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BACKGROUND

Fragile X Syndrome (FXS), was first described in 1943 as a form of intellectual disability (ID). A meta-analysis of fifteen studies that included 7,475 individuals showed that FXS is the second cause of ID after Down Syndrome (DS). The disorder is linked to an unstable expansion of CGG repeat (>200) within the fragile X mental retardation 1 gene (FMR1) causing a loss of function in the gene.

The clinical spectrum of FXS is wide including intellectual disability and other multi-system symptoms. Therefore, confirmed diagnosis is made based upon the detection of alterations to FMR1 gene. While males tend to present with intellectual disability, females tend to present with learning disability and less sever intellectual limitations.

Individuals diagnosed with Fragile X Syndrome (FXS) are predisposed to sleep disorders including obstructive sleep apnea (OSA). The aim of this study is to assess the prevalence of sleep disorders and comorbid associated sleep problems in this population along with appropriate pharmacological and/ or non-pharmacological interventions.

METHODS

A literature search was conducted using the following search engines: google scholar, PubMed, Ovid, Cochrane library, and PLOS. All English language published articles were identified by searching for “Fragile X Syndrome” crossed by “obstructive sleep apnea” and “sleep problems”. Literature review was done on selected studies to assess a possible increased risk of OSA in individuals with FXS or lack thereof and best options for management. Crossing OSA, sleep problems, FXS, and management was used to identify articles with patient management options in different populations and their outcomes.

RESULTS

Epidemiology and causes of Sleep Difficulties in FXS

Polysomnography (PSG) has been used as the reference standard for the diagnosis of OSA, especially in children. Other diagnostic methods were utilized in multiple studies including: pulse oximetry or parental reports (e.g., studies using OSA-18 questionnaire). However, these later modalities while cheaper and easier to implement, is not as accurate as the in-laboratory PSG. Sleep disorders as well as OSA is more common in FXS than in the general population (35-50% in FXS vs 1-10% in normal children). An analysis of 90 children with FXS using parents reported CSHQ found that 47% of children with FXS had clinically significant sleep problem. Parents of FXS patients reported a number of sleep problems including: difficulty falling asleep, frequent awakening, and restless sleep.

A recent national survey using body mass index (BMI) data from 718 children, found that male children with FXS had a higher prevalence rate of obesity (31%) when compared to age matched control children (18%). This higher prevalence of obesity in FXS individuals might be one of the major contributors to OSA in this population. Other causes includes: narrow oropharynx, retrognathia, hypotonia and connective tissue disease.

Comorbid Self-Injurious Behavior in FXS Patients with Sleep Difficulties

Self-injurious behavior (SIB) was reported in 58% of the participants, with age of onset around 3 years old. The primary form of frequent (i.e., daily) self-biting or chewing is directed toward the hand or arm which adds additional challenge and burden to the caregivers of patients with FXS.

Pharmacological and non-pharmacological Interventions

Behavioral strategies including: circadian rhythm management, positive bedtime routines, white noise, graduated extinction, scheduled awakening and parent training programs showed significant results in alleviating sleep problems.

Many FXS children might not show adequate response to the above strategies and will benefit from a pharmacological intervention as melatonin, GABA receptor agonists and alpha-2- agonist. In a study involving 127 FXS carrier gene compared to 86 controls, RLS symptoms were increased by 1.9 fold. Since FMRP and FMR1 has been involved in dopamine activity, it is thus expected that dopaminergic agents might help sleep in this population.

Sample image

CPAP is considered the gold standard treatment for OSA and was shown effective in reducing symptoms of sleepiness and improving the quality of life measures in patients with moderate and severe OSA, the compliance to CPAP has long been reported to be poor. Therefore, surgical interventions can be helpful in alleviating the OSA symptoms in non-compliant and CPAP refractory patients. Surgical interventions includes: rapid maxillary expansion (RME), mandibular distraction osteogenesis (MDO), and mini tracheotomies

CONCLUSION

The overall discrepancy in the prevalence of sleep disorder in children with FXS between the studies in the literature can probably be attributed to differences in study design, sample size, and data collection protocols. However, it appears that both sleep disorders as well as OSA is more common in FXS than in the general population.

Patients showed improvement in sleep in response to behavioral interventions, melatonin, GABA receptor agonists and alpha-2-agonist. While CPAP is the gold standard for OSA treatment, compliance is poor and challenging in FXS patients. CPAP refractory patients can benefit from several surgical interventions.

More epidemiological research is needed on individuals diagnosed with FXS, including a focus on identifying the possible role that factors such as gender, age, BMI, and other comorbid medical problems which may be risk factors for OSA.

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