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Lujan-Fryns Syndrome Phenotype with Autism-Like Behavior and Atypical Psychotic Symptoms: Case Report

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SUMMARY

Lujan-Fryns Syndrome (LFS) is defined as a set of symptoms including mild-moderate mental retardation, marfanoid appearance, hypotonia at birth, hypernasal speech, characteristic craniofacial appearance and normal testis size. The frequency of the syndrome is not known thus the information obtained is solely based on case reports. Hereby, we present a patient with LFS diagnosis.

The 29-year old male patient had mental retardation, aggression, and persecutory delusions, characteristic craniofacial and marfanoid features. During his speech pronominal reversal was observed ('the hurt him, he is so upset' when talking abour himself). After examination and genetic analysis, fragile X, Klinefelter, Marfan and Down syndromes and homocystinuria were eliminated as causes of mental retardation. A preliminary diagnoses of LFS done. No mutation was detected in exon 22 of the MED12 gene; but whole Exome Sequencing (WES) is ongoing. The patient was started on risperidone (4 mg/day) for psychotic symptoms and carbamazepine (200 mg/day) for impulse control and as an antiepileptic. After a follow up of 8 months, impulse control, psychotic symptoms and aggression improved significantly.

Since the specific gene mutation of LFS was not determined in our case, we solely had to depend on clinical evaluation and genetic analysis. Although it is not easy to fully define or classify these syndromes, we believe every reported case will be a step in overcoming these difficulties.

Keywords: Lujan Fryns Syndrome, psychotic disorders, autism, MED 12, delusion, Fragile X syndrome

INTRODUCTION

The Lujan-Fryns Syndrome (LFS) was first recognized when Lujan et al. (1984) reported 4 male cases sharing symptoms of marfanoid appearance, X chromosome linked mental retardation, hypernasal speech, behavioral disorders, atrial septal defect and joint hyperextensibility. The framework of LFS became clearer following the report of 2 similar cases by Fryns and Buttiens (1987).

The major clinical diagnostic criteria for LFS were reported to include: 1) mild-to-moderate mental retardation; 2) marfanoid appearance; 3) diffuse hypotonia and hyper-nasal sound at birth; 4) normal secondary sex development and testicle size; 5) characteristic craniofacial appearance with prominent forehead, long narrow face, maxillary hypoplasia, long nose with high and narrow nasal bridge, short and deep philtrum, thin upper lip and highly arched palate (Fryns 1991). Although the diagnostic criteria for LFS do not include psychiatric symptoms, cases of comorbid behavioral disorders and psychiatric symptoms including psychotic symptom (Lalatta et al. 1991), aggression (Lacombe et al. 1993), autistic behavior (Purandare and Markar 2005), cognitive disorders (Wittine et al. 1999), timidity (Purandare and Markar 2005), hyperactivity (Purandare and Markar 2005) and eating disorder (Alonso et al. 2006) have been reported.

Here, we present an LFS case accompanied by autistic behaviours and psychotic symptoms.

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CASE

The 29-year old single male lycée graduate working as a disabled government employee consulted our outpatient clinic with his family. The patient did not believe he had complaints. His history, obtained from the family, included complaints of repetitive behaviors, irritability, limited communication and persecutory delusions. The family reported an anxious condition that impaired his social relations. The patient had displayed increased impulsive behaviors with sexual implications such as physical contact with parents, watching sexual videos over the previous 1 month. His relations reported that the patient made changing facial expressions, clapped hands, clenched and shook his fists when excited; and that since his childhood he had communication problems and maladaptive behaviours such as yelling inappropriately in the classroom, hitting his friends, violating game rules and crying when his will was not fulfilled. Although persecutory ideations were present since he attended the lycée, they had reached to a delusional level within the previous 3-4 years. During his interview, the patient referred to himself in the third person with pronominal reversal (for example, "They hurt him, he is so sad"). The patient did not have a history of alcohol or substance use, previous head injury or previous central nervous system infection. The patient had a history of simple, partial epileptic seizures which started at 8 years of age and was treated with sodium valproate over 6 years for these seizures. The last epileptic seizure had taken place 11 years previously. He was also using risperidone at varying doses (maximally 6 mg/day) since he was 10 years old.

Family history included diagnosis of hypothyroidism in his mother during pregnancy which was under treatment, who also had been exposed to radiation at unknown doses in the healthcare center where she worked as nurse. The patient was born in a hospital at full term with normal delivery and birth weight. He did not have respiratory distress requiring ventilator or incubator support. However, he had supplementary bottle feeding due to weak suck from 3 months onwards. His vaccinations were all timely. The patient had limited eye contact since infancy and delayed gross motor skills, social skills and language development such as walking and speech.

It was learned that the patient displayed childhood hyperactivity and violent behaviors of hitting, pushing or injuring others with sharp objects such as the pen tip or the compass needle. The patient attended classes for special education due to his mental disability. His violent behaviours persisted in adolescence with increased sexual implications and difficulty in forming social contact. The patient was diagnosed with mental-motor retardation (IQ=45) and was excluded from the compulsory male military service. He had been employed during the previous 1 year as a disabled civil servant in a document registration office with 3 co-workers and received help from them when facing difficulty. His problems with difficulty in waking up or unwillingness to attend work were tolerated by his superior and co-workers. The patient's 53-year old mother, formerly employed as a nurse; was now caring for her children. She was diagnosed with chronic depression 8 years previously and was using sertraline (100 mg/day). She did not have any medical illness other than hypothyroidism. The father, a retired mechanical engineer, was 59-years old without a history of mental or physical illness. The parents were not consanguineous and did not have history of genetic or psychological disorder. The patient had a 21-year old sibling using valproic acid (750 mg/day) since diagnosis with fragile X syndrome and epilepsy at 15 years of age. Figure 1 shows at the phenotypes of the patient and of his family members.

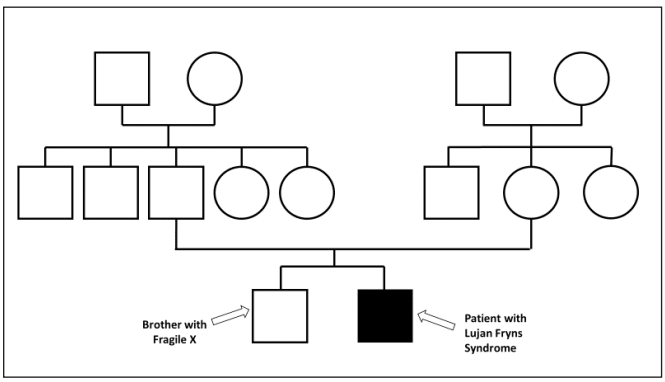

Figure 1. Patient's Family Tree

During his psychiatric examination the patient's self-care was seen to be partly reduced, that he was uninvolved with the interviewer and almost did not have any eye contact. He was conscious with normal orientation; had poor spontaneous and voluntary attention and poor short-term memory but normal long-term memory and instant recall. He had poor abstract thinking, normal objective thinking and normal perception. His speech was tangential and there were persecutory delusions in his thought contents. His mood was irritable with constricted and labile affect. His speech was not spontaneous and had blocks. His judgment was impaired by persecutory delusions, insisting that his teachers deliberately had not taught him anything and that they were still disturbing him with support from his father.

He had difficulty sitting still during the interview, raising his voice and yelling when his thought contents were queried, indicating that his impulse control was reduced. Although the IQ of the patient was not tested, it was decided, on the basis of the psychiatric examination, that he had mild mental retardation. The previous diagnoses of moderate-to-severe mental retardation might have resulted from maladaptation to test and having epileptic seizures in the past. Elevated

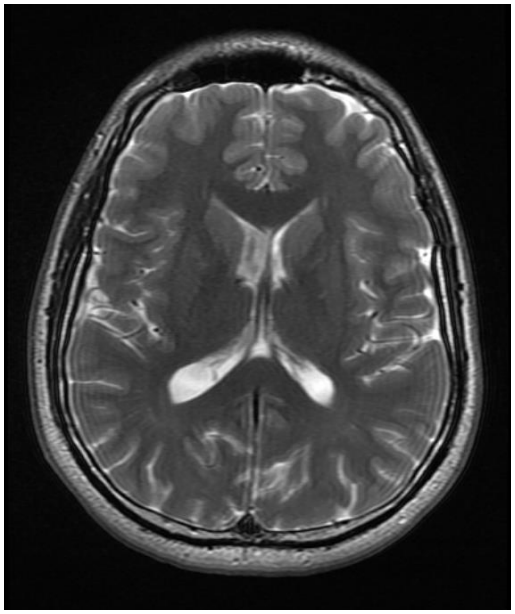

Figure 2. T2 Axial MR Image of the Patient

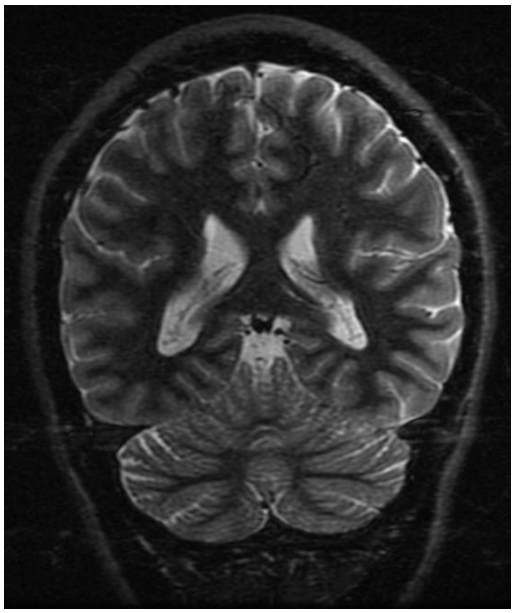

Figure 3. T2 Coronal MR Image of the Patient

prolactin level (70.48 ng/mL) was the only biochemical anomaly determined and this was attributed to antipsychotic agent he was using. The EEG results supported partial-onset of epilepsy on a background of diffuse, mild cerebral dysfunction. The cranial MRI was suboptimal due to the movements of the patient but the imaging was within normal limits and without diffusion restriction (Figure 2 and 3).

Given the diagnosis of fragile X syndrome in the patient's sibling, the patient's own syndromic characteristics as the marfanoid appearance with a height of 189 cm, arm span of 201 cm, an upper [apex-symphysis pubis]: lower extremity [symphysis pubis-base] ratio of 0.75; talking with pronominal reversal, were evaluated in consultation with the medical genetics department. The patient was determined by physical examination to have a narrow-low shoulder, prominent supraorbital protuberance, thick eyebrows tending to fuse in the midline, long philtrum, high palate, kyphosis, wide thumb and toe on the left hand and foot and low hairline at the neck.

Evaluating together the existing syndromic data, mental retardation and the marfanoid appearance, preliminary diagnoses of homocystinuria and the Fragile X, Marfan, Klinefelter, Down and Lujan-Fryns syndromes were considered. The patient did not have chromosomal mutation but was of the 46XY karyotype in the genetic analyses done at the time of diagnosing the fragile X syndrome in the patient's sibling. The Fragile X syndrome was ruled out due to lack of macroorchidism which is commonly seen in this syndrome (95%) (Rajaratnam et al., 2017). Determination of normal plasma homocysteine (<10 μmol/L) and its absence in the urine eliminated homocysteinuria. The 46XY karyotype eliminated the Klinefelter and the Down syndromes. Differential diagnosis for Marfan syndrome based on ophthalmological examination for lens luxation and myopia gave negative results.

At the stage of discharge from the hospital, cardiology examination was scheduled for cardiac disorders comorbid with LFS and the other genetic disorders. However, the patient did not attend his cardiology examination; thus, data could be not be obtained on cardiac problem. The patient also missed two echocardiography appointments made during follow up. The ECG performed at admission to hospital had not indicated any cardiac problems, but lacking data on echocardiography remains as an important limitation. Marfan syndrome was ruled out because skin elasticity, ocular examination and ECG were within normal limits. In addition, the presence of mental retardation was one of the reasons that distanced Marfan syndrome. Hence, genetic testing for the associated FBN1 gene analysis was not requested. As the patient had perseverative behavior disorder, impaired intellectual skill, marfanoid appearance, delayed development as compared to his contemporaries, normal secondary sex characteristics, normal testicular size and characteristic craniofacial appearance, his condition was considered to be associated with LFS. Although the patient had a high palate anomaly, he did not have hypernasal speech. Based on these findings, mutation analysis was performed on the 22nd exome of MED12 gene (NM 005120). DNA extracted from peripheral blood did not have any pathogenic mutation in the region coding for exon 22. Therefore, the currently ongoing Whole Exome Sequencing (WES) was started. However, this analysis has not yet been concluded.

Before the assessments in our outpatient clinic, the patient was using amisulpride (200 mg/day) and risperidone (2 mg/

day). Given the aggression and the persecutory delusions, amisulpride treatment was withdrawn and risperidone dose was titrated to 4 mg/day. As the patient's behavioral problems partially persisted on the first month follow-up visit, carbamazepine (200 mg/day) was added to ensure impulse control and antiepileptic effect. During a nearly 8-month follow-up, there were partial improvements in sex related behaviours and persecutory delusions and marked improvement in aggression. His social activity had partially increased despite persistence of the limitation in eye contact. There was not any change in his moderate level of performance in the work environment.

DISCUSSION

MED12, the mediator complex subunit 12, encodes a subunit of a macromolecular mediator complex with more than 25 subunits that together regulate gene activity. Also, MED12 role has been implicated in RNA polymerase II transcription (Narayanan and Phadke 2017). LFS has been associated with MED12 gene mutation. However, MED12 gene mutation was also reported in Opitz-Kaveggia syndrome and Ohdo syndrome (Prescott et al. 2016), suggesting that the major differences between these syndromes results from differences in both clinical findings and exon mutations. One of the basic criteria distinguishing LFS from these syndromes is the presence of marfanoid appearance. The mutation in exon 22 of MED12 gene is partially specific to LFS but not sufficient for diagnosis (Prescott et al. 2016). It has been also reported that there may be a relationship between LFS and terminal deletion in the short arm of chromosome 5 (Stathopulu et al. 2003). These reports in the literature indicate that mutational studies about LFS are not yet conclusive such that LFS diagnosis depends on clinical findings rather than genetic analysis.

Although psychiatric symptoms were not part of the diagnostic criteria for LFS in the past, at least one psychiatric symptom has been reported in 90% of LFS patients (Lerma-Carrillo et al. 2006). Comorbidity of behavioral disorders were also reported in 80% of LFS cases (Purandare and Markar 2005). Autism-like behaviours are the most frequently seen symptoms in LFS (Lerma-Carrillo et al. 2006), such as those related to difficulties of making social relationships, extreme shyness and self-isolation. Autism-like symptoms such as limitation in eye contact, negative experiences in social relations, communication problems, stereotypic movements and pronominal reversal were also seen in our patient. Pronoun reversal was considered as impairment in concepts of 'the self and the other' in mutual relationship; and has been also reported in disorders such as mental retardation, deafness and blindness. The incidences of these disorders are not known (Gernsbacher et al. 2016). Emotional lability is the second most common symptom cluster reported in LFS (Lerma-Carrillo et al. 2006). However, these symptoms are not specific to LFS and are seen in most of the patients with disabilities. Aggression and anxiety were major complaints in our patient, resulting in further limitation in his social network.

Psychotic symptoms have been reported in only 9.37% of LFS cases (Lerma-Carrillo et al. 2006). In our patient thoughts about being harmed that had started at the lycée stage of his education had developed to delusions within the 3-4 years previous to the psychiatry consultation. Among the 4 LFS patients reported by Lalatta et al. (1991), psychotic symptoms of auditory hallucinations were observed in one and positive and negative symptoms in another. From the perspective of psychiatry, emotional and behavioral symptoms may be interesting and unusual in LFS, resulting in difficulty in diagnosing such symptoms. It was also reported that physical phenotype of LFS changed over time making diagnosis difficult before adolescence (Fryns 1991). De Hert et al. (1996) emphasized that LFS should be included in the differential diagnosis on patients presenting with symptoms of schizophrenia and mental retardation.

Seizures and EEG abnormalities have been seen in MED12 related disorders one of which is LFS (Lyons 2008). However, seizures were rarely reported in LFS cases in the literature (Schwartz et al. 2007). Simple, partial seizures started at 8 years of age in our patient, who used valproate for 6 years. The last seizure had occurred 11 years previously. Current EEG supported partial onset of epilepsy on a background of diffuse cerebral dysfunction. Antiepileptic treatment was not started with the absence of epilepsy in the clinical presentation of the patient. However, later in the course of follow-up, carbamazepine (200 mg/day) was prescribed to ensure impulse control and antiepileptic effects. Lujan et al. (1984) reported a similar case of a patient who had experienced focal-motor seizure detected on EEG at 9 years of age, which resolved with primidone (500 mg/day) and phenytoin (300 mg/day). Fever related seizures for 8 years were reported in another case.

CONCLUSION

In LFS, diagnosis is based on history, clinical symptoms and genetic evaluation. There is not a specific treatment for LFS. The treatment is directed to the detected symptoms. Although a psychiatric disorder specific to LFS has not been named, early recognition and treatment of impulse control problems, aggression, psychotic symptoms, seizure and sleep disorders in these patients are important. Beside the symptoms and the psychiatric disorders in our patient, pronoun reversal was observed, which was often associated with autism but was not reported in LFS. This symptom detected in our

patient indicate the need for detailed speech and language assessment in LFS patients. The correlated genetic mutations being currently under investigation and the delay in time-consuming genetic tests are among the unsolved problems further complicating the difficulty of diagnosing LFS. Given these data on LFS in the literature, each psychiatric symptom considered as unusual should be evaluated comprehensively and monitored as long as possible in collaboration with other disciplines. Although it is difficult to define or classify these syndromes, each case will be a step forward to overcome these challenges.

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