Clinical Medicine Insights: Ear, Nose and Throat

ORIGINAL RESEARCH

Effect of Recurrent Otitis Media on Language Profile in Children with Fragile X Syndrome

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Objective: Language is almost always affected in fragile X syndrome (FXS), and a delay in language acquisition is one of the first characteristics. The aim of this work was to study the effect of recurrent middle ear infections on the language profile in boys with FXS. Study design: Prospective case series.
Setting: Academic Medical Center.
Subjects and Methods: The present study was conducted on 30 males, ranging in age from 4–10 years. They were diagnosed as having a full mutation of DNA. The males were divided into two groups: Group A included 15 children with a history of recurrent middle ear infections more than four times per year during the first 4 years of life, and Group B did not have a history of recurrent middle ear infections during the first 4 years of life. Language assessments were done for all participants using the Standardized Arabic Language test.
Results: Results showed significant delays in language development in children with FXS. Relative strengths in semantics compared to syntax and pragmatics were observed in all boys. The recurrent ear infections of the boys played an important role in the language development delay. The mean of receptive, expressive, and total language age was better and higher among boys without a history of recurrent middle ear infections compared to boys with recurrent middle ear infections.
Conclusion: Recurrent otitis media in boys with FXS exacerbates the language problems that exist in this syndrome.

Keywords: fragile X syndrome, language assessment, language test, recurrent middle ear infections

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Introduction

Fragile X syndrome (FXS) is the most common cause of inherited mental retardation, affecting approximately 1 in 4000 males and 1 in 8000 females.[1] It is caused by an expansion mutation in the Fragile Site Mental Retardation 1 gene (FMR1) located on the X chromosome.[2] This syndrome is associated with the expansion of a single trinucleotide gene sequence (CGG) on the X chromosome, and results in a failure to express the FMR1 protein, which is required for normal neural development. There are four generally accepted states of the chromosome region involved in FXS that relate to the length of the repeated CGG sequence. Normal alleles have approximately 5–44 repeats (not affected by the syndrome); premutation alleles have approximately 55–200 repeats (may be affected in some respects); full-mutation alleles have more than 200 CGG repeats (affected); and intermediate alleles (also termed "gray zone" or "borderline") have approximately 45–54 repeats.[3]

Aside from intellectual disability, prominent characteristics of the syndrome include an elongated face (vertical maxillary excess), high-arched palate, large or protruding ears with soft cartilage, flat feet, hyperextensible finger joints, larger testes (macroorchidism), soft skin, and low muscle tone.[4] These characteristics may be related to changes in the elastin fibers of connective tissue.[5] Behavioral problems, including inattentiveness, hyperactivity and autistic-like behavior have been frequently noted in males with FXS.[6] Many studies have evaluated the FXS-autism link over the past decade. These studies have shown the percentage of children with FXS who have autism varying from 15% to 33%.

Recurrent otitis media and hearing loss are common in many genetic disorders.[7] Children with FXS may be at increased risk for chronic middle ear infections (otitis media).[8] Patients with FXS have significantly more events of otitis media than their normal siblings. They have indeed proved to be a high-risk group not only for recurrent otitis media, but also for persistent effusion, which can lead to sequelae of middle ear disease.[9] These patients may have a floppier Eustachian tube that collapses more readily, preventing adequate drainage of the middle ear. Also, the craniofacial structure in FXS includes a long narrow face and a high-arched palate, which may cause subtle changes in the angle of the Eustachian tube, and which may affect drainage from the middle ear.[9]

Recurrent ear disease may exacerbate the cognitive, language, and behavior problems that exist in this syndrome.[9] Speech and language disorders are common in FXS.[10]

Most males show moderate-to-severe delays in communication skills, while the communication skills of females are considerably less affected. Males with FXS have been reported to have delays in grammatical and vocabulary development, although some researchers suggest that there may be a specific deficit in syntax and/or semantic aspects of language development. Grammatical skills and vocabulary levels of males with FXS appear to be consistent with their nonverbal cognition level. Higher scores in comprehension than in the production of syntax and vocabulary have been reported in a few studies.[11] Males with FXS have been reported to have atypical pragmatic language, including frequent perseveration of words, sentences, and topics; self-repetitions; poor topic maintenance in conversation; difficulty answering direct questions; and gaze aversion. The cause for these pragmatic impairments has most often been attributed to hyperarousal, although word retrieval difficulties, syntactic difficulties, and executive function deficits also have been cited as possible causes.[11]

Language and speech assessment have important clinical implications for developing specific speech and language intervention programs, focusing on areas of strengths to improve areas of weakness in patients with FXS.[12]

Subjects and Methods

Subjects

Throughout the course of 4 years, 30 Arabic-speaking males who were proven to have FXS based on DNA analysis were included in this study. They were selected from the outpatient clinics of Saudi German Hospital in Jeddah, Saudi Arabia. They were diagnosed with the full mutation (>200 repeats). They were divided into two groups; Group A included 15 children with a history of recurrent middle ear infections more than four times per year during the first 4 years of life with variable duration of each attack ranging from 5–15 days for each attack, and Group B did not have a history of recurrent middle ear infections during the first 4 years of life. The two

groups at the time of study did not have any degree of hearing impairment. We selected boys with approximately the same physical and functional abilities, as well as similar cognitive aptitudes. All males had mild intellectual disability with no autistic features. This was decided upon according to the results of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association),[13] and the Stanford-Binet Intelligence Scale. The two groups were subjected to the same language assessment protocol.

Methods

Both groups were subjected to the following assessment protocol:

- Interviewing parents and history taking: the males had a history of hearing difficulty, information on social interaction, behavior, function in the educational setting, and language development.
- General examination including neurological examination.
- Vocal tract examination for oral and dental abnormalities, and a high-arched palate.
- Ear examination: aside from the characteristic large ears with soft cartilage, the boys were examined for signs of recurrent otitis media, which included abnormal tympanic membrane color such as amber or blue, opacification, decreased or absent mobility by pneumo-otoscopy, and a retracted or concave tympanic membrane with air bubbles or air-fluid level.
- Audiological assessment: tympanometry and auditory brainstem response (ABR).
- Psychometric evaluation test: Stanford-Binet Intelligence Scale.[14] The scale measured several cognitive abilities including perception, abstraction, problem-solving, arithmetic, and general comprehension. It assessed the mental ages of the children and measured their intelligent quotients. In this study, all boys had mild intellectual disability.
- The DSM-IV (American Psychiatric Association)[13] was used to rule out autistic features.
- Molecular genetics testing: many different polymerase chain reaction protocols have been developed for the fragile X CGG repeat, with differing degrees of amplification abilities. Normal alleles with approximately 5–44 CGG repeats provided a fragment length of 400–490 bps. Full mutant alleles (>200 CGG repeats) provided more than 940 bps fragments (always undetectable on gels). Some boys came to us undiagnosed (only complaining of delayed language development). This test was applied to those undiagnosed boys.
- Language assessment: The Standardized Arabic Language Test (Kotby et al[15]). The test was performed either in one or more sessions according to the ability of each child. It was used to assess the attention of the child, the ability to imitate actions and sounds, semantics of the language, syntactic receptive abilities, syntactic expressive abilities, pragmatics, and phonology. Cards of colored pictures and figures were used to perform this test. To test semantics, the test included an assessment of the child's ability to identify and name pictures of objects, to understand contrasts, to put objects into semantic groups, to understand time factors, and to complete objects or to put similar objects together. To test pragmatics, the test included an assessment of the child's ability to analyze the situation, to choose the suitable words for this situation, to enter into a dialogue, and to elongate the dialogue or to finish it. To test for syntax, the test included an assessment of the child's ability to understand and utter short and long sentences, his ability to say his name, answer questions, understand long orders, and to understand and express the tense of sentences, the singular and plural, pronouns, adjectives, adverbs, negations, contrasts, numbers, possessions, comparisons, superlatives, passive sentences, time indicators, place indicators, and functions of objects. A sample of spontaneous speech was included to comment on the length of the sentence and its degree of intelligibility.

The advantage of this test is the wider age range it addresses and the more test items it assesses. The high validity and reliability of this test proves its sensitivity and objectivity. The test validity was proven by two methods: the face validity and construct validity. The test reliability was shown to be high using the test-retest technique.

- Statistical analysis: 30 males were subjected to statistical analysis. The data were coded, entered, and analyzed using the Statistical Package for the Social Sciences version 12. The descriptive

statistics were computed to summarize the mean and standard deviation for the quantitative variables, and the percentage for qualitative variables.
- The Mann-Whitney test was used for quantitative variables. *P*-values < 0.05 were considered significant.
- We got approval for doing this work from the Saudi German Hospital ethical committee dated October 15, 2008.

Results

This study included 30 males diagnosed with the full mutation (>200 repeats) with mild intellectual disability and no autistic features. Their ages ranged from 4–10 years with the mean age of 7.1 years for Group A and 6.4 years for Group B. The auditory brainstem response conducted for all the boys showed normal waves, denoting an absence of any hearing impairments (Fig. 1).

Studies of receptive language age, expressive language age, semantics age, prosody age, pragmatics age, and total language age showed significant language delays in all language age parameters. Studying various language age parameters among the studied boys (Table 1) showed that both groups (A and B) had marked delays in language development. A wider gap between various age parameters and chronological ages in Group A was observed when compared to Group B.

The mean receptive language age (3.35 years), expressive language age (4.05 years), and total language age (4.05 years) was better and higher among the boys in Group B when compared to the mean receptive language age (3.2 years), expressive language age (2.8 years), and total language age (3 years) among the boys in Group A. (Fig. 2).

Discussion

Recurrent otitis media and hearing loss are common in many genetic disorders.[7] Children with FXS may be at increased risk for chronic middle ear infections (otitis media).[8] Hagerman et al[6] have noticed that recurrent otitis media is a frequent finding in the medical history of boys with FXS. Nielsen[16] has also noted frequent otitis media in the case history of males with FXS.

Studies on the hearing of young males with FXS are generally lacking. A few studies have suggested that a significant proportion of individuals with FXS demonstrate prolonged ABR latencies. Atypical outer ear morphology is characteristic of FXS and may serve as a marker for abnormal auditory function.[17] Males with FXS were similar to typically developing males who were matched for developmental age level or chronological age level on all measures. They had normal hearing sensitivity and middle ear function, and scored similar to the typically developing children on the measures of auditory brainstem

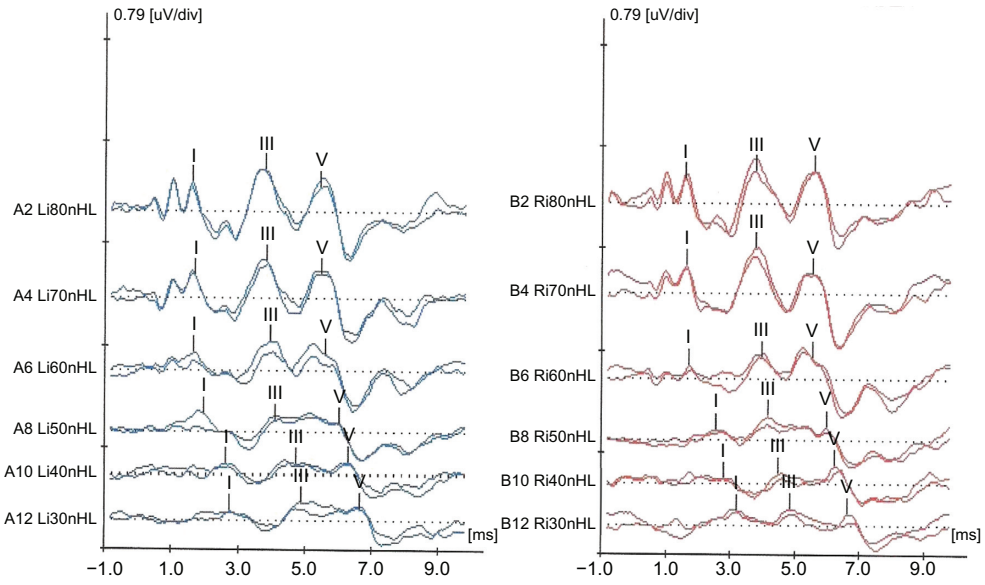

Figure 1. Normal auditory brain stem response waves.

Table 1. Comparison between the studied groups regarding various language age parameters.

Item	Mean	Standard deviation	Minimum	Maximum	*P* value	Significance (Mann-Whitney test)
Receptive age						
Group A	3.2	1.49	2	7	0.428	Not significant
Group B	3.35	1.51	2.5	7.5		
Expressive age						
Group A	2.86	1.42	2	6.5	0.026	Significant
Group B	4.05	1.81	2	8		
Semantics age						
Group A	3.46	1.71	2	8	0.008	Significant
Group B	5.9	2.1	2.5	8		
Prosody age						
Group A	2	0	2	2	0.428	Not significant
Group B	2.6	1.72	2	7.5		
Pragmatics age						
Group A	2.166	0.52	2	4	0.16	Not significant
Group B	2.4	0.51	2	3.5		
Total language age						
Group A	3	1.71	2	8	0.031	Significant
Group B	4.05	2.15	2	8		

pathway integrity. In summary, ABRs in young males with FXS were within normal limits.[17] However, the long-term effects of mild or fluctuating hearing loss associated with recurrent otitis with effusion is more controversial.[18–20] More than 40% of children with otitis media have persistent effusion in the middle ear that lasts for weeks after antibiotic treatment.[21] This persistent middle ear fluid is the cause of a fluctuating hearing loss of 16 to 40 dB in over 90% of patients.[22] However, comparing males with mild intellectual disability and no autistic features is a limitation in this study.

The effect of frequent otitis media infections is unknown; however, language delays are usually the first sign of developmental problems in males with FXS.[23] The occasional male child with FXS presenting with cognitive development in the low normal range will also demonstrate speech and language problems, including auditory processing deficits and cluttered speech.[10]

Males with FXS typically have communication deficits;[24] they are delayed in many domains of speech and language.[24] Most males show moderate to severe delays in communication skills.[25]

We acquired our data concerning recurrent middle ear infections during the first 4 years of life by history from the children's parents (retrospective). All boys were monitored in other centers other than our hospital and they did not have any databases for the previous records. According to the history, all boys in Group A had a history of recurrent middle ear infections occurring more than four times per year during the first 4 years of life, with variable durations ranging from 5–15 days for each attack. Also, there are variations in the presentation of each attack; some parents gave a history of only otalgia and deafness, and some gave history of suppurative otorrhea indicating acute suppurative otitis media with a perforated eardrum. It might be more difficult to identify otitis media in males who may not be able to communicate

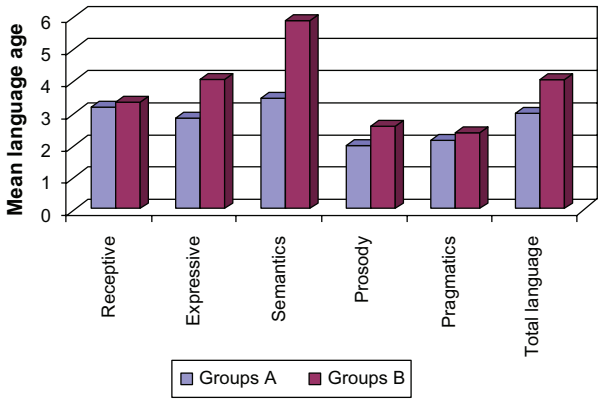

Figure 2. Comparison between the studied groups regarding various language age parameters.

that their ears hurt. The exact number of each attack cannot be given precisely by the parents' history. However, none of the boys now has significant hearing loss or manifestations of central auditory processing disorders.

Language assessments among our studied males showed significant delays in both Groups A and B. Harris-Schmidt[26] attributed the etiology of speech and language delay in patients with FXS to several factors. She specified the speech and language patterns of persons with FXS to be different from the speech and language of persons with other causes of developmental disorders, such as Down' syndrome and autism. She reported that the speech and language of boys with FXS were often affected by differences in physical structures. Ear infections, oral-motor sensitivity, and the structure of the palate may cause problems in both language and speech. She also mentioned that auditory processing problems were reported in those patients such as problems in attention, memory, word retrieval, and auditory sequencing, which in turn affected both the comprehension and production of speech and language.[26]

The study of the various language age parameters among our boys showed that both groups (Group A and Group B) had marked delays in language development. A wider gap between various age parameters was observed in Group A compared to Group B.

In our study, the mean receptive language age (3.35 years) and expressive language age (4.05 years) was better in FXS boys without a history of recurrent otitis media compared to the mean receptive language age (3.2 years) and expressive language age (2.86 years) in FXS boys with a history of recurrent otitis media. Most of the evidence, however, suggests that the sequelae of recurrent otitis with effusion includes not only problems with speech articulation and language delays, but also academic,[27] cognitive, and behavioral problems, including inattentiveness, impulsivity, and hyperactivity.[28]

Because most males with FXS suffer from significant language deficits and attentional problems, which have also been identified as sequelae to recurrent otitis media, it would seem reasonable to treat the recurrent otitis media most vigorously in FXS. Such treatment would help to avoid these sequelae, which can be devastating when combined with the cognitive deficits that are always present in affected males.[9] Management may also require the surgical insertion of drainage tubes (tympanostomy).[8]

Conclusion

Finally we concluded that recurrent otitis media in boys with FXS exacerbate the language problems that exist in this syndrome. Efforts must be done for early diagnosis and management of any attack of acute otitis media to avoid unfavorable sequelae of this delay.

Author Contributions

Conceived and designed the experiments: HB. Analyzed the data: HB, SN. Wrote the first draft of the manuscript: HB, SN. Contributed to the writing of the manuscript: HB, KA, SN. Agree with manuscript results and conclusions: HB, KA, SN. Jointly developed the structure and arguments for the paper: HB, KA, SN. Made critical revisions and approved final version: HB, KA, SN. All authors reviewed and approved of the final manuscript.

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Disclosure and Ethics

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