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Case Report

Infancy narcolepsy: Streptococcus infection as a causal factor ☆

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ABSTRACT

Streptococcal infections are suggested as a risk factor for narcolepsy. This hypothesis is supported by the presence of anti-streptolysin antibodies in 65% of patients with narcolepsy. These infections are associated with the activation of general immunity and concomitant increased permeability of blood–brain barrier after T cell activation during inflammation and fever.

It has also been shown a significant association between birth order and narcolepsy in genetically susceptible patients, with positivity for HLA-DQB1*0602 allele. Watson and colleagues showed a significant association between birth order and narcolepsy in genetically susceptible patients, with positivity for HLA-DQB1*0602 allele. In that study, the disease was predominant in young children cases compared to controls.

We report here the case of a child diagnosed with narcolepsy with cataplexy, positivity for the HLA-DQB1*0602 and previous history of streptococcal infection.

1. Introduction

Narcolepsy is characterized by excessive daytime sleepiness with or without sudden loss of muscular tonus (cataplexy). Associated characteristics include sleep paralysis and hypnagogic and hypnopompic hallucinations. Narcolepsy is strongly associated with the presence of the HLA-DQB1*0602 allele, a variant of the HLA-DQB1 gene, located on the short arm of chromosome 64 and its symptoms result in the destruction of the hypocretin-secreting neurons of the hypothalamus [1].

Infections are recognized as having an important role upon the physiopathology of the auto-immune diseases [2]. Among narcolepsy, two types of superior airway infections have been suggested as susceptibility factors: the ones caused by H1N1 influenza A and the ones caused by streptococcus. Picchioni et al., in a case-controlled study, associated

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inexplicable fevers and flu with increased risk of 3.9 and 1.8 times, respectively, for narcolepsy [3].

The latency, for the beginning of the disease, also showed a highly seasonal characteristic in children, with an incidence 6 times higher in China, in April as relation to December, suggesting a prevalence of 5–6 months after winter [4]. Dauvilliers et al. found an increased risk of narcolepsy in individuals born in March and a reduced risk in patients born in September [5].

Neurological disorders with a hypothesis of auto-immune disease, such as Sydenham chorea and, of a more controversial manner, obsessive-compulsive disorder, nervous twitches and some encephalitis, have been associated with streptococcal infections [6,7].

Watson et al. demonstrated a significant association between birth order and narcolepsy in genetically susceptible patients, or the ones with positivity for the HLA-DQB1*0602 allele, a definitive marker, especially, among narcoleptics with cataplexy. In this study, the affection was prevalent among the younger sons of the cases when compared to controls [8]. The association of this disease with birth order generally reflects the influence of environmental factors, specifically the exposition to infections during the initial phases of life and has been observed in some auto-immune diseases [9,10]. The role of environmental factors is strongly implicit, being the agreement rate with narcolepsy between monozygotic twins of only 20–35% [11,12].

2. Case report

G.N.A, white, male, from São Paulo, arrived at the ambulatory of Diurnal Excessive Sleepiness of the Department of Psychobiology of the Federal University of São Paulo, when he was 11 years and 7 months of age, complaining of daytime excessive sleepiness (DES) for the past 7 months. A week before the appearance of the DES symptoms, he reported a case of streptococcal tonsillitis, receiving therapy with antibiotic and also had arthralgias. He demonstrated sleep paralysis, cataplexy and hypnagogic hallucinations (referred "rock sound"), besides waking up screaming and crying at night after episodes of nightmares, according to his mother. At the beginning of the sleepiness symptom, he showed hyper sleepiness associated with hyperphagia, but denied the presence of hyper sexuality during this period.

The patient was born through a C-section, weighing 3.330 g; among his previous personal morbidities there were chicken pox and circumcision; he was updated as far as immunization procedures were concerned. Among his familiar morbidities, his father had a diagnostic of sleep obstructive apnea syndrome (SOAS).

He also referred nocturnal agitation and dry lips which worsened with dorsal decubitus, besides his daytime symptoms, as substitute oral breathing, nasal obstruction and irritability.

At physical examination, he showed adenoidal facies, obstructive nasal deviation at right and pallor of the inferior cornices, tonsils 2+/5+, Mallampati score of grade IV, ogival hard palate, lateral-posterior open bite, and globoid abdomen, due to fat tissue. His percentiles for weight and height at his age were within normal standards.

We performed the Conners short scale, a diagnostic and prognostic questionnaire to evaluate patients with attention/hyperactivity deficit, which demonstrated to be within the normal standards, with a score of 13.

The following tables demonstrate the exams that were altered (Tables 1–5).

His genetic test for the presence of HLA-DQB1*0602 allele was positive.

Other tests like nuclear magnetic resonance, skull CAT scan, Blood complement (CH50), urine Type I, albumin, globulin, albumin/globulin ratio, blood urea, blood creatinine, total blood protein, creatinine clearance, Doppler echocardiogram and electroencephalogram during vigil and sleep, all of which were within normal standards.

Facing the diagnosis of narcolepsy, we indicated programmed naps and physical activity, therefore, decreasing the Epworth Score (13/21).

After ear, nose and throat evaluation, a tonsillectomy was performed, with the introduction of 1,200,000 IU of intramuscular penicillin G-benzathine during 48 h before the surgery. The patient initiated treatment with an orthodontist due to his ogival palate.

In this reported case, ASLO remained elevated; we initiated treatment for rheumatic fever with penicillin G-benzathine, every 21 days. After 3 doses of this prophylactic

Table 3 – Epworth sleepiness scale.

Normal value (Johns, 1991)	Patient score
Between 0 and 10 points	17 points

Table 1 – Polysonographic results.

	Normal values (Marcus et al., 1992)	Patient results
Sleep latency (min)	<30	63.6
Sleep efficiency (%)	>85	69.50

Table 2 – Test for multiple latencies of sleep (TMLS).

	Normal values (Thorpy et al., 1992)	Patient results
Average sleep latency (min)	Between 10 and 20	1.8
REM episodes	<2	2

Table 4 – Result for anti-streptolysin type O (ASLO).

Positivity criteria (Shet et al., 2002)	Patient result
Isolated value >333 Todd units or 2 times increase of dilution between the acute and convalescent serum samples	812 Todd units

Table 5 – Laboratory exams.

	Laboratory reference values	Patient results
Leucocytes (cells/ml)	4.000–11.000	14.680
Segmented neutrophils (cells/ml)	2.000–7.500	9.439
Monocytes (cells/ml)	200–1.500	1.923
Immunoglobulin E (KU/l)	<200 (for ages between 10 and 14 years)	552

antibiotic, antibody levels decreased, but maintained elevated. After 13 treatment doses, ASLO leveled off and the narcolepsy symptoms were reduced.

3. Discussion

Recent populational epidemiological studies have shown that the risk of narcolepsy is increased by 5.4 times for individuals with a medical history of oropharyngeal streptococcal infection [13]. The correlation between streptococcal infections and seasonality is associated with protective or deleterious immune factors, for those that are under the influence of the yearly climatic changes [5].

The involvement of streptococcal infections upon the disease's development is supported by the presence of anti-streptococcal antibodies in 65% of the patients, in comparison to the 26% of paired controls [14].

Streptococcal infections can also increase the risk of narcolepsy through its nonspecific effects, such as the general immunity activation or increased hematoencephalic barrier permeability to T-active cells, caused by inflammatory agents or fever [15,16].

Previous infection by streptococcus of the A group and serum positivity of anti-streptolysin O (ASLO) is related to narcolepsy and auto-immunity [13,14]. Streptococci of the B group are part of the normal intestinal and genital flora, and are present in 20–40% of all women. The colonization is positively associated to the number of previous pregnancies and to the exposition to neonatal infection and can occur during the birth, in colonized women [17]. Although infection by group B streptococci are not known to be associated with auto-immunity, the results of Watson et al., associating narcolepsy to birth order suggest that the exposition to group B streptococci, during birth, might have a role in the development of narcolepsy in genetically susceptible individuals [8].

According to Kornum et al., the possible ways for the role of *Streptococcus pyogenes* and H1N1 virus upon the development of auto-immunity for the hypocretin-producing cells, would be the stimulus of T or B cells, through their molecular mimetism, beginning with streptococci super-antigens, the production of auto-antibodies, general immune activation and the migration of lymphocytes to the central nervous system. It has been suggested that these pathogens have a tropism for the hypocretin-secreting neurons, making them activate the microglia and increase the signals through the molecules of the main histocompatibility complex (MHC), class II, inducing the neurotoxicity through the release of quinolinic acid or glutaminase [18].

With a few exceptions, such as the celiac disease in older children, auto-immune diseases rarely affect children. During the last years, however, the number of children with diagnostic of auto-immune disorders has increased. It has also been established that children below 10 years of age and senior citizens with 65 years or more, have increased susceptibility to complications after a seasonal infection and a decreased response to vaccination [19].

Natarajan et al. reported a case where a child of 8 years of age could have had narcolepsy triggered by a streptococcal infection. In this case, the patient showed increase in the ASLO values when diagnosed with this affection. ASLO is an indication of a previous contact (during the past 2 months) with *S. pyogenes* (beta-hemolytic streptococcus of the A group) [20].

In this case report, the child came for consultation complaining of sleepiness, which was objectively detected with the Epworth Sleepiness Scale. Genetic test for the presence of the HLA-DQB1*0602 allele was positive and associated with the TMLS results, led to the diagnostic of narcolepsy. However, after programmed naps, the routine orientation to narcoleptic patients, the Epworth score decreased.

At the beginning of the ambulatory evaluation, the patient showed elevation of the ASLO levels. This factor associated with leukocytosis and neutrophilia, indicated a case of streptococcal infection.

After treatment with antibiotic, there was a reduction of the ASLO level and of the symptoms of narcolepsy, which reinforced the hypothesis of a streptococcal infection as the causal factor for the narcolepsy.

4. Conclusion

This case report seems to illustrate the environmental influence upon the risk of narcolepsy by way of a streptococcal infection during infancy.

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