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Case Report

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Psychosis:The Beginning to a Mosaic Trisomy 8 Diagnosis

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Abstract

Mosaic trisomy 8 (also known as Warkany's Syndrome) is a rare chromosomopathy whose clinical presentation has a wide phenotypic variability. Intellectual disability is the most common psychiatric feature and there are few reports of psychotic presentations in these patients.

We report the case of a 23-year-old woman, with no family nor personal psychiatric history until the age of 20, when she was first admitted at a psychiatry emergency service, presenting behavioural and sleep disturbances and psychotic symptoms, leading to her first psychiatric inward admission. The psychotic symptoms resolved and she was discharged, nevertheless, she was not able to restart her academic studies. After 1 year she was again admitted in an inward facility with behavioural disturbances, loosening of associations, delusions of guilt and psychomotor retardation. After this episode, she never fully recovered, maintaining the disorganized thinking. On her third inward admission, she presented with thought blockings, loosening of associations, perplexity and disorganized behaviour. For maintaining a huge psychomotor retardation, Internal Medicine observed the patient and the suspicious of a genetic disorder came across, and was then confirmed by the karyotype-Mosaic trisomy 8.

Being a rare disease, with few available case reports, there are a lot of unanswered questions. Regarding psychiatric symptoms, it is still unknown if they are a part of the syndrome or a comorbidity, making it difficult to treat. In this case, extensive investigation led to the genetic diagnosis, otherwise she would have just had the psychiatric diagnosis and the needed genetic follow up would have probably never occurred.

Keywords: Psychosis• Trisomy 8• Warkany's syndrome• Psychotic symptoms

Introduction

Trisomy 8 mosaicism, also known as Warkany's Syndrome is a rare viable condition with an estimated prevalence of 1:25 000 to 1:50 000 and is estimated to occur in about 0.10% of recognized pregnancies [1]. It is found to be more prevalent in males than females in a proportion of 5:1 [2], and the clinical presentation has a variable phenotype ranging from normal individual to minimal or severe malformations [3], that can affect multiple systems including central nervous, cardiac, gastrointestinal, genitourinary, musculoskeletal and ophthalmologic. Regarding psychiatric features, patients often present variable degrees of intellectual disability, although some patients may have normal to borderline intelligence [4]. There are only a couple of articles that mention the presence of psychotic symptoms in these patients [5,6]. In this paper, we intent to present a clinical report of a woman with trisomy 8 mosaicism that caught medical attention at first, due to her psychiatric symptoms.

Clinical Report

Patient identification

F. is a 23-year-old single woman, unemployed, that lives with her mother (her parents got divorced when she was 5 years old, and she has been living with her mother since). She has a younger brother (19 years old) that lives with their father. She was a Social Work student when she was first admitted to emergency department at the age of 20.

Medical and psychiatric history/psychiatric familiar history

F. had no relevant psychiatric history before she was 20 years-old. Psychiatric familiar history was also denied. She also had no significant medical history, besides rosacea.

Regarding her personal history, she was born of a desired pregnancy of Caucasian non-consanguineous parents, with no relevant complications. The birth was eutocic, although she was a premature baby (34 weeks of pregnancy). She had a normal psychomotor development, achieving the childhood milestones at the proper ages (smiling, sitting, talking, and walking). There is no history of head trauma, relevant medical diseases or psychopathological symptoms of childhood.

She was raised by her mother, at home, with whom she stayed after her parents' divorce, when she was 5 years old, keeping a close relationship with her father and brother (who stayed together).

As a teenager, she always had a very small group of friends and claims that she never had a boy/girlfriend, nor sexual relationships. Her menarche occurred at the age of 15.

She was an affectionate, reserved girl that had difficulties with social interaction, but still managed to keep a couple of friendships. Alongside, her mother was very protective over her and never encouraged her on being more socially active, which reflected on her social deficit. Her mother described her as having always been an immature, dependent person, who needed help from other people to manage her decisions.

Nevertheless, her academic course was averaged; she began basic studies at 6 years old and had no disapprovals. She finished the 12th grade at 18 years old, with a grade of 12.5 points out of 20 possible.

At school, she had good relationships with her teachers, but had difficulties making friends, describing herself as a very shy person. She also described situations of being bullied at school because of being small, shy and spending time reading in the library, instead of playing in the playground. She never had psychological follow-up back then.

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At 18, she got accepted at a Business Management degree, but she only took classes for about a month. She had difficulties in moving to a different city (even though she went living to a relative´s house) and adjusting to the new group of colleagues and teachers. She also described that she was not feeling satisfied with the University classes she was attending. Supported by her mother, she decided to move back home with her.

When F. was 19 years old, she applied to a Social Work degree at her home town and got accepted. During the months she was attending classes, her academic performance decreased and she started having negative scores. She never had any working experience and she was a first-year student when she was admitted at the emergency service for the first time.

History of the problem

F. was first admitted at a psychiatric emergency service when she was 20 years-old. About a week before the admission, her parents, namely her father, related that she was "*different, saying and doing weird things" sic*.

She started to present behavioural disturbances that never occurred before, for instance, she started to leave her house in the middle of the night, barefoot, and walk to the pinewood, climb up to trees, among other unusual behaviours. Alongside, she presented an incoherent speech, with disorganized thinking "*you have to believe me, my stuffed animals were looking at me, I lost control of myself" sic*. Sleep regularity was also disturbed during that week.

Because that was her first episode, she was initially evaluated by Internal Medicine and Neurology colleagues. At the neurological examination, there were no relevant abnormalities. A slight dysmorphia of the hands and feet were noticed. A cranial CT scan and laboratorial tests were requested and no significant alterations were detected. A psychiatric evaluation was then demanded.

At the psychiatric examination, F. was clearly disorganized, disoriented in time and space, with distractibility, racing thoughts, expressing ideas of reference. She also admitted started having auditory verbal hallucinations, namely the voices of her colleagues and teachers conversing or arguing about her, a couple of weeks before the emergency admission. She had no insight about her condition.

Despite her mother´s objection, F. was admitted to the psychiatric inward. During her stay, drug abuse testing, serologies, vitamin deficiency and thyroid function tests were performed, with no relevant abnormal results.

Familiar interviews with her parents were conducted, separately, to help to get further information of F's history. Her mother had a defensive, hostile behaviour towards the health professionals, always saying that she wanted to take her daughter home with her.

During the interview with F's father, he reported that he also has hand and foot dysmorphia. He described her daughter as being *"a shy person since she was young, she always had trouble making friends, and she was always a bit immature for her age, besides that, she is a sweet girl" sic*. He also said that, before F. was admitted to the emergency department, *"she was acting really different, saying things that she never said before" sic*.

During her inward time, a psychological assessment was also requested and no major changes were detected, namely regarding her IQ. The hypothesis of an autism spectrum disorder has been suggested, although it was not assessed at the time.

After a few days, her sleep was restored and she had no psychotic ideas or changes in sensory perception, so she was discharged, with the diagnosis of a first psychotic episode, medicated with Olanzapine 10 mg id (at night) and Lorazepam 1 mg SOS (if insomnia).

She went back to her mother's house, but was not able to restart her academic studies, according to her mother because *"she was taking a lot of medication" sic*.

About a year later (at 21 years old), F. was again admitted at the psychiatric emergency department, accompanied by her mother, who had stopped bringing F. to her follow up appointments and stopped giving her the medication.

That time, F. presented disorganized and incoherent speech, psychomotor retardation, thoughts blocking and loosening of associations. She was very distressed and restless and her speech reflected the presence of delusions of guilt and suicidal thoughts because of these ideas *"I hurt my brother, I don't know if I raped him, I have to turn myself to the police, I cannot live like this anymore, maybe I have to kill myself (…) I stole some books from the library a couple of years ago (…) I'm a violent person, this is all my fault" sic*.

At that episode, no sensorial perception changes were detected. Her mood was depressed. Regarding the insight, F had absolutely no insight for her clinical condition.

F's mother also described sleep disruption a few weeks before this admission and claimed that *"she was talking a lot about the past, making strange associations, about everything" sic*. Again, F. was admitted to the psychiatric inward facility.

During this inward time, all the laboratorial examinations that were requested previously were repeated and no significant changes were found. She was also submitted to an electroencephalogram, that had no relevant abnormal results

Her recovery was very gradual and, by the time of her discharge, she still had some bizarre ideas of guilt, although they were less frequent in her speech. F's thought was also still a bit disorganized, but she was then temporally and spatially oriented. Her sleep had also been restored and she had no suicidal thoughts.

When she went back home, her psychiatric medication included: Olanzapine 10 mg id (at night), Aripiprazol 5 mg id (at breakfast) and Clomipramine 75 mg id (at night).

After her discharge, she stayed at her father's house for a few weeks, but then returned to her mother's.

At her follow up appointments, F. showed less psychomotor retardation, improved coherence of her speech and did not express delusional ideas spontaneously. Regarding her mood, her affects were blunted and she did not have any kind of suicidal thoughts.

Her mother kept her inquiring attitude towards health professionals, always questioning the medication and frequently dropping off the medication and the appointments but coming back when she felt F. was worsening.

About 4 months after her second inward admission, F. was proposed to attend an outpatient facility (Day Hospital) to promote her self-empowerment, improve her social skills and to keep a psychological follow up.

During her first weeks at the Day Hospital, F. was a bit reserved, but then she started to engage in the daily activities (namely painting and craftwork) in a spontaneous way. Self-care and self-empowerment were a few of the main interventions that were conducted with her and, slowly, the results started to show up.

After a few weeks, her communication and social skills got improved and she developed a good relationship with the health professionals, as with the other patients of the group.

Being more organized in terms of behaviour and thinking, allowed her to start making plans, including volunteering at a kindergarten as an assistant and attending an educational assistant degree (6 months program with an internship).

A few months later, she started taking classes for the educational assistant degree and she was really satisfied about it, but she struggled on planning her activities by herself, always in need of health professionals'

help with the planning of her schedule, as well as a high level of distractibility. Besides, she showed several difficulties in abstraction, exposing a concrete way of thinking.

Nevertheless, she managed to finish her classes and started her internship. She was discharged of the Day Hospital by that time (after 10 months), demonstrating a clear improvement on her behaviour and thinking.

About 2 weeks after she was discharged from the Day Hospital, F. was admitted to the psychiatric inward for the third time (at 23 years old).

At that time, she was taken to the emergency department by both her parents and presented mental confusion, loosening of associations, thoughts and behavioural blocking, temporal and spatial disorientation and perplexity.

According to her parents *"she was worried about the internship, she got anxious and she restarted saying strange things like that she was going to go to jail because of what she had done" sic.*

Within the inward, F's behaviour did not get better, she showed signs of apathy, huge psychomotor retardation, making it difficult to maintain a conversation with her.

During the short periods she was able to keep a dialogue, F. admitted she was scared, distressed (sometimes she was found in her room, hiding and crying) and reported hearing voices *"they want me to solve the problems, I have to face a lot of things I did wrong" sic*, but she was not capable of keeping a complete conversation, since she had difficulties expressing her ideas due to thoughts blocking and loosening of associations. Ideas of reference also seemed to be present since she frequently said *"they are talking to me in the television, I feel scared" sic.*

On most of the days in the inward facility, she did not cooperate in the activities, including doing her personal hygiene or eating, always in need of someone to tell her what do next.

Since she was not improving, laboratorial and imaging exams were requested and, also, a request for Internal Medicine observation of the patient.

A complete physical examination was then performed and considering her dysmorphic hands and foot and short stature, x-ray exams were solicited.

Giving her distractibility, huge psychomotor retardation (despite the reduction of medication), temporal and spatial disorientation, it was proposed to perform a lumbar puncture, but F's mother promptly said that she did not want that procedure.

Although her mother's permission was not needed, F. was a little bit better at the day the procedure was supposed to happen and there were no changes in the haematological laboratorial tests, so the Internal Medicine colleagues decided not to go through with the procedure.

X-ray results showed kyphoscoliosis and hypoplasia of the 3rd, 4th and 5th metacarpals. Given these results, her widely spaced nipples and her short stature (with a short trunk), the hypothesis of a genetic disorder was considered, namely Turner's syndrome, resulting in a solicitation of a genetic study.

About a month later, the karyotype confirmed the existence of a genetic disorder, but instead of a Turner's syndrome, the result was a rarest chromosomophaty-Trisomy 8 mosaicism, also known as Warkany's syndrome-(47,XX,+8/46,XX) (Figure 1).

This diagnosis needed further investigation, so F. was submitted to a battery of imaging exams.

According to the few case reports of this syndrome, phenotypical features are of variable clinical manifestations. F's phenotype is characterized in Table 1.

Literature	F's phenotype
Stature	Short stature | present
Short trunk | present	45 – 64
Brain malformations	Agenesis of corpus callosum | absent
Facial and oral dysmorphia	Prominent forehead | present
Long facies | present	45 – 64
Open mouth appearance | present	45 – 64
Plump and broad nose | present	45 – 64
High-arched palate | present	45 – 64
Low sat ears | present	45 – 64
Ocular manifestations	Hipertelorism | present
Strabismus | absent	45 – 64
Deep set eyes | present	45 – 64
Neck anomalies	Short and wide neck | present
Skeleton anomalies	Kyphoscoliosis | present
Vertebral anomalies | absent	45 – 64
Costal anomalies | absent	45 – 64
Chest anomalies	Pectus excavatum | absent
Widely spaced nipples | present	45 – 64
Cardiovascular anomalies	Congenital heart disease | absent
Genitourinary anomalies	Hydronephrosis | absent
Enlarged kidney | absent	45 – 64
Irregular menses | absent	45 – 64
Abnormalities of extremities	Sloping shoulders | present
Deep palmar and plantar furrows | present	45 – 64
Hypoplasia of 3rd, 4th and 5th metacarpals | present	45 – 64
Campodactyly of fingers | absent	45 – 64
Psychiatric features	Mental retardation | absent
Psychotic symptoms | present	45 – 64
Schizophrenia | under consideration	45 – 64
Autism spectrum disorder | under consideration	45 – 64

Table 1. Phenotypical features are of variable clinical manifestations.

Regarding psychiatric manifestations, mental retardation is the most reported abnormality. To our knowledge, concerning other psychiatric features, there are not many case reports, and the existing ones are referred to schizophrenic or autistic patients [5-7].

In F's case, her psychotic symptoms are the most prominent ones, since they were the reason why she caught medical attention in the first place and led her to the subsequent investigation, which led to the genetic disorder diagnosis.

Unfortunately, after the diagnosis was confirmed, F's mother persuaded her to leave the inward facility, which led to her discharge. She was slightly better in terms of behaviour and thinking, although there was no marked improvement.

Intensive psychoeducation was given to F. and her mother, namely regarding the need to maintain the medication and to attend the psychiatric follow up appointments and the internal medicine and genetic ones.

When she was discharged, she was medicated with Risperidone 1 mg id (in the morning), Risperidone 2 mg (at night) and Sertraline 100 mg (at breakfast) (Figure 1).

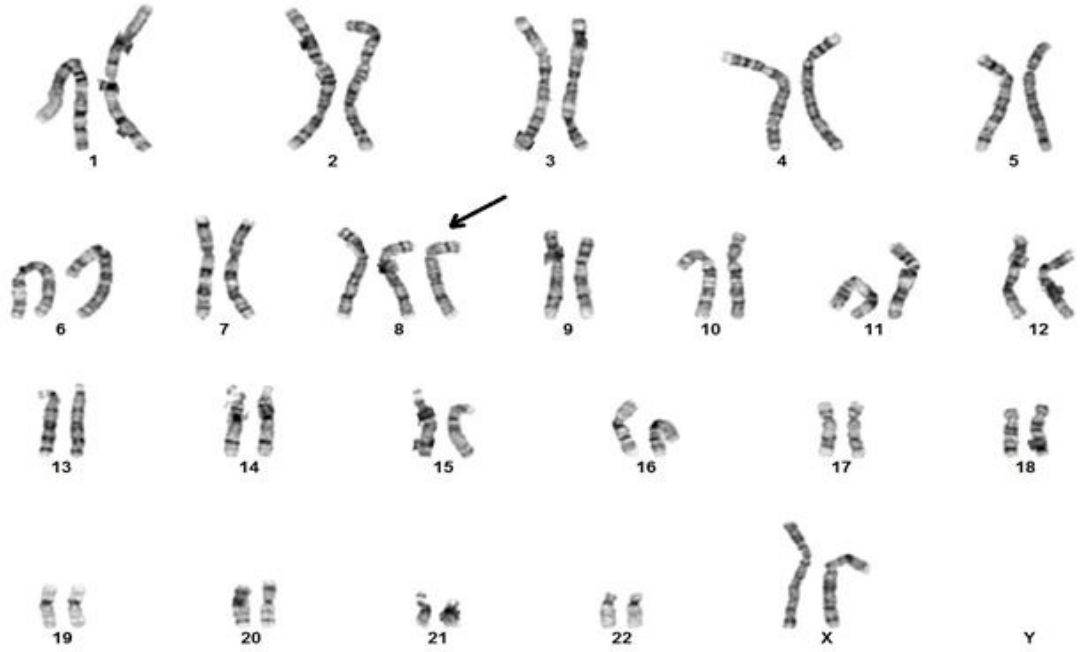

Figure 1. Karyotype showing three copies of chromosome 8.

Results and Discussion

In this case, the psychiatric diagnosis is still under consideration, since there are a few possibilities. F. is a girl who always had difficulties within social interactions. She had a small group of friends, but she never seemed to have much interest in other people and preferred to be by herself. Her history led us to hypothesize the possibility of an Autism spectrum disorder. A complete psychological evaluation should be performed, in order to clarify this possible diagnosis.

Considering the diagnosis classifications, and even though the possibility of an Autism spectrum disorder has never been ruled out, F. fulfills both ICD-10 and DSM5 criteria for schizophrenia, possibly a hebephrenic schizophrenia. She presented with both delusions and auditory verbal hallucinations, but her disorganized thinking and behaviour is still the most prominent feature of her clinical condition. Despite anti-depressive treatment, her affects were blunted, she lacked volition and she had a tendency for social isolation.

The addition of a genetic disorder was another topic to consider within the psychiatric diagnosis, since it is still unknown if the psychotic and behavioural symptoms may be a part of the Trisomy 8 syndrome or a comorbidity.

F's mother's hostile attitude and the constant refusing of any kind of treatments offered, has also been an obstacle to the correct diagnosis and treatment, since she was always compromising the medical agenda, not bringing her daughter to the appointments and not giving her the medication.

In the future, the possibility of a reintegration at the Day Hospital should be considered, since, after her first psychotic episode, her time at the outpatient facility was the period when F. was more interactive and presenting fewer psychotic symptoms. Besides, another psychological evaluation should be performed (regarding, for instance, the possibility of an Autism spectrum disorder) and it would be easier for F. to do it in the outpatient clinic.

F's family genetic study would also be helpful, bringing some responses to the unanswered questions, complementing her own genetic follow up and the need for further investigation.

There are already several studies analyzing the relationship between psychotic symptoms, namely schizophrenia, and chromosomal abnormalities, in order to help understand the genetic etiology of the disorder.

Although, nowadays, no specific loci for schizophrenia have been identified, molecular cytogenetic techniques helped identifying chromosomal abnormalities in schizophrenia, mainly in a certain type of patients: dysmorphic features, early age onset or learning difficulties/mental retardation [8].

It has been suggested that the chromosomal abnormality may have an important impact on the genetic expression and, subsequently, on the neurodevelopment process, causing the schizophrenic symptoms later [6].

A lot of papers reflect that it would be of great importance if clinicians started to consider performing genetic studies in selected psychiatric patients, not only to improve the patient's prognosis (regarding psychiatric treatment, and other medical conditions that could be associated), but also to help researchers to find regions of interest for gene localization [9]. This author also emphasizes that a genetic diagnosis could be extremely important for the patients and their families, since it may be able to relieve relatives of inappropriate feelings of guilt.

Conclusion

In F's case, the slow progress and lack of improvement led to an extensive investigation that culminated in a rare genetic diagnosis, otherwise she would have probably just had a psychiatric diagnosis and lacked her genetic follow up, seriously compromising her future.

Declaration of Authorship, Good Practices and Assignment of Rights

The authors declare the absence of potential conflicts of interest. All the authors participated in the elaboration of the article and can be held responsible for its contents.

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