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Case study

Successful treatment of cataplexy in patients with early-infantile Niemann–Pick disease type C: Use of tricyclic antidepressants

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ABSTRACT

Cataplexy is a brief episode of bilateral loss of muscle tone with intact consciousness, triggered by a variety of strong emotions such as anger, laugh, humor or surprise and it is considered to represent the physiologic atonia of rapid eye movement sleep. On the other hand, Niemann–Pick Type C is a neurodegenerative lysosomal storage disease, characterized by the accumulation of cholesterol and glycosphingolipids. Cataplexy is a relatively specific and common neurologic sign seen in almost 50% of all patients with Niemann–Pick Type C. The aim of this report is to demonstrate the successful treatment of cataplexy with the use of a tricyclic antidepressant imipiramine, in two patients between the ages 6–9, with mild to moderate mental retardation, molecularly diagnosed as Niemann–Pick Type C 1 and currently under miglustat treatment and to discuss the possible mechanisms of drug action in the light of cataplexy and Niemann–Pick Type C pathophysiology.

1. Introduction

The term cataplexy, first described by Henneberg in 1916 is derived from the Greek word "kata" meaning down and "plexis" meaning stroke.[1] Cataplexy is a brief episode of bilateral loss of muscle tone with intact consciousness, triggered by a variety of strong emotions such as anger, laugh, humor or surprise.[2] The loss of muscle tone may be partial or can spread to other muscles in seconds, and can result in sudden collapse with severe loss of muscle tone. Patients are usually able to brace themselves to prevent serious injury. Cataplexy is considered to represent the physiologic atonia of rapid eye movement (REM) sleep. Cataplexy in childhood is rare and has been described in narcolepsy, Niemann-Pick type

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C disease (NPC), Norrie disease, Prader–Willi syndrome, and Coffin-Lowry syndrome.[2] The term "gelastic", is used when cataplexy is triggered by laughter. Gelastic cataplexy is a strong predictor of NPC, although it may also be seen in patients with narcolepsy. Cataplexy may develop during the course of NPC and rarely it may also be the first presenting symptom.[3]

NPC is a neurodegenerative lysosomal storage disease, characterized by the accumulation of cholesterol and glycosphingolipids. Two genetic complementation groups, NPC1 and NPC2 have been identified. NPC1 is involved in 90–95% of the cases and NPC2 is known in rare families.[3] Birth prevalence estimates range from 0.35 to 2.20 per 100,000 but the true prevalence of NPC remains unknown due to under recognition of the clinical features and the relatively difficult diagnostic procedure.[4] NPC shows an extreme clinical heterogeneity. Age of onset ranges from neonatal period to adult life, but usually first symptoms occur at the age of 2–4 years. Core symptoms in the early-infantile subgroup are developmental delay, ataxia, organomegaly, hypotonia, and gaze palsy. Cataplexy is a relatively specific and common neurologic sign seen in almost 50% of all patients with NPC. It is suggested that impaired function of hypocretin-containing cells due to lysosomal storage products are responsible for sleep abnormalities and cataplexy.[5]

The aim of this report is to demonstrate the successful treatment of cataplexy with the use of tricyclic antidepressants (TCA) in two patients with early infantile NPC and to discuss the possible mechanisms of drug action in the light of cataplexy and NPC pathophysiology.

2. Case studies

Three girls, from the NPC cohort of 24 patients at Hacettepe University Children's Hospital, between the ages 6–9, with mild to moderate mental retardation, were currently under miglustat treatment. All three patients had first presented with difficulty in walking between the ages of 14 months–2 years. Developmental delay, ataxia, oculomotor apraxia and splenomegaly were present at admission. They were molecularly diagnosed as NPC1 between the ages of 3–5, and were under miglustat treatment since then. All girls developed cataplexy triggered by laughter or giggling in the last 12 months while they were under miglustat treatment. Frequent (3–20 times/day) cataplexy episodes lasted about a minute with a sudden loss of bilateral muscle tone mostly in antigravity muscles, resulting a sudden collapse to the ground. Parents could not let the girls to stand up or play without close adult supervision and one of the girls had to wear a crash helmet when she was going outside because of the frequent episodes. None of the patients described excessive day-time sleepiness or hypnagogic hallucinations. Awake and sleep electroencephalography studies were normal.

Sodium oxybate, the only approved medication for cataplexy treatment is not available in Turkey. Since, antidepressants, especially monoamine uptake inhibitors, are also said to be effective drugs on cataplexy, a tricyclic antidepressant imipiramine was used. Two girls benefitted from imipiramine (max 1.5 mg/kg) treatment in the first four-six weeks of tratment, one girl free of cataplexy for the last 9 months and one girl for the last 6 months. One of the girls did not respond to imipiramine (max 1.5 mg/kg), fluoxetine (max 30 mg/day) or methylphenidate (max 1.2 mg/kg tid). She is currently receiving sodium valproate treatment (20 mg/kg). Timeline showing the course and treatment of cataplexy in the three patients is shown in Fig. 1.

3. Discussion

The neurobiological mechanisms underlying cataplexy are not fully understood yet. Most research has been conducted for cataplexy in narcolepsy. In terms of current neurophysiological and pharmacological studies, cataplexy is considered to be a complex REM-related phenomenon involving multiple neurotransmitter systems responsible for regulating sleep and postural muscle tone. Two major systems are said to be working together in regulating REM sleep. The REM-On networks promote REM sleep and the REM-Off networks inhibit REM sleep.[6] A part of the REM-On network is also in charge of generating atonia during REM sleep. When an individual is in REM sleep, motor neurons are strongly inhibited by GABAergic and glycinergic neurons in the spinal cord and medial medulla so nearly all skeletal muscles are paralyzed.[7] These inhibitory GABAergic and glycinergic neurons are activated by glutamatergic neurons in the sublaterodorsal nucleus (SLD), they are thought to be a part of the REM-On network.[6,8] On the other hand, during wakefulness, these atonia producing pathways are hold back by monoaminergic neurons of the REM-Off network in the ventrolateral periaqueductal gray and adjacent lateral pontine tegmentum (vlPAG/LPT). It is hypothesized that cataplexy occurs when there is a loss in the excitatory noradrenergic and serotonergic neuron activity of the REM-Off network, so that atonia emerges while the individual is not sleeping and the REM-On network is not active. During cataplexy, wakefullness is also preserved by the active histaminergic neurons of the tuberomammillary nucleus, maintaining consciousness.[8] Additionally, the hypocretin system is also thought to be involved in this complex phenomenon. The orexin peptides help to maintain muscle tone by activating the monoaminergic neurons of the REM-Off network in the vlPAG/LPT and directly exciting the motor neurons.[9] The role of strong emotions in initiating cataplexy is explained with the central nucleus of the amygdala having excitatory projections to the REM-On network in the SLD and inhibitory projections to the REM-Off network in the vlPAG/LPT. Strong emotions activating the limbic cortex are thought to increase the chance of cataplexy in individuals with disturbed REM sleep and muscle tone maintaining networks.[6]

Despite the whole work in the neurobiology of sleep, narcolepsy and cataplexy, the association of cataplexy and NPC is quiet unique and sleep studies in NPC patients and common underlying neurobiological mechanisms with narcolepsy are lacking. In NPC cases with cataplexy, triggers for muscle atonia episodes are typical and the symptom responds to antidepressant therapy as shown in our cases. One hypothesis is that reduced hypocretin-1 levels may be responsible for the occurrence of cataplexy in the course of neurodegeneration in