A brief review on *Gilles de la Tourette* syndrome: A rare disease

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Abstract

Tourette syndrome is a rare disease with various physical and vocal tics that begin in childhood, last at least a year, and are not caused by other medical conditions or medicines. Tics can be easily identified using clinical diagnostic criteria and their distinct look and characteristics. In this article we are going to see the etiology, factors due to which the Tourette syndrome occurs and the ways to treat this syndrome.

1 Introduction

Despite rare diseases afflicting a tiny number of people (less than 1 in 2000 in any WHO area), there are over 7000 different forms of rare diseases. The load that exists on a global scale is considerable. Currently, almost 300 million people have uncommon illnesses. Individuals in low- and middle-income nations regularly face neglect and marginalization (1). Approximately 80% of rare diseases have a genetic basis, with over 70% presenting in childhood. Approximately 95% of rare diseases do not have authorized therapies, with an average diagnostic time of 4.8 years. Additionally, approximately 30% of children with rare diseases dies before reaching the age of five (2). In 2021, the UN adopted the first resolution to address the issues faced by individuals with rare diseases and their families (3,4). The resolution encourages Member States to offer reliable and reasonably priced health services, especially at the primary care level.

2. Types of rare diseases

2.1 Genetic disorders: Many rare diseases are caused by genetic mutations or abnormalities. These can include disorders like Duchenne muscular dystrophy, Huntington's disease and cystic fibrosis.

2.2 Autoimmune diseases: Some autoimmune diseases are rare and can affect various organs or systems in the body. Examples include systemic lupus erythematosus (SLE) and autoimmune hemolytic anemia.

2.3 Metabolic disorders: These are rare conditions that involve problems with metabolism, such as phenylketonuria (PKU) or Gaucher disease.

2.4 Rare cancers: Certain types of cancer are considered rare because they occur infrequently compared to more common forms like lung or breast cancer. Examples include mesothelioma and some types of paediatric cancers.

2.5 Neurological disorders: There are various rare neurological conditions, like amyotrophic lateral sclerosis (ALS), Huntington's disease and Rett syndrome.

2.6 Rare infectious diseases: Some infectious diseases are rare, either due to their geographic distribution or the nature of the pathogen. Examples include Chagas disease and Ebola virus disease (1).

2.7 Rare paediatric diseases: Many rare diseases affect children. These can range from rare genetic disorders to specific paediatric cancers.

2.8 Rare haematological diseases: Certain blood disorders fall under the category of rare diseases, such as aplastic anaemia or haemophagocytic lymphohistiocytosis (HLH).

2.9 Rare respiratory diseases: Conditions like pulmonary arterial hypertension (PAH) or idiopathic pulmonary fibrosis (IPF) are considered rare diseases affecting the lungs.

2.10 Rare rheumatological diseases: Some rare diseases affect the joints and connective tissues, such as Behçet's disease or relapsing polychondritis (5).

It's vital to take note that there are thousands of rare diseases, and new ones are continually being discovered. The impact of rare diseases on individuals and families can be profound due to the challenges in diagnosis, limited treatment options, and often lack of awareness and research (6). Efforts in rare disease research, advocacy, and support aim to improve the lives of those affected by these conditions (7,8). Table 1, explains the prevalence of rare diseases throughout the world.

Table 1. Prevalence and types of action towards rare diseases in different countries

S No.	Criterion	United states	UK	China	Japan	Taiwan
1.	Criterion for prevalence of rare diseases (%)	0.75	0.5	0.11	0.4	0.1
2.	Affected population	25-30 million	27-36 million	27-36 million	NA	More than 2000
3.	Administrative bodies involved	FDA/OOPD	EMA/COMP	TGA	MHLW	DOH
4.	Legal framework	Orphan Drug Act (1983), Rare Diseases Act of (2002)	Regulation (EC) No.141/2000 (1999)	Orphan Drug Policy (1997)	Revised orphan drug regulations (1993)	Rare Diseases Control and Orphan Drug Act
5.	Financial subsidies	Government grant for clinical research	Frame work programs plus national measures	NA	Government grant for research	Government grants and awards from the central competent authority
6.	Market exclusivity (years)	7	10	5	10	10

7.	Tax credits	Upto 50% for clinical expenses	Managed by member states	Not applicable	15% tax credits	Not applicable
8..	Protocol assistance	Yes	Yes	Yes	Yes	Yes
9.	Administrative bodies involved	Market driven	Depending on member states	Same as other drugs	Price negotiation	Not applicable
10.	Medical expense reimbursement	Yes	Yes	Yes	Yes	70% for patients, upto 100%for low income family

3. Tourette syndrome

Tourette syndrome, initially defined by *Gilles de la Tourette* in 1885, is a hyperkinetic mobility condition characterized by many motor tics and at least one phonic tic that continues for more than a year after start, but not always concurrently. Tics must start before age 18 and not be caused by other circumstances. A tic is a repeating muscular action or vocal sound that lacks rhythm. Individuals with Tourette syndrome endure varying degrees of disability and tics, which may change over time. Tics can induce muscular exhaustion and pain from repeated contractions and motions(9,10).

3.1 Etiology

The exact etiology of Tourette syndrome (TS) It is not completely understood, although it is thought to entail a mix of environmental, genetic and neurological influences(10). Here are few key aspects of TS etiology.

3.2. Genetic factors

Tourette syndrome has a strong genetic component. Studies have shown that TS runs in families, with identical twins having a higher concordance rate than fraternal twins. Multiple genes are thought to contribute to the genesis of TS, with each likely having a little influence. However, no one gene has yet been proven to be the sole cause of TS.

3.3 Neurobiological factors

Dysregulation of neurotransmitters TS is linked to disorders in neurotransmitter systems, namely serotonin, dopamine, and Neurobiological Factors: Dysregulation of neurotransmitters TS is linked to disorders in neurotransmitter systems, namely serotonin, dopamine, and norepinephrine. Dysfunction in these systems may lead to the development of tics and related symptoms. Dysfunction in these systems may lead to the development of tics and related symptoms.

3.4 Changes in brain structure and function

Neuroimaging studies have identified abnormalities in the structure and function of certain brain areas in TS patients, including the frontal cortex, basal ganglia and limbic system. These regions are important in motor control, inhibition, and emotional regulation, which suggests that TS symptoms may be caused by anomalies in these circuits.

3.5 Environmental factors

While inherited factors play an essential role, environmental circumstances can also impact the development or progression of TS symptoms. Some occurrences have been linked to environmental factors such as prenatal and neonatal problems, mothers who smoke during pregnancy and access to specific chemicals or viruses.

3.6 Immune system dysfunction

There is growing evidence that immune system problems and inflammatory responses can add to the pathophysiology of TS. Autoimmune processes and neuroinflammation have been suggested as possible contributing causes.

3.7. Psychosocial factors

Anxiety, stress, and emotional discomfort can all impact the intensity and frequency of tics in people with TS. Stressful life events or social demands may worsen symptoms, but supportive surroundings and good coping skills might help alleviate them.

Recent research reveals that tic disorders, such as Tourette syndrome, may be genetic, while this is still considered hypothesis. Some evidence indicates that serotonin may have a role in TS-related tics, while the specific mechanism is uncertain. Small sample sizes and concurrent obsessive-compulsive disorder have made it difficult to confirm a role for serotonin in this concept. Dopaminergic activity appears to influence the pathophysiology of the condition, although further data is needed. Tics associated with TS have been connected to premonitory desire. These uncomfortable feelings of stress arise before and are temporarily relieved after a tic. Although premonitory wants are an important component of tics, their physiological source is unclear. Neuroimaging demonstrates that the motor circuit in TS is identical to that in normal voluntary behaviours. Currently, abnormal activity in these areas is thought to be causal. A study of children with TS at the Danish National Tourette Clinic found that the severity of tics, ADHD, and OCD in childhood was significantly related to the severity scores in early adulthood. In the same cohort, 18% of individuals over 16 had no tics, 60% had minimal or mild tics, and 22% had moderate to severe tics, showing that tics diminish with age(11).

3.8 Treatment for Tourette syndrome:

Treatment of TS, a neurological illness characterised by recurrent, involuntary movements and vocalisations known as tics, can vary depending on the severity of symptoms and their impact on daily life. While there is no cure for Tourette syndrome, various approaches can help manage symptoms effectively. Here are common treatment options(12):

3.8.1 Behavioural therapies

Comprehensive Behavioural Intervention for Tics (CBIT) helps persons with TS get more conscious of their tics and learn how to regulate or suppress them. CBIT might include habit reversal training, that involves identifying tic triggers and replacing them with alternate movements or actions.

3.8.2 Cognitive behavioural therapy (CBT)

It can assist patients with Tourette syndrome manage stress and anxiety, potentially reducing the frequency and intensity of tics.

3.8.3 Medications

- Neuroleptics or antipsychotics: Haloperidol, pimozide, risperidone, or aripiprazole can reduce tics by affecting dopamine levels in the brain. However, they may cause serious adverse effects and must be closely monitored. Alpha-2 Adrenergic Agonists: Guanfacine or Clonidine can be used to treat tics, ADHD, and impulse control concerns.
- Botulinum Toxin (Botox) injections help alleviate motor tics by targeting particular muscle groups. This therapy is most typically used for people who have severe and incapacitating tics.

3.8.4 Deep brain stimulation (DBS)

This surgical therapy involves implanting electrodes in specific areas of the brain to regulate abnormal nerve impulses that cause tics. DBS is explored when previous therapies have been ineffective or poorly tolerated.

3.8.5 Supportive therapies

- Occupational Therapy: Occupational therapy can assist persons with Tourette syndrome in developing coping strategies and improving motor abilities.
- Speech therapy can help manage vocal tics and enhance communication skills.
- Education and support: Healthcare experts, support groups, and advocacy organisations may help individuals and families cope with Tourette syndrome(13).

People with Tourette syndrome should engage together with their healthcare professionals to build a comprehensive treatment plan to meet their unique requirements and concerns. Treatment strategies may evolve over time based on changes in symptoms and individual response to therapies.

4. Conclusion

To summarise, uncommon illnesses represent a significant public health concern and a challenge to medical care. In recent years, there has been significant progress in several regions of Asia, notably Japan, South Korea, and Taiwan, with the passage of legislation and subsequent regulation of rare illnesses and orphan pharmaceuticals. Tourette syndrome is a neuropsychiatric condition that causes physical and vocal tics in children and can lead to concomitant psychopathology in up to 90% of cases. Diagnosing tics can be difficult due to their shifting course, variable symptomatology, and co-occurring mental and movement disorders. However, diagnostic criteria and crucial clinical factors can consistently identify tics from their imitators. ADHD and obsessive-compulsive disorder are common comorbidities that can worsen disability and lower quality of life. To prioritize treatment goals, patients should undergo a comprehensive neuropsychiatric assessment, including collateral history and severity scales. Most Tourette syndrome patients enjoy reduced tic intensity during adolescence. However, a minority of patients continue to suffer tics in adulthood, leading to greater rates of anxiety, low self-esteem, unemployment, and lower socioeconomic position. More study is needed to understand the influence of motor and mental symptoms on function and quality of life in people with Tourette syndrome across time.

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