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Adolescent with 22q11.2 Microdeletion Syndrome, Cognitive Delay, Autism Spectrum Disorder and Psychotic Features

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Abstract: Microdeletion 22q11.2 syndrome (22q11.2DS) is a common microdeletion syndrome, also described as DiGeorge syndrome (DGS). It has a prevalence estimated to be within 1 per 2148 livebirths. Eighty-four percent of the children with 22q11DS had at least one psychiatric disorder, including autism spectrum disorder (ASD), schizophrenia, neurocognitive delay and other neuropsychiatric disorders. Sometimes is not easy to detect psychiatric diagnosis in developmental disorders, so it is important to look for psychiatric symptoms, etiological factors and clinical report about child development, including parent's perceptions. We present a female adolescent patient with a mild cognitive delay, and underdiagnosed ASD, that had a microdeletion 22q11.2 Syndrome, identified at the first year of life. She was evaluated in psychiatric consultation only at 15 years, for psychotic symptomatology. At that time some ASD features were identified, and lately confirmed, with parental information and psychological evaluation instruments, like Autism Diagnostic Interview Revised (ADI-R). This paper aims to alert to the possibility of confluence of 22q11.2DS with ASD and psychotic symptoms, at the same time. We also want to enhance the importance of a multidisciplinary team in developmental disorders, paying attention to developmental report and parents 'information, which may possibility early intervention and an accurate diagnosis.

Keywords: Autism, Psychotic Features, 22q11DS, Cognitive Impairment, Diagnostic Problems

1. Introduction

Microdeletion 22q11.2 syndrome (22q11.2DS) is a common microdeletion syndrome also described as DiGeorge syndrome (DGS), velocardiofacial syndrome (VCFS), conotruncal anomaly face syndrome (CTAF), among others.

The prevalence is estimated to be within 1 per 2148 livebirths but could be even greater due to the higher variable clinical expressivity [1, 2].

The majority occur as de novo events unrelated to maternal or paternal age but approximately 5% to10% are inherited from a parent who may be unaware of their genetic diagnosis, with no or mild clinical features [1, 3].

The main clinical features include congenital heart disease, particularly conotruncal malformations (ventricular septal defect, tetralogy of Fallot), palatal abnormalities, immune deficiency, characteristic facial features, and learning difficulties [4, 5]. About 85% of patients presents a 2.54-Mb microdeletion with coordinates around 18,912,231-21,465,672 (NCBI Build GRCh37/hg19) resulting in the loss of several genes of interest.

Eighty-four percent of the children with 22q11DS had at least one psychiatric disorder, including Anxiety Disorders, Attention Deficit Hyperactivity Disorder (ADHD) and about 16% met strict criteria for Autism Spectrum Disease (ASD) [6].

One in four individuals with 22q11.2 deletion syndrome (22q11DS) have a risk for schizophrenia and other psychotic disorders [7]. Microdeletion 22q11.2 syndrome is considered

the highest known genetic risk factor for psychosis and for ASD.

We report about a 15-year-old female patient with 22q11.2DS and ASD, evaluated in psychiatric consultation for the first time for inaugural psychotic symptomatology. Symptoms of ASD were not detected previously, because they were initially interpreted as cognitive impairment.

This paper aims to highlight the possibility of combination of 22q11.2DS with ASD and psychotic symptoms, and the possibility of a misdiagnosis, because occasionally mild ASD symptoms could be undiagnosed and interpreted as cognitive delay and vice versa. It is important to get a complete clinical report since childhood, being extremely useful the parents 'contribute.

We want to stress the importance of a multidisciplinary team, including the evaluation by a child psychiatrist, in developmental disorders.

2. Clinical Report

15 -year- old female, Caucasian, student, living with parents. In the family history it is relevant to point out the death of her baby sister due to a cardiomyopathy.

She was evaluated for the first time at 3-months, in a paediatric consultation, presenting developmental motor delay, cleft palate and a DiGeorge Syndrome suspicion. MLPA confirmed the presence of the deletion within chromosome 22q11.2. More recently, to characterize the size of the deletion an array CGH was performed using the Agilent 4x180K platform. The arrays nomenclature was described according to ISCN 2020 as 22q11.2 [GRCh37] (18919942_21464119) x1 and represents the 22q11.2 recurrent (DGS/VCFS) region (proximal, A-D) (including TBX1) (of about 2,54 Kb) described in ClinGen [8].

She had learning difficulties with limitations in abstraction, planning, writing and attention in childhood. All these symptoms were interpreted as developmental delay related to 22q11.2DS. ASD was not diagnosed at that time. She had social difficulties, and she spent a lot of time talking about TV cartoons and imitating their words without playing with other children.

In 8th grade of school, in June, when she had to study a lot, with a great pressure, she began to talk and laugh alone, with mood instability and some delusional thoughts. She started to feel persecuted and said that "someone from TV wanted to kill her and steal her power". All these symptoms got worse in September, when classes began and she got more confused and anxious, repeating that someone wanted to kill her. She went to a psychiatric emergency service, and was hospitalized for 15 days, medicated with aripiprazole 10 mg and clonazepam 2mg, getting better. When she went to the psychiatric consultation, after this episode, she spoke about her interests, with a childish perception of everything. She had low self-esteem, anxiety with school and with routines changing. It was evident the presence of some impairment in social understanding and lack of empathy. No delusional thoughts were detected but she had a poor organization of speech, mixing reality with imagination without self-criticism.

At this time, when we talked with her parents about clinical history, we understood that she always had social impairment, restricted interests and routines, good visual memory, and high sensitivity to noise, since childhood. Her parents didn't know how to deal with her behaviour or limitation at school. We collected all the clinical data suggesting ASD Diagnosis, that was lately confirmed with Autism Diagnostic Interview Revised (ADI-R).

3. Discussion

22q11.2DS is often associated to developmental and psychiatric symptoms including Attention Deficit and Hyperactivity Disorder, Anxiety, ASD and Psychotic symptomatology, that sometimes are underdiagnosed. According to literature about 60% of the adults have a psychiatric disorder, and schizophrenia is identified in approximately 1/4 of individuals. Anxiety and depressive disorders also considered quite common [7].

Microdeletion 22q11.2 syndrome is the highest known genetic risk factor for psychosis, and one of known genetic risk factors for autism. However, some studies involving adolescents with this condition have shown that the vulnerability for psychopathology begins in a very early age, so it is important to understand a clinical and a developmental perspective.

A study examined the associations of parents' expressed emotion and parenting stress, with children with 22q11.2 deletion syndrome and idiopathic autism. The study highlighted the need for targeting parents' expressed emotion and parenting stress as integral elements in the screening and prevention of behavioral problems of young children with 22q11DS and ASD [9]. That screening could have been important in our case.

22q11.2 deletion syndrome (22q11DS) is a clinically heterogeneous genetic syndrome, which clinical presentation may be influenced by environmental factors, although this correlation is poor understood. Some studies performed on clinical cohorts have mainly investigated the role of parental factors, stress, and substance use, and reported significant effects of these factors on the clinical profile. Case-control studies, on the contrary, showed almost no reports of significant effects of the environment. Authors suggested a main role of the environmental factors in the 22q11.2DS clinical heterogeneity based in the interaction with genes and environment and their involvement in the molecular pathways present in this region [10]. In accordance, we think that in our case, environmental factors may have had an important contribute for the psychiatric disturbance, one example may be when she was under great pressure with school.

It is not known that the 22q11.2 deletion predisposes to psychiatric disease and some studies tried to understand this association. One of recent studies, used pluripotent stem cells from 22q11.2DS deletion carriers and controls, and

CRISPR/Cas9 technology to introduce a heterozygous deletion into the control cell line. They showed that upon differentiation into neural progenitor cells, the deletion acted in trans to alter transcripts associated with risk for neurodevelopmental disorders, including autism and schizophrenia. They tried to define the minimal protein-protein interaction that best explains gene expression alterations and found that many genes in 22q11.2 interact in presynaptic, proteasome, and JUN/FOS transcriptional pathways. These findings suggested that the 22q11.2 deletion compromise genes that may converge with psychiatric risk loci to influence disease manifestation in each deletion carrier [11].

Another study using whole-genome sequencing data from 519 unrelated individuals with 22q11.2DS, conducted genome-wide comparisons of common and rare variants between those with schizophrenia and those with no psychotic disorder, at age ≥25 years. Available microarray data enabled direct comparison of polygenic risk for schizophrenia between 22q11.2DS and population samples, with no 22q11.2 deletion, with and without schizophrenia. Authors found that polygenic risk for schizophrenia within 22q11.2DS was significantly greater for those with schizophrenia. These findings suggested that in addition to the deletion conferring a risk to schizophrenia, the risk is higher when the 22q11.2 deletion and common polygenic risk factors that contributes to schizophrenia are both present [12].

Catechol-O-methyl transferase (COMT) deletions result in increased vulnerability for neuropsychiatric disorders [13]. DiGeorge syndrome patients exhibit an approximately 3-fold increased risk for psychiatric disorder [7]. Studies suggest that neuronal development impairment in DiGeorge syndrome, is due to deletions of major neurotransmitter gatekeeping enzymes, such as COMT, which degrades dopamine. [13].

Social cognition impairments have been reported in 22q11DS, such as impairment in face memory, face recognition, and emotion identification, for example. Theory of mind (ToM) describes the ability of an individual to understand that other people have mental states different from one's own and to make attributions about the mental states of others. Several studies report deficits in ToM in individuals with 22q11DS, but the impact of age may be important, since in typical development, this ability continues to improve during adolescence and early adulthood. Campbell et al. reported associations between both domains of social cognition and social outcomes [14].

It is also known that, in children with ASD, some idiosyncratic fears, misperceptions and anxiety reactions, may increase the risk of psychosis [15]. We can hypothesize that emotional, social and cognitive vulnerability, associated to ASD, could facilitate the appearance of psychotic disorganization in this adolescent, when she was under great pressure.

Further studies and psychological evaluation would be important to understand this connection between 22q11DS, ASD and Psychosis in our patient.

Additionally, we would like to stress the importance of a multidisciplinary team with expertise in the area, access to various subspecialties that could improve diagnosis and healthcare to these patients. A recent study published by Meneses *et al*., showed the benefits and positive outcomes of a Multidisciplinary Program for 22q Deletion and Duplication Syndromes in a Community Hospital in Florida. This is particularly important to prevent incomplete care and provide all the subspecialties that these patients need [1].

4. Conclusion

This case enhances the importance of a multidisciplinary evaluation, in developmental disorders, including child psychiatry contribute. It is also important to evaluate parents 'emotions and perceptions about children behaviour.

Screening children with 22q11.2DS for psychiatric illnesses, before the age of ten, may provide an opportunity for early diagnosis and intervention, improving long-term prognosis.

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