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Brief Communication

Thinking outside the box: cataplexy without narcolepsy

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ABSTRACT

Cataplexy is a transient loss of muscle tone that can be triggered by emotions such as laughter, excitement or fear. Other causes of cataplexy include Niemann-Pick type C Disease, Angelman Syndrome, Norrie Disease, Prader-Willi Syndrome. In addition, cataplexy can be a side effect of several drugs (eg, lamotrigine, clozapine, and gamma-hydroxybutyrate). Yet, the most prevalent causes of cataplexy without narcolepsy are rare genetic diseases; which explains why cataplexy is classically linked to narcolepsy. Therefore, it is essential disconnecting cataplexy from narcolepsy especially in pediatric population and after use of a few medications. In this review, we described few conditions of cataplexy not related to narcolepsy. We performed a review of literature (MEDLINE and EMBASE database), without limited date or publication restrictions.

1. Introduction

Cataplexy is a sudden and paroxysmal loss of striated skeletal muscle tonus during wakefulness, and is usually triggered by strong emotions (eg, laughter, happiness, exaltation, fear, anger, fright, stress, orgasm and pain) [1]. Cataplexy cannot be considered as a pathognomonic symptom of narcolepsy. However, manuscripts about cataplexy without narcolepsy are less common. There is a tendency to believe that the occurrence of cataplexy without narcolepsy is an uncommon event [2].

Cataplexy is not a finding exclusive to narcolepsy. Several studies show that 30% of total cataplexy attacks are from other neurological disorders associated with hypothalamic/pontine structural lesions (eg, Niemann-Pick Type C Disease (NPC), Angelman Syndrome (AS), Norrie Disease (ND), Moebius Syndrome Prader-Willi Syndrome (PWS), Coffin-Lowry Syndrome [3–8].

Attacks of cataplexy can impair neuropsychomotor development in children and clinical characterization can be a challenge. Special attention must be paid to cataplexy in the pediatric population, both with and without narcolepsy, as initial clinical presentation may differ from the frequently described in adults. This review article proposes to discuss possible causes of cataplexy in patients without narcolepsy.

2. Methods

2.1. Literature review

2.1.1. Sources of information

To identify studies of cataplexy without narcolepsy, a systematic search was performed in the MEDLINE and EMBASE databases with no limited period range. The following search terms were used to track articles: [cataplexy without narcolepsy] and [cataplexy and medications].

2.1.2. Study selection

Our review included studies that were: (a) experimental methods in adult humans, defined in terms of research; (b) integrative and systematic literature review studies; (c) studies investigating an association between cataplexy and narcolepsy; (d)

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research on cataplexy and medications (e) published articles; and (f) written in English. Exclusion criteria were: animal studies, book reviews, conference procedures, monographs, or editorials (see Fig. 1).

3. Results

The research in the MEDLINE and EMBASE databases used the word combinations (cataplexy without narcolepsy) or (cataplexy and medications), which generated the location of 78 publications.

Overall, 13 articles were included. During the full review of these articles, reference lists were also checked for other possible studies relevant to our review. These 13 selected studies showed that the main causes of non-narcolepsy with cataplexy are Niemann-Pick type C syndrome, with a total of (seven articles), Angelman Syndrome (one article), Norrie Disease (one article), Prader-Willi Syndrome (two articles), and use of medications (three articles).

The details of these manuscripts were organized in Table 1.

In this review, the following clinical conditions in which cataplexy may occur are:

3.1. Niemann-Pick type C Disease

Niemann-Pick type C Disease (NPC) is a disease with a prevalence of 1 case per 120,000 live births. NPC is an autosomal recessive disorder caused by genetic alterations in the NPC1 (95%) and NPC2 (5%) genes, which leads to cholesterol and glycosphingolipids accumulation in several tissues, generating visceral symptoms such as fetal hydrops and splenomegaly. In addition, cataplexy is recognized as a symptom, particularly among patients aged 0–6 years [9–11]. The occurrence rate of cataplexy was between 5 and 50% and without other symptoms of narcolepsy [12–18].

3.2. Angelman Syndrome

Angelman Syndrome (AS) is a neurogenetic disorder resulting from lack of expression of a gene ubiquitin-protein ligase EA3 (UBE3A). This syndrome is caused by deletion of part of the mother's chromosome leading to deficiency of UBE3A. The deletion increases susceptibility to neurodevelopmental problems including delayed psychomotor development, speech impairment, autism spectrum disorder, epilepsy, ataxia and happy puppet face [19,20].

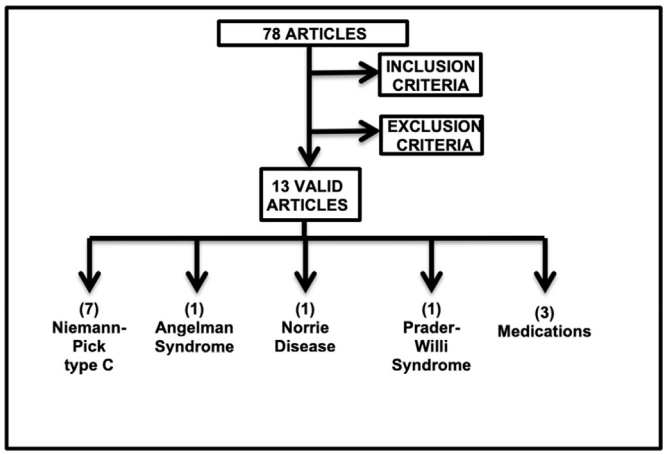

Fig. 1. Articles identified after exclusion and inclusion criteria.

3.3. Norrie Disease

Norrie Disease (ND) is a X-linked recessive disorder with optic atrophy, retinal dysgenesis, congenital blindness, deafness, and dysmorphic features. Moreover, ND is commonly associated with mental retardation, sensorineural hearing loss, and muscular hypotonia. The article included in this review, described three cases of patients with Norrie's disease and cataplexy. Authors described an abnormal REM sleep but without other findings of narcolepsy in these cases [21,22].

3.4. Prader-Willi Syndrome

Prader-Willi Syndrome (PWS) is a rare genetic disorder that occurs in 1 in 10,000 to 25,000 live births. Hypotonia, neuropsychomotor development delay and ophthalmologic features are the most common features. In addition, behavioral disturbances, hyperphagia, and obesity may occur. PWS results from lack of expression of maternal genes imprinted in the q11-q13 region of chromosome 15 due to absence or mutation of the paternal copy. The article describes a patient previously diagnosed with PWS who presented cataplexy after arousal and happiness attacks [4,23].

3.5. Medication use

It has been previously identified that, depending on the dosage, some drugs (eg, lamotrigine, clozapine, modafinil and gamma-hydroxybutyrate) may cause a person to develop cataplexy as a side effect [24–27]. However, the cataplexy is reversible and disappears after patients stop taking those medications.

4. Discussion

Narcolepsy is a rare, yet well-known disease with a global prevalence of 15–70 cases per 100,000 inhabitants per year [28]. Narcolepsy type 1 is characterized by excessive daytime sleepiness accompanied by cataplexy due to hypothalamus involvement with hypocretin deficiency [28,29].

Notably, cataplexy without EDS can be related in patients with lesions in non-hypothalamic structures. Cataplexy is not strictly related to hypocretin deficiency in symptomatic narcolepsy or genetic cases. In fact, there is a heterogenous scenarios in symptomatic narcolepsy and genetic syndromes with patients with absence of HLA-DQB1*0602 and normal levels of hypocretin [8,30].

The pathophysiology of cataplexy has been thoroughly discussed. Muscle weakness and paralysis during cataplexy are related to reduced noradrenergic and increased inhibitory input to motor neurons causes after positive emotions trigger over amygdala and medial prefrontal cortex neuronal pathways [31].

In NPC patients, cataplexy may have been explained by disbalance between locus coeruleus and pedunculopontine tegmental neuronal activities. There is an increased cholinergic activity and decreased monoaminergic activity in the upper pontine structures with consequent cataplexy [17]. Indeed, Vossler et al., related cataplexy and monoaminoxidase deficiency in patients with ND, reinforcing the theory of this disbalance [32].

It is noteworthy to identify cataplexy in two different circumstances. First is the cataplexy related to hypocretin deficiency and EDS, in narcolepsy and PWS patients. On the other hand, such as a reversible side effect without EDS seen as an isolated symptom.

Table 1
Articles that related cataplexy without narcolepsy.

Author and year of publication	Types of studies	Age group	Causes of cataplexy	Protocol	Cataplexy and the clínical description
Winstone et al., 2017	Case series	Infant	Niemann-Pick disease type C (NP-C)	53 subjects (29 females and 24 males). Acquisition of data from British Pediatric Surveillance Unit database.	17 children (32%) had cataplexy as a neurological symptom. Associated with prolonged neonatal jaundice and/or hepatosplenomegaly.
Pineda et al., 2016	Cohort	Infant		200 subjects (106 with NP-C, 31 false negative NP-C and 63 controls). Acquisition of data from nine specialized centers in seven countries.	Six of 106 patients with NP-C (5, 6%) presented with cataplexy. In addition, they had neonatal jaundice and/or hepatosplenomegaly.
Chamova et al., 2016	Cohort	Infant and adult		11 subjects (five males and six females). Acquisition of data from the Department of Neurology of the University of Sofia from 2010.	Five of 11 (45%) subjects had cataplexy. In addition, they had neonatal jaundice and/or hepatosplenomegaly and/or psychiatric disorder.
Abela et al., 2014	Cohort	Infant, juvenile and adult		14 subjects (seven males and seven females). Acquisition of data through medical records of patients.	Two (14%) subjects had cataplexy. In addition, they also had neonatal jaundice and/or hepatosplenomegaly and/or psychiatric disorder.
Anheim et al., 2014	Case series	Infant, juvenile and adult		Five subjects (one male and four female). Data acquisition not reported.	They describe cataplexy as an expected symptom in Niemman-Pick type C disease.
Nevsimalova; Malinova, 2015	Case series	Infant, juvenile and adult		22 subjects (gender not specified). Acquisition of data through medical records.	Six patients with cataplexy (27%)
Ren et al., 2018	Cohort	Infant		10 subjects (five male and five female aged 42 days to 14 years). Acquisition of data through medical records.	Five patients (50%) had gelastic cataplexy. No symptoms and narcoleptic signs were mentioned.
Mertz et al., 2016	Cohort	Infant	Angelman syndrome	39 subjects (19 male and 20 female). Acquisition of data from the Danish national registry, cytogenetic register and neurological department.	Six children had episodes of cataplexy triggered by laughter (15% of all cases).
Vossler et al., 1996	Case series	Infant	Norrie disease	three male subjects. Acquisition of data from Johns Hopkins University.	Three patients with cataplexy were revealed after the diagnosis of the disease, occurring during pain and laughter.
Lee and Doja, 2017	Case report	Infant	Prader-Willi Syndrome	Four-year-old female children	Patient had sudden fall after awakening, associated with loss of tone, remaining with eyes open during the episode, suggesting cataplexy. EEG was normal. There were no other narcoleptic signs or symptoms.
Alonso-Navarro et al, 2016	Case report	Adult	Drug: Lamotrigin.	Female patient, 37 years admitted to the psychiatric ward.	Patient began having episodes of cataplexy after reaching 200 mg/day of Lamotrigine.
Desarkar et al., 2007	Case report	Adult	Drug: Clozapine	Female patient, 29 years old, diagnosed with schizoaffective disorder, manic type.	Patient started episodes of cataplexy induced by clozapine after reaching 150 mg/day. There was no other symptoms related to sleep disorders.
Mamelak and Sowden, 1983	Pilot study	–	Drug: Gamma-hydroxybutyrate	–	Gamma-hydroxybutyrate (GHB) can promote cataplexy when administered during the day.

5. Conclusions

Further studies must be done to improve our knowledge about cataplexy pathophysiology. It is important to add cataplexy such as a potential diagnosis of weakness, especially in the pediatric population with genetic conditions or taking any drug with this potentially side effect.

Cataplexy is a transient loss of muscle tone that is often triggered by emotions such as laughter, excitement or fear. There is no loss of consciousness associated and the recovery usually occurs within seconds. Although it is a classic symptom of narcolepsy, cataplexy should not be considered a pathognomonic symptom of this disease. It is important to extend the differential diagnosis of cataplexy, especially in the pediatric population with genetic conditions as well as patients taking any drug with this potential side effect.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.03.006.

References

[1] Dauvilliers Y, Arnulf I, Mignot E. Narcolepsy with cataplexy. Lancet 2007;369:499–511.
[2] Dauvilliers Y, Billiard M, Montplaisir J. Clinical aspects and pathophysiology of narcolepsy. Clin Neurophysiol – Offic J Int Federat Clin Neurophysiol 2003;114:2000–17.
[3] Thorpy MJ. Classification of sleep disorders. Neurotherap – J Am Soc Exp Neuro Therap 2012;9:687–701.
[4] Tobias ES, Tolmie JL, Stephenson JB. Cataplexy in the Prader-Willi Syndrome. Arch Dis Child 2002;87:170.
[5] Tyagi A, Harrington H. Cataplexy in association with Moebius Syndrome. J Neurol 2003;250:110–1.

[6] Fryssira H, Kountoupi S, Delaunoy JP, et al. A female with Coffin-Lowry syndrome and "cataplexy". Genet Couns 2002;13:405–9.
[7] Challamel MJ, Mazzola ME, Nevsimalova S, et al. Narcolepsy in children. Sleep 1994;17:S17–20.
[8] Nishino S, Kanbayashi T. Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system. Sleep Med Rev 2005;9:269–310.
[9] Patterson MC, Mengel E, Wijburg FA, et al. Disease and patient characteristics in NP-C patients: findings from an international disease registry. Orphanet J Rare Dis 2013;8:12.
[10] Cak HT, Haliloglu G, Duzgun G, et al. Successful treatment of cataplexy in patients with early-infantile Niemann-Pick disease type C: use of tricyclic antidepressants. Eur J Paediatr Neurol 2014;18:811–5.
[11] Garver WS, Francis GA, Jelinek D, et al. The National Niemann-Pick C1 disease database: report of clinical features and health problems. Am J Med Genet A 2007;143A:1204–11.
[12] Winstone AM, Stellitano LA, Verity CM. Niemann-Pick type C as a cause of progressive intellectual and neurological deterioration in childhood. Dev Med Child Neurol 2017;59:965–72.
[13] Pineda M, Mengel E, Jahnova H, et al. A Suspicion Index to aid screening of early-onset Niemann-Pick disease Type C (NP-C). BMC Pediatr 2016;16:107.
[14] Chamova T, Kirov A, Guergueltcheva V, et al. Clinical spectrum and genetic variability in Bulgarian patients with niemann-pick disease type C. Eur Neurol 2016;75:113–23.
[15] Abela L, Plecko B, Palla A, et al. Early co-occurrence of a neurologic-psychiatric disease pattern in Niemann-Pick type C disease: a retrospective Swiss cohort study. Orphanet J Rare Dis 2014;9:176.
[16] Anheim M, Lagha-Boukbiza O, Fleury-Lesaunier MC, et al. Heterogeneity and frequency of movement disorders in juvenile and adult-onset Niemann-Pick C disease. J Neurol 2014;261:174–9.
[17] Nevsimalova S, Malinova V. Cataplexy and sleep disorders in Niemann-Pick type C disease. Curr Neurol Neurosci Rep 2015;15:522.
[18] Ren SC, Tian ZX, Deng YX, et al. Clinical features and gene mutation analysis of patients with Niemann-Pick disease type C. Zhonghua Yi Xue Za Zhi 2018;98:284–8.
[19] Burnside RD, Pasion R, Mikhail FM, et al. Microdeletion/microduplication of proximal 15q11.2 between BP1 and BP2: a susceptibility region for neurological dysfunction including developmental and language delay. Hum Genet 2011;130:517–28.
[20] Conant KD, Thibert RL, Thiele EA. Epilepsy and the sleep-wake patterns found in Angelman syndrome. Epilepsia 2009;50:2497–500.
[21] Pettenati MJ, Rao PN, Weaver Jr RG, et al. Inversion (X)(p11.4q22) associated with Norrie disease in a four generation family. Am J Med Genet 1993;45:577–80.
[22] Joy JE, Poglod R, Murphy DL, et al. Abnormal protein in the cerebrospinal fluid of patients with a submicroscopic X-chromosomal deletion associated with Norrie disease: preliminary report. Appl Theor Electroph 1991;2:3–5.
[23] Weselake SV, Foulds JL, Couch R, et al. Prader-Willi syndrome, excessive daytime sleepiness, and narcoleptic symptoms: a case report. J Med Case Rep 2014;8:127.
[24] Alonso-Navarro H, Montes JM, Plaza-Nieto JF, et al. Cataplexy possibly associated with lamotrigine. J Clin Psychopharmacol 2016;36:400–2.
[25] Desarkar P, Goyal N, Khess CR. Clozapine-induced cataplexy. J Neuropsychiatry Clin Neurosci 2007;19:87–8.
[26] Mamelak M, Sowden K. The effect of gammahydroxybutyrate on the H-reflex: pilot study. Neurology 1983;33:1497–500.
[27] Lopes E, Pereira D, da Silva Behrens NS, et al. Cataplexy as a side effect of modafinil in a patient without narcolepsy. Sleep Sci 2014;7:47–9.
[28] Goldbart A, Peppard P, Finn L, et al. Narcolepsy and predictors of positive MSLTs in the Wisconsin sleep cohort. Sleep 2014;37:1043–51.
[29] Baumann CR, Mignot E, Lammers GJ, et al. Challenges in diagnosing narcolepsy without cataplexy: a consensus statement. Sleep 2014;37:1035–42.
[30] Vankova J, Stepanova I, Jech R, et al. Sleep disturbances and hypocretin deficiency in Niemann-Pick disease type C. Sleep 2003;26:427–30.
[31] Dauvilliers Y, Siegel JM, Lopez R, et al. Cataplexy–clinical aspects, pathophysiology and management strategy. Nat Rev Neurol 2014;10:386–95.
[32] Vossler DG, Wyler AR, Wilkus RJ, et al. Cataplexy and monoamine oxidase deficiency in Norrie disease. Neurology 1996;46:1258–61.