate	▪ Surveillance for scoliosis ▪ Physical therapy for laxity symptoms.
Neurology	▪ Seizures – males 15%, females 5%, in childhood, often resolve, increased with macrocephaly, most common complex partial, all types reported ▪ Tic disorder 6% ▪ Macrocephaly 50%, cerebral cortical atrophy 7.5% ▪ Sleep issues 33%, sleep apnea 3.4%	▪ EEG wake & sleep for symptoms. Notable rates of abn EEG w/o seizures. ▪ Monotherapy w/ carbamazepine, valproate ▪ Stimulants may worsen tics. Clonidine, guanfacine may help. ▪ Screen for sleep apnea. Behavior mngmt, melatonin, clonidine, trazodone may help.
Mental Health	▪ Increased anxiety, behavior obsessions, disruptions	▪ Screen mood and behavior.

References: Lozano R, et al. Fragile X syndrome: A review of clinical management. Intractable Rare Dis Res. 2016 Aug;5(3):145-57.

Salcedo-Arellano MJ, et al. Fragile X syndrome & assoc disorders: Clinical aspects & pathology. Neurobiol Dis. 2020 Mar;136: 104740.

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