Tourette syndrome: Review of literature

Síndrome de La Tourette: Revisão de literatura

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SUMMARY

Introduction: Tourette Syndrome (TS) was described for the first time in 1825, and it is a neuropsychiatry disease, initially begins in childhood, affects more males, characterized by remarkable social and psychological commitment, impacting the lives of patients and family. Until recently, this disease were considered a rare condition, but current studies show that the prevalence rate may vary in 1% to 2,9% in a few groups.

Objective: Perform a review of literature over the main aspects related to Tourette syndrome.

Data synthesis: The TS is a genetic disorder, associated with neuroanatomical and neurophysiological alterations, characterized by compulsive phenomenon, whose etiology is still unknown. The clinical profile is composed, mostly, by motor tics and vocal tics, that which are divided in simple and complex. Its association with Obsessive Compulsive Disorder and Attention Deficit Hyperactivity Disorder is very common. The diagnosis is mainly clinical and do not exist. Until now, there is no specific laboratory test that confirm this pathology. The treatment is based mainly on psychological theory. However when there is need for the use of drugs, the most widely used are the antagonists of dopamine receptors.

Conclusion: The TS causes many damages as psychosocial and educational for the individual and the family. However, the diagnosis and the early treatment are able to minimize or cancel this damages. This way, knowing the general aspects that guide the TS is of utmost importance to preserve the quality of life for the patients with the disease.

Keywords: Tourette syndrome, tics, otorhinolaryngologic diseases, voice disorders.

RESUMO

Introdução: A Síndrome de La Tourette (ST) foi descrita pela primeira vez em 1825 e se trata de uma patologia neuropsiquiátrica de início geralmente na infância, que acomete mais o sexo masculino, caracterizada por notável comprometimento psicológico e social, causando impacto na vida dos portadores e familiares. Até pouco tempo, essa patologia era considerada uma condição rara, porém, estudos atuais demonstram que a taxa de prevalência pode variar de 1% a 2,9% em alguns grupos.

Objetivo: Realizar uma revisão de literatura sobre os principais aspectos relacionados à Síndrome de La Tourette.

Síntese dos dados: A ST é um distúrbio genético, associado a alterações neurofisiológicas e neuroanatómicas, caracterizado por fenômenos compulsivos, cuja etiologia ainda é desconhecida. O quadro clínico é composto, principalmente, por tiques motores e vocais que se subdividem em simples e complexos. A sua associação com Transtorno Obsessivo Compulsivo e Transtorno do Déficit de Atenção e Hiperatividade é relativamente comum. O diagnóstico é feito principalmente, por tiques motores e vocais que se subdividem em simples e complexos. A sua associação com Transtorno Obsessivo Compulsivo e Transtorno do Déficit de Atenção e Hiperatividade é relativamente comum. O diagnóstico é eminentemente clínico e não existe, até o momento, nenhum teste laboratorial específico que confirme esta patologia. O tratamento é fundamentado, principalmente, na terapia psicológica. Porém, quando há necessidade do emprego de fármacos, os mais utilizados são os antagonistas de receptores de dopamina.

Conclusão: A ST causa diversos prejuízos psicossociais e educacionais para o indivíduo e familiares. Porém, o diagnóstico e tratamento precoces são capazes de minimizar ou anular estes danos. Desta forma, conhecer os aspectos gerais que norteiam a ST é de fundamental importância para preservar a qualidade de vida dos portadores da doença.

Palavras-chave: síndrome de Tourette, tiques, otorrinolaringopatias, distúrbios da voz.
INTRODUCTION

The first description of a patient with tics and behaviors that characterize the Tourette syndrome (TS), occurred in 1825, by the French doctor Jean Marc Gaspar Itard, that diagnosed the curse of tics in the Marquis of Dampierre (1).

However, only in 1884, this pathology received the name of syndrome of Gilles de La Tourette (TS), when the student Gilles de La Tourette, in the Hospital de La Salpêtrière, reported the pathology as a disorder characterized by multiple tics, including the involuntary use or inappropriate of obscene words (coprolalia) and the involuntary repetition of a sound, word or phrase from another (echolalia), based in report of Itard itself (2, 3).

There were times where the TS were like a curse, and whoever had it was doomed to manifest bizarre behaviors until the end of his life. Still is seen today, as a disorder that causes integration difficulties and sometimes unsuitability of its bearers in many contexts (4). Children and teenagers that suffer from the disease are frequently discriminated and have disadvantages in terms of psychosocial development. This condition can contribute for a chronicity of symptoms, so as to the appearance of others personality disorders (5).

The TS consists in a neuropsychiatry pathology from the beginning of childhood, characterized by the psychological and social commitment of the affected ones, causing more impact in the life of the carriers and family (3, 6). She is generally associated still in a great variety of behaviors and emotional problems (7). Is classified in CID-10 in the group of Emotional and Behavioral Disorders with the beginning usually in Childhood and Adolescence, with code F95.2 and described as Disorder of multiple vocal and motor tics combined (8).

Until recently, this pathology was considered a rare condition, with very low rate of incidence in the world population (0.5/1000, in 1984) (9). This fact was probably undiagnosed cases, since this disorder, in most of the times, it is of a light intensity and many patients don't even search for help (10). However, it is been observed that, today, through the prevalence studies, the increase of its incidence in the last years (6, 11, 12, 13).

Recente studies showed that the prevalence rate can variate from 1% to 2.9% in some groups (14, 15). International statistical data show that the syndrome is found in many countries, independent of social class or ethnicity, affecting about three to four times more the males than the females (16, 17, 18). Studies show that the prevalence of TS is ten times bigger in children and teenagers, of which, when tics are considered separately, the frequency approximated varies from 1% to 13% in boys and 1% to 11% in girls (3). The reason for such increase in the detection in the world incidence of TS seems to be because of the improvement in the disclosure and the awareness of the clinical characteristics of TS, among the health professionals (3, 6, 19).

Considering that the TS represents a paradigm for a better understanding of the close relationship existent between the emotional-cognitive activity and the motor function, the present study proposes to approach, broadly, many aspects of the TS, including its definition and etiology, physiopathology, clinical picture, associated pathologies, diagnostic approach, differential diagnoses and treatment.

Definition and etiology

The TS is a genetic disorder, from a neuropsychiatry, characterized by compulsive phenomenon, that, many times, result in a sudden series of multiple motor tics in one or more vocal tics, during at least a year, starting before 18 years old (20,21,22,23). These tics can be classified as motor and vocal, subdividing, still, in simple and complex. Usually, patients with TS present, initially, simple tics, evolving to more complexes; however, the clinical picture can vary from patient to patient (24, 25).

The tics are defined as abnormal movements, chronic, brief, quick, without purpose and irresistible. Are exacerbated by situations of anxiety and emotional tension; alleviated by rest and by situations that requires concentration. Can be suppressed by will (for seconds or hours), soon followed by secondary exacerbations. Others manifestations, like, echolalia, echopraxia, coprolalia and copropraxia can, also, be present (26).

As knowledge about the TS expands, it becomes more and more obvious that is not only a movement disorder that manifests merely through motor and vocal tics, but also is characterized by complexes neurobehavioral alterations. The association of Attention Deficit Hyperactivity Disorder (ADHD) and Obsessive Compulsive Disorder (OCD) is relatively common. This way, what is frequently presented as a clinical manifestation by the patients, represents only the tip of the iceberg (26,27).

Since the sixties, researchers in the entire world have described new aspects of this disease. It is known today that this condition is associate to neurophysiologic alterations and neuroanatomical of etiology, however, still unknown. There is the numerous gaps to be cleared such
as: a precise neurobiological model, the way of genetic transmission and the clinic spectrum of the disorder (28).

During the last decade, has been possible to observe significant progress in the genetic investigation of the etiology of TS. Chromosomal Anormalities in individuals and families suffering with TS has been studied, in order to indentify the genes like the A gene of monoamine-oxidase (MAOA) (29) and chromosomal regions like 18q22 (30), 17q25 and 7q31 (29), that seems to be involved in this pathology (31).

In this process of identification, evidences suggests that the TS is a genetic disorder of autosomal dominant, since the frequency of tic cases and manifestations obsessive-compulsive between the family of the patients, observed in multicity center studies (3, 16, 17). Until now, it was not possible to identify the genetic marker in a definitive way for the TS (29).

The degree of concordance between the pair of monoyzygotic twins is bigger than 50%, while that in dizyzygotic twins is of 10%. If include twins with chronic motor tics, the degree of concordance increases to 77-90% between the monoyzygotic and 30% for the dizyzygotic. The differences between the degrees of concordances in the pair of monoyzygotic twins and dizyzygotic indicates that the genetic factors play a important role in the origin of the syndrome of Gilles de la Tourette (9).

Other factors have been associated to the pathogenesis of TS, such as, the possible role of the streptococcal infections in the emergence of the tics. In some cases, the affected for the second time for the Streptococcus are directly associate with the recurrence of neuropsychiatric symptoms (32). Recent studies suggest that a inflammatory process, because of the acute or chronic infection, or even from a self immune post-infectious, can be involved in the TS pathogenesis. Researches about the function of the immune system in the TS are not yet analyzed like factors that could contribute to the development of tic disorders and the pathogenesis of the disease (9, 17). This way, because of the fact of not be determined, still, all the involved factors in the abnormal neurological condition of TS, it cannot exclude the possibility of the same to be a syndrome of multiple causes.

**Physiopathology**

Regarding to the physiopathology of the syndrome, important advances have occurred in the last years, thanks to the information from researches involving neural anatomy, neural biology and functional studies *in vivo* through Magnetic resonance imaging (RMI) (35).

There is an agreement that, at brain level, it is distinguished several parallel neuronal circuits, that leads the information from the cortex until the subcortical structures (basal ganglia) and return to the cortex passing through the thalamus, known as cortico-striatal-thalamic-cortical (CSTC) circuit; they are responsible to intermediate the activity of motor, sensory, emotional and cognitive. We thought that the patients with TS have a deficiency in the inhibition of these circuits, that in a motor level it expresses like hyper sensibility to the stimulation from both internal and external environment (10, 35).

The suppression of the tics in patients submitted to leucotomoy and thalamotomies, by the interruption of the CSTC circuit, point to the direct involvement of them in the TS, and so this fact it is observed through the functional visualization of MRI, from the analysis of the measures of the traumatic brain injury, the intoxication by carbon monoxide, the abuse of cocaine, the withdrawal of opiates or the pharmacological treatment with neuroleptic can also associate to the syndrome genesis. There are evidences that the long-term treatment with neuroleptic, can elevate the risk of development of tics in some patients. They are called “Touret” or secondary tics (9).

Pre or post events can also be connected to TS, where the gravity of the stressors during the pregnancy has been analyzed like factors that could contribute to the development of tic disorders and the pathogenesis of the disease (9, 17). This way, because of the fact of not be determined, still, all the involved factors in the abnormal neurological condition of TS, it cannot exclude the possibility of the same to be a syndrome of multiple causes.
the area of the corpus callosum and by the metabolism of the glucose and blood flow in the cortical areas (3, 7).

Abnormalities in the volume of the basic ganglia in the callosal body also were observed in the TS carriers (3). Studies of neural imaging in adults with the syndrome, without the realization of the treatment with long-term antipsychotics, revealed volumes significantly smaller in the caudate nucleus, lenticular and globus pallidus when compared with the control group, both the right side and the left side. Similar results were found in other studies, when comparing children with TS and control groups, observing the important difference of the volume of the left globus pallidus and lenticular asymmetry (37).

Researches involving emission tomography have revealed still hypo metabolism and hypo perfusion in regions of the frontal cortex and temporal, in the cingulated, striate and thalamus of patients with TS. These researches of metabolism analysis of glucose and blood flow in the cortico-striatal region have identified abnormalities, mainly involving the basal ganglia and cortical areas of these individuals (3, 9). These findings confirm that the morphological disorders and functional of the basal ganglia and CSTC circuit, are key factors for the persistency from both the tics and the obsessive-compulsive symptoms (37).

In the neurochemical point of view, many hypothesis suggest the involvement from the system dopaminergic in the pathogenesis of TS, since the neuroleptic, dopamine antagonists, are considered effective in the treatment of this disease, because promote great reduction of the tic. By the other hand, the stimulants like the methylphenidate, the cocaine, the pemoline and the L-dopa cause exacerbation of tics (3, 7).

Immunohistochemical studies have been lately performed in the TS, particularly the ones that refer to the dopaminergic system, noradrenergic and serotonergic (9). With base in the data, the literature suggest a few mechanisms by which the system dopaminergic could be involved, such as, abnormalities in the liberation of dopamine, hyper innervations dopaminergic and presence of hyper sensitive dopaminergic receptors (7, 29).

The first hypothesis, hyper sensibility of D2, was not confirmed, in other words, was not demonstrated that the homovanillic acid, main metabolite of dopamine, is reduced in the cerebrospinal fluid (CSF). The second, hyper innervations dopaminergic of the striated, would lead to the increase in the concentration of dopamine (9). A recent study, involving post-mortem analysis of tissues from the frontal cortex and striated, showed elevated density from the dopaminergic receptor D2 in the pre-frontal region of patients with TS (3). This way, the hyper innervations would lead to a increased stimulation in the circuit of CSTC, suggesting so, that the TS is associated to the lack of inhibition from the mini circuits of CSTC. In this context, the obsessions and the obsessive need for symmetries and precision would be the result of the lack of inhibition from pre-frontal mini circuits (12, 13).

The role of others neurotransmitters, such as, acetylcholine, gaba, endogenous opioid system, serotonin and norepinephrine (13, 17, 23) has been studies, since we cannot discard the involvement of others neurotransmitters inside the circuit of the CSTC (23).

The evidence of involvement from the noradrenergic system in the physiopathology of the syndrome is based in the good benefits of clonidine and guanfacine, which are traditionally selective agonists from the D2 receptor adrenergic. The studies in the CSF of patients with TS, have evidenced reduction of the main metabolite of serotonin, the hydroxy-indoleacetic acid. In post-mortem tissues, preview studies have also showed that the serotonin is globally reduced in the basal ganglia. This metabolic alteration, however, is related to the patients with OCD (9, 22).

**Clinical Picture**

The clinical Picture can be split into three categories: motor tics, vocal tics and sensitive tics.

The tics are defined as abnormal movements, clonic, brief, fast, sudden, without purpose and irresistible, that persist through the sleep. Are exacerbated by situations of anxiety and emotional tension; attenuated by rest, relaxation and for situations that demand concentration. Can be suppressed by will (for seconds or hours), soon followed by secondary exacerbations (3, 38).

The tics happen daily, usually presenting in settings, occurring many times in a single day, although they can present itself in a intermittent way through the year (3). There is a periodic variation in the number, the frequency, in the type and localization of the tics, being that the intensity from the symptoms also have a fluctuating character, may even disappear for weeks or a few months (11, 12, 39).

Besides the notable social prejudice caused by the presence of the tics, in a work performed by Miranda (1999) (35), was observed a case of retinal detachment because of the cervical dystonic tics and fractured ribs because complex motor tics, where the patient struck severely his chest. Besides can occur also orthopedic
problems (by flexing his knees, excessively turn the neck or the head) and skin problems (by pinching himself).

The begin of the symptoms usually appear through childhood or youth, eventually reaching to stages classified as chronicle. But, in the pass by of adult life, frequently, the symptoms go to the softening and gradually decreasing (3, 40, 41).

Motor Tics

The motor tics are classified as simple and complex. The first involves contractions of muscles groups functionally related (ex: blink the eyes and make movements like twisting the nose and mouth), are abrupt, fast, repeated and without purpose, usually noticed as involuntary (3). Are included in this classification the complex tics, however, they are more slow, involve muscle groups non related functionally, seems to be purposeful and they are, sometimes, noticed as involuntary. The complex motor tics include imitation of gestures of others, even if they are common (echokinesis) or obscene (echopraxia), besides the realization of obscene gestures (copropraxia). (35).

The simple motor tics most frequent are: blinking the eyes, deviations of the eyeball, funny faces, spin the head, movements like twisting the nose and mouth, click the jaw, clenching, hunch, movements of the fingers, kicks, abdominal contraction or other parts from the body, shakes of the head, neck, or other parts of the body. The most found complex motor tics are: facial gestures, stretch of the tongue, maintenance of certain looks, hand gestures, clap the hands, throw an object, push, touch people or things, jump, hit the foot, crouching, little jumps, bend, twirling or spinning when walking, spin, twist, dystonic posturing, eye deviations, licking hands, fingers or objects, touch, hit in or analyze part of the bodies, from other person or objects, kiss, arrange, pinch, write the same letter or word, go back on the same steps, hit with the head, bit the mouth, the lips or other part of the body, echopraxia and copropraxia (5,8,10,26,28,35).

In most of the cases, the Carrier patients of La Tourette Syndrome present, initially, simple tics, evolving to more complexes ones. But, the clinical picture can vary from patient to patient (3).

Vocal Tics

The vocal tics also are divided into simple and complex. The simple include the emission of sounds, like, hawk, grunt, snuffle and even screams. The complex are of involuntary use and inappropriate use of obscene words (coprolalia), repetition of words or phrases (palilalia) and repetition involuntary of the phrases of other person (echolalia) (27, 39). It is observed, yet, the repeated use of random words, characterized by complex sonority or exotic, arbitrarily placed in the between or in the middle of phrases (42).

Among the main simple vocal tics are scratching the throat, spit, click the tongue, cluck, snore, sizzle, whistle, scream, grunt, gurgle, groan, howl, hiss, fizz, aspirate and many other sounds. The act of uttering syllables, words or phrases out of the context or inappropriate, short phrases and complexes, the palilalia, coprolalia and echolalia, besides other abnormalities of speech as a block of speech, are the complex vocal tics most common (2,8,10,28,35).

Sensitive Tic

The sensitive tic is defined as a somatic sensation at the articulations, in the bones and muscles (weight, lightness, empty, cold or hot), that make the patient to execute a voluntary movement to obtain relieve. Its presence it is not obligatory for the diagnosis (3).

Associated Pathologies

Researches have shown that individuals with TS present more psychiatric comorbidities and consequently higher operating damages (40, 41).

The symptoms more commonly associate to the La Tourette Syndrome are obsessions and compulsions. In a clinical study of 58 cases made by Fen (2001) (28), was found association with the Obsessive Compulsive Disorder in 39,6% of the cases.

Hyperactivity and distraction also are relatively common, and many patients with TS present initially symptoms of the Attention Deficit Hyperactivity Disorder (ADHD). This way, it is necessary distinguish if the symptoms of ADHD occur in the context of TS or if exist a comorbiditie from TS with ADHD (4).

Impulsivity and social discomfort with the sensation of being observed by others, shame and depressed humor also can manifest ate together with the TS (3).

The presence of self aggressiveness can reach 30% of the patients and the patients with TS exhibit a greater incidence of phobias, anxiety disorders and panic than the general population (10).

Besides all the foregoing, the social functioning,
academic or occupational can be damaged, because of the rejection by others or anxiety into having the tics in social situations, so, the syndrome also can be associated to the Learning Disorder (9, 35).

**Diagnosis**

The diagnosis of the Syndrome de La Tourette is eminently clinical, not existing today, no specific laboratorial test that confirm this pathology (3). But, the American Association of Psychiatry (2002) (38), in order to systematize and make easier for the diagnosis, created the following criteria:

A. Multiple motor tics and one or more vocal tics had been present in some moment of the disease, although not necessary at the same time.
B. The tics occur many times per day (usually in strikes) almost every day or intermittently during a period of over a year, and during this period there were not even a phase free of tics superior to three consecutive months.
C. The beginning is before 18 years old.
D. The disturbance is not because of the physiological effects of a substance (for ex.. stimulants) or a general medical condition (like: Huntington disease or post viral encephalitis).

The diagnosis of TS must be done carefully, because 10% of children present some tic in a moment of their life (3, 4). And so, although the complementary exams (EEG, tomography or blood analysis) are not useful to affirm the diagnosis of TS, they can be of great value in the differential diagnosis, once they contribute for the exclusion of other disorders that have similar symptoms (43).

Although the neural image exam are not used for the certain diagnosis of TS, a study that did not make a long use of anti psychotic, have showed decreased volume in the caudate nuclei and lenticular, compared to the control group. The volume of the caudate nuclei demonstrated, yet, have a predictive value in relation to the severity of the tics in children (33, 34).

**Differential Diagnosis**

The Huntington Disease, the brain vascular accident, the Lesch Nyhan syndrome, Wilson disease, Sydenham's chorea, multiple sclerosis, post-viral encephalitis and traumatic brain injury are medical conditions that can come accompanied of abnormal movements that must be differentiated from the presented tics in the TS. Besides those pathologies, direct toxic effects of a substance also can simulate the presence of tics (38, 44, 45).

The tics also must be differentiated from the stereotyped movements seen at the Stereotyped Movements Disorder and in Pervasive Developmental Disorders. The difference is not always easy, but usually, the stereotyped movements seem to be more directed and intentional, while the tics present a involuntary quality and are not rhythmic (38).

The TS also can be differentiated from the Obsessive Compulsive Disorder (OCD), more complex pathology, where the movements are executed in respond to a obsession or according to rules that must be strictly followed (28). The compulsions are preceded by persistent worries, while the tics are preceded by physical tension transients in a part of the body. But, is valid to point that the association of two pathologies is not uncommon, so, if there is symptoms of both the disorders, the two diagnosis can be justified in case the clinical picture fits the criteria of diagnosis in each one of them (4).

Certain motor tics or vocal present in the syndrome also must be differentiated from the behavior disorganized or catatonic from Schizophrenia.

Other tics disorders, (Motor Tic Disorder or Chronic Vocal, Transient Tic Disorder and Tic Disorder Without Further Specification) are also included in the differential diagnosis of TS (38).

These co-occurrences of symptoms can lead to a diagnostic confusion. And so, must be attempt to the peculiarities of the clinical picture and private developments of each disease and, still, have the knowledge that some of them can be a co-morbiditie (40, 41).

**Treatment**

Because of the notable sociocultural and educational implications that govern the TS, is important that the treatment is instituted the fastest as possible, to minimize or avoid damage to the patient.

The choice of kind of treatment must be appropriated to each carrier of the TS, and can include a pharmacological and psychological approach (3). This last one is of a great importance, once that, besides the psychotherapeutic treatment for the patient, guide parents, family and people next to them, about the characteristics of the disease and the best way to deal with the affected individual (4).

The TS do not have a cure, and so, the pharmacological treatment is used only to relieve and control the presented symptoms. Because of the considerable number of collateral effects, the pharmacological approach must be considered
only when the benefits of intervention were superior than the adverse effects (3). Besides, most of the patients do not need a specific treatment for the tics, being enough to explain the nature of the picture and the good prognosis of most of the cases, for the family and the teachers and people next to the patients (35).

But, when is relevant the use of drugs, the most used are the receptor antagonists of dopamine, once that many studies suggest that the block of dopaminergic receptors type 2 is the main point for the efficacy of the treatment (3, 34).

The Haloperidol, is one of the medications most used for the treatment of TS, presents many collateral effects, like extrapyramidal symptoms from parkinsonian characteristics, sedation, dysphoria, hyperphagia with weight gain and late dyskinesia. The pimozide has similar efficacy to the haloperidol without the inconvenient of the extra pyramidal effects, but present collateral effects involving the cardiovascular system, including sedation and cognitive dysfunction (3, 10).

Today, there is a tendency to substitute the typical antagonists of dopaminergic receptors (ex: haloperidol, pimozide), by the atypical antagonists (ex: risperidone, olanzapine andquetiapine) or for antagonists of receptors alpha-2-adrenergic (ex: clonidine and guanfacine), because they present a smaller profile of collateral effects (3, 33, 34, 42).

The risperidone has as main collateral effect the sedation, increase of appetite and elevation of the prolactin levels. The olanzapine is a good alternative for the control of the aggressive symptoms and does not have severe collateral effects, but patients with cardiovascular problems and of epilepsy must used with caution, and patients with glaucoma must avoid him (3, 33, 34, 42).

The clonidine and guanfacine, have been showing very effective in the treatment of the TS, but, because they are antihypertensive agents, must be done an accompaniment of blood pressure (3, 33, 34, 42).

The ministrated doses of each drug must be individualized to attend the need of the patient, causing the less number of collateral effects possible.

A few studies show that the injection of botulinic toxin can be a good therapeutic option for the treatment of motor tics and in some cases for the vocal tics (39). Recent experiments discuss yet the use of immune modulating therapy and anti-inflammatory, also the use of magnetic stimulation repetitive transcranial, profound brains stimulation and electroconvulsive therapy for the treatment of TS (33, 34).

CONCLUSION

The La Tourette Syndrome is a disorder that courses with significant motor and vocal tics, causing many sociocultural and educational damages for the individual, being that the damages can be reduced when the diagnosis and the treatment are done earlier. This way, known the general aspects that surround the etiopathogenesis, clinic presentation and treatment of the disease in question are indispensable.

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