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Autism Spectrum Disorder Comorbid with Gilles De La Tourette Syndrome in a Child of in Vitro Fertilization: About A Case and A Review of the Literature

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Abstract **Original Research Article**

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder characterized by persistent impairment in reciprocal communication and social interactions and a restricted repetitive pattern of behaviors, interests, or activities. Tourette syndrome (TS) is a neurological disorder with a genetic component characterized by involuntary, sudden, brief and intermittent tics, resulting in movements (motor tics) or vocalizations (sound tics). Although a differential diagnosis of the two conditions can often be made, there are also cases of comorbidity in the same patient. Recently, a number of studies have attempted to explore modifiable environmental risk factors for ASD and TS. Among these risk factors is in vitro fertilization, an assisted reproduction technique, which has become increasingly common. The aim of our work is to highlight via a clinical case and a review of the literature on the association between the use of in vitro fertilization, the risk of autism spectrum disorder and Tourette syndrome. Compared to spontaneous conception, in vitro fertilization treatment as a whole was associated with a small but statistically significantly increased risk of autism spectrum disorder and Tourette syndrome.

Keywords: Autism spectrum disorder, Gilles de la Tourette syndrome, Tics, in vitro fertilization, assisted reproduction techniques, neuro-developmental disorders and IVF.

INTRODUCTION

Autism Spectrum Disorder (ASD) is one of the most common neurodevelopmental disorders, characterized by persistent impairment in reciprocal communication and social interactions and a restricted repetitive pattern of behaviors, interests or activities [1]. The signs of ASD are usually detected during early childhood, and ASD is diagnosed four to five times more often in boys than in girls [2]. It is estimated that one in 160 people worldwide has an autism spectrum disorder [3].

Tourette Syndrome (TS) is a common, inherited, childhood-onset neuropsychiatric disorder characterized by multiple motor tics and one or more phonic tics, lasting at least 1 year, with a onset in childhood or adolescence.

Although initially thought to be rare, Tourette syndrome is more common than expected, with a suggested overall prevalence of 1/200 in children. This disorder is reported worldwide in all cultures and is more common in men than in women [4].

The diagnosis of Tourette syndrome (TGS) is one of the differential diagnoses to consider when reduced socialization and repetitive behaviors are present, especially for children aged 6-12 years. ASD and GTS share the common feature of being complex developmental syndromes, more common in boys than in girls, and beginning in childhood. Genetic transmission is important in both conditions. They also share comorbidities with anxiety disorders, socialization difficulties, and atypical responses to sensory stimulation (e.g., auditory or tactile hypersensitivity). However, several clinical features related to their onset and course help to distinguish them.

Although a differential diagnosis of the two conditions can often be reached, there are also cases of comorbidity in the same patient. Chronic tics of the

SGT type are found in 9% of patients with ASD. On the other hand, an estimated 4.8% of individuals with ASD have GTS, while a similar proportion of patients with GTS are also reported to have ASD [5].

The etiopathogenesis of these disorders is complex and multifactorial. The role of genetic and environmental factors in its emergence is well documented.

Recently, a number of studies have attempted to explore modifiable risk factors for neurodevelopmental disorders. Among these risk factors, assisted reproductive technologies (ART) have been widely discussed due to their acceptability by an increasing number of people. In vitro fertilization (IVF) is one of the most standardized methods of assisted reproduction, and more than 5 million children are born through these procedures worldwide [6].

Growing interest in a possible correlation between IVF and the risk of these disorders has prompted a great deal of work.

OBJECTIVES AND METHODS

The aim of our work is to highlight via a clinical case and a review of the literature on the association between the use of in vitro fertilization, the risk of autism spectrum disorder and Tourette syndrome.

We describe here the case of a child resulting from in vitro fertilization and who is followed in the child psychiatry department of the Ar-razi hospital in Salé for an autism spectrum disorder comorbid with Tourette syndrome.

OBSERVATION

The child IO aged 12 years, living in Rabat, and educated in CE3, having consulted around the age of 7 years in our formation for a delay of the acquisitions.

The patient is of average socio-economic level, father is a civil servant of the public administration and mother is a housewife. He is the youngest of two boys.

The pregnancy is the result of in vitro fertilization with good follow-up. He was born at full term by Caesarean section with no notion of neonatal suffering, the birth weight was 3 kg 400. His psychomotor development was marked by delays, particularly in terms of cleanliness, motor skills and language. Having a rich family history: his brother is followed for ASD, his mother followed for persistent motor tics and his maternal cousin followed for Asperger's syndrome.

From an early age, the patient presented a profound language delay with absence of response to his first name, avoidance of contact and gaze, unmotivated laughter, verbal and motor stereotypies, a communication disorder with very limited social interactions, and restricted interests. This motivated his follow-up for diagnostic and therapeutic management. Thus, the child would have benefited from several investigations, including the M-CHAT questionnaire which was suggestive of an ASD, his symptomatology fulfilled all the DSM 5 criteria for ASD, an ADOS test revealing a high score autism, a speech therapy assessment and a psychomotor assessment with rehabilitation, and a psychological follow-up for parental guidance. The evolution was marked by an improvement of his stereotyped behaviors, expression of emotions as well as non-verbal communication.

For two years, unusual and exaggerated blinking has insidiously set in, which has improved over the following weeks.

Several months later, the child presented with multiple tics:

- Motor: the child would compulsively touched people, jumped for no reason,
- Vocal: he cleared his throat, spit everywhere, even in the soup, yawned loudly, stuttered, barked and repeated the word: "I eat", in any situation (at home, in the street, in the toilet , ...).

His parents took him back to his pediatrician, who performed a full physical exam, including a detailed neurological exam. The results were normal, the doctor reassured the family that the patient just had a few "nervous tics" and would get over them.

However, in the last few months, the child's repetitive behaviors have become more numerous, more frequent and more vigorous, so much so that it has been necessary to isolate him and interrupt his schooling.

At the same time, phobic character traits (claustrophobia) became more pronounced. The syndrome worsened with the onset of self-mutilation: he was hitting his ears and face hard and involuntarily, and biting his wrist. On examination, he was an overweight, intelligent, visibly anxious child. He presented the previously mentioned tics, incoercible, with a very high frequency. The biological examinations (including the study of copper metabolism) were normal as well as the electroencephalogram.

Huntington's disease, viral encephalitis and cocaine use were ruled out and the diagnosis of Tourette syndrome was made according to DSM-5 criteria.

The therapeutic management of the patient was based on a multimodal, bio-psycho-social treatment approach:

Psychoeducation, which is an essential step explaining to the patient and his family the state of knowledge about the prevalence, etiology and course of the disease, to better understand the difficulties associated with this disorder.

Supportive psychotherapy as well as cognitive behavioral therapy sessions that include habit reversal therapy and relaxation techniques.

On the social level, we worked on parental attitudes: do not stigmatize their child by asking him to stop making tics because this attitude tends to exacerbate them.

From a pharmacological point of view, the patient was put on risperidone, which reduced the intensity of the tics and reduced their impact on the psychosocial functioning of the child.

A speech therapy follow-up was also part of the treatment with a real benefit on the sound tics.

DISCUSSION

Autism Spectrum Disorder, as classified by the DSM-5, is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction in multiple contexts, as well as patterns of behavior and restricted and repetitive interests or activities. In a 2012 review, the worldwide prevalence of ASD was estimated at a median of 62 cases per 10,000 people [7].

Tic disorders in patients with ASD were first described in single case reports and in small case series. Only a few studies have analyzed the prevalence of comorbid Tourette syndrome in large clinical samples of ASD.

The rate of Tourette syndrome (TS) reported in the ASD population ranges from 2.6 to 11%. A transient association between Tourette syndrome and autism spectrum disorders has also been reported in one case series: Zappella described 12 young patients with early comorbidity of TS with reversible autistic behaviors. However, comorbidities between TS and ASD in most cases persist over time, and cases of ASD in TS specimens have also been described. Clinical studies using TS samples show a prevalence of ASD in patients with TS which can vary from 2.9 to 20%.

Of the 6 studies found in the literature, only one assessed comorbidity between TS and ASD using an autism-specific scale (eg, Autism Spectrum Quotient, AQ; Childhood Autism Assessment, CARS). Of the sample-based clinical studies mentioned, the largest clinical sample of TS patients reported the most accurate characterization of ASD comorbidity in our opinion. Analyzing 7288 patients from the International Tourette Syndrome Database Consortium Registry, the authors found that 334 (4.6%) TS individuals had comorbid ASD. In patients with TS and comorbid ASD, the rate of additional comorbidities increased significantly (98.8% of TS + ASD patients had one or more comorbidities versus 13.2% in participants with TS only). A possible limitation of this work is represented by the fact that the diagnosis of ASD was confirmed using a structured report format based on DSM criteria instead of an assessment using specific instruments [7].

Tourette's syndrome (TS) is a neurological disease with a genetic component characterized by involuntary, sudden, brief and intermittent tics, resulting in movements (motor tics) or vocalizations (sound tics). TS was first described in the 19th century by French neurologist Georges Gilles de la Tourette [8].

Although initially thought to be rare, TS is more common than expected, with a suggested overall prevalence of 1/200 in children. TS is reported worldwide in all cultures and is more common in males than females (M/F ratio ranging from 1.6:1 to 9:1). Comorbidities and coexisting pathologies in TS are also common. Hirschtritt et al. in a large clinical study, analyzed 1374 patients with TS and found a lifetime prevalence of any psychiatric comorbidity among 85.7% and that 57.7% of patients involved at least 2 psychiatric disorders.

As evidenced by recent literature, TS shares similar genetic makeup and risk factors with other neurodevelopmental disorders, which ultimately produce similar neuropathological alterations. In particular, recent studies have found similar connectivity alterations in patients with ASD, ADHD, and TS. Given all of these findings, the aim was to provide an in-depth review of comorbidity in TS and other neurodevelopmental disorders.

Kadesjo and Gillberg examined 435 school-aged children and found a prevalence of 0.15% TS. 22% had comorbid ASD using the Autism Spectrum Screening Questionnaire (ASSQ) (5% Asperger's, 17% PDD-NS).

Another epidemiological study conducted in Sweden on a population of 4479 children measured a frequency of 0.6% of TS. In the TS group, the rate of ASD was 20% (16% Asperger's, 4% PDD-NOS) [9].

Tourette Syndrome (TS) is a disorder of complex etiology. Twin and family studies of SGT individuals have shown a high level of heritability suggesting that genetic risk factors play an important role in disease etiology. However, identifying the main

susceptibility genes to TSS has been difficult, probably due to the complex interplay between several genetic factors and environmental influences [10].

Several neurotransmitter systems have been implicated in the pathogenesis of the disease and of these, the dopaminergic and serotonergic pathways are the most widely studied.

TS is a complex disorder, in which several environmental factors (such as streptococcal infections, birth complications, and maternal smoking) are thought to interact with several genes in yet unknown ways. It is also suggested that impaired immune regulation predisposes to inflammation and infection, thereby triggering TS, and there is growing evidence for dysregulation of the brain's resident immune cells, microglia. Several lines of evidence suggest that TS has a strong genetic component, and it has been suggested as one of the non-Mendelian neuropsychiatric disorders with the highest heritability [8].

In our study, we focused on the analysis of the possible involvement of in vitro fertilization in the development of ASD and TS in children born from this technique,

Assisted reproductive technology (ART) has been shown to be variably associated with adverse short- and long-term perinatal outcomes, including cerebral palsy, autism, and cancer. However, there is uncertainty as to whether the reported issues are related to the ART procedure itself, infertility-related factors, other medical and environmental factors, or a combination thereof. .

In vitro fertilization has also been shown to be variably associated with adverse short- and long-term perinatal outcomes [11].

The question of their impact on the mental development of the child is at the center of many studies. The results are contradictory, but several of them find an association with certain mental disorders.

The aim of this study is to assess the association between mental disorders and the performance of IVF, by comparing the prevalence of these pathologies in children and adolescents born through IVF with that of those resulting from conception natural.

A very slight increase in motor or verbal tics (HZ: 1.40, 95% CI [1.01-1.95]). In particular, there was a risk of autism spectrum disorders (HZ: 1.20, 95% CI [1.05-1.37]), hyperactivity with attention deficit (HZ: 1.23, 95% CI [1.08-1.40]), behavioral and emotional disorders (HZ: 1.21, 95% CI [1.02-1.45]) as well as tics (HZ: 1.51, 95% CI [1.16-1.96]) [12].

Another Nordic study demonstrated similar results, in children born from in vitro fertilization, there was a higher adjusted risk of learning and motor functioning disorders (HR, 1.01 [0.96–1, 07]; aHR, 1.17 [1.11–1.24]) and a tendency towards a higher risk of autism spectrum disorders (HR, 1.12 [1.04–1.21]; aHR, 1 .07 [0.98–1.16]) and attention deficit/hyperactivity disorder and conduct disorder (HR, 0.82 [0.77–0.86]; aHR, 1.17 [0.99 –1.12]) [10].

A 2017 meta-analysis assessing the association between assisted reproductive technology (ART) use and risk of autism spectrum disorder (ASD) in offspring suggests increased risks of autism or developmental delay and of cerebral palsy with the use of IVF.

As has been found, IVF may be an independent risk factor for ASD. A possible mechanism linking IVF and ASD is epigenetic changes induced by repeated exposure to hormones, sperm preparation, freezing of embryos and gametes, use of culture media, embryo growth conditions and delayed insemination. Epigenetic mechanisms such as defects in genetic imprinting are increasingly recognized as playing an important role in several neuropsychiatric disorders, such as Rett and Fragile X syndromes, characterized by autism-like features in some patients [13].

Melnyk *et al*., found abnormal methylation is particularly implicated in ASD context-related IVF imprinting disorders [14].

Abnormal DNA methylation could not be consistently identified in IVF children. In summary, IVF was associated with a significantly higher risk of ASD in the offspring. IVF is likely to be an independent risk factor for ASD in offspring [15].

Epidemiological studies on maternal and pregnancy risk factors for autism spectrum disorder (ASD), including the use of assisted reproductive technology (ART), have found conflicting results. This study included the following objectives: to assess the frequencies of IVF in a large group of ASD; examine confounding birth and familial risk factors in the ASD with IVF group; examine possible relationships between ART and autism severity, coping skills, and developmental trajectory.

The IVF rate in the ASD group was significantly higher (10.7%) than in a large Israeli population (3.06%).

This pilot study highlights the role of assisted reproduction as a risk factor for ASD. However, this group of ASD with FIV does not represent a distinct clinical phenotype in ASD.

An increased rate of assisted reproductive technology is documented in a large group with well-

defined autism spectrum disorder. Although maternal age is higher in the ASD group, even young mothers (<29 years) have increased rates of IVF. The confounding risk factors for ASD, prematurity, low birth weight, and genetic susceptibility do not affect the rate of IVF in ASD. Assisted reproduction is not linked to a single clinical profile in ASD [16].

CONCLUSION

Autism spectrum disorder and Tourette syndrome are neurodevelopmental disorders. These disorders are a major public health problem worldwide. A rapid diagnosis of the comorbidity between TS and ASD is important and crucial not only to understand the etiological basis of neurodevelopmental disorders but also, as a clinical relevance, for a rapid definition of therapeutic approaches.

Compared to spontaneous conception, in vitro fertilization treatment as a whole was associated with a small but statistically significantly increased risk of autism spectrum disorder and Tourette syndrome.

Our conclusions should be taken with caution. Further studies are needed to verify the impact of IVF on the risk of ASD and TS in children.

REFERENCES

1. Lisa, C., & Nazish, I. (2018). Autism spectrum disorder, *British Medical Bulletin*, 127.
2. Autism Spectrum Disorder in Children and Youth in Canada 2018, National Autism Spectrum Disorder Surveillance System.
3. Elsabbagh, M., Divan, G., Koh, Y. J., Kim, Y. S., Kauchali, S., Marcín, C., ... & Fombonne, E. (2012). Global prevalence of autism and other pervasive developmental disorders. *Autism research*, *5*(3), 160-179.
4. Cravedi, E., Deniau, E., Giannitelli, M., Xavier, J., Hartmann, A., & Cohen, D. (2017). Tourette syndrome and other neurodevelopmental disorders: a comprehensive review. *Child and adolescent psychiatry and mental health*, *11*(1), 1-12.
5. Dr Pierre Lalonde and collaborators, CLINICAL PSYCHIATRY, Bio-psycho-social approach 4th edition.
6. Adamson, G. D., Tabangin, M., Macaluso, M., & de Mouzon, J. (2013). The number of babies born globally after treatment with the assisted reproductive technologies (ART). *Fertility and Sterility*, *100*(3), S42. [http://www.fertstert.org/article/S0015-0282(13)02586-7/pdf].
7. Elena, C. (2017). Emmanuelle Deniau Tourette Syndrome and Other Neurodevelopmental Disorders: A Comprehensive Review, *Child and Adolescent Psychiatry Mental Health.*
8. Levy, A. M., Paschou, P., & Tümer, Z. (2021). Candidate Genes and Pathways Associated with Gilles de la Tourette Syndrome—Where Are We?. *Genes*, *12*(9), 1321.
9. Noton-Durand F., I. Jalenques Tourette's syndrome: Clinical features and psychiatric comorbidity in childhood.
10. Rönö, K., Rissanen, E., Bergh, C., Wennerholm, U. B., Opdahl, S., Romundstad, L. B., ... & Tiitinen, A. (2022). The neurodevelopmental morbidity of children born after assisted reproductive technology: a Nordic register study from the Committee of Nordic Assisted Reproductive Technology and Safety group. *Fertility and Sterility*, *117*(5), 1026-1037.
11. Mary Elaine, G., Angie, J., & Alexander, H. H. (2022). Assisted Reproduction: Short and Long Term Outcomes, *Dev Med Child Neurol*, 1-12.
12. Increased risk of mental disorders in children and adolescents born by ART: a cohort study, September 2013.
13. Melnyk, S., Fuchs, G. J., Schulz, E., Lopez, M., Kahler, S. G., Fussell, J. J., ... & Jill James, S. (2012). Metabolic imbalance associated with methylation dysregulation and oxidative damage in children with autism. *Journal of autism and developmental disorders*, *42*(3), 367-377.
14. Huffman, S. R., Pak, Y., & Rivera, R. M. (2015). Superovulation induces alterations in the epigenome of zygotes, and results in differences in gene expression at the blastocyst stage in mice. *Molecular reproduction and development*, *82*(3), 207-217.
15. Gao, J., He, X., Cai, Y., Wang, L., & Fan, X. (2017). Association between assisted reproductive technology and the risk of autism spectrum disorders in the offspring: a meta-analysis. *Scientific reports*, *7*(1), 1-8. doi:10.1038/srep46207
16. Zachor, D. A., & Itzchak, E. B. (2011). Assisted reproductive technology and risk for autism spectrum disorder. *Research in developmental disabilities*, *32*(6), 2950-2956.