Narcolepsy-Cataplexy and Precocious Puberty May Be Linked

By Regina Patrick, RPSGT

Scientists have noted that children with narcolepsy-cataplexy have an increased prevalence of overweight/obesity.[1-3] More recent studies have linked narcolepsy-cataplexy with precocious puberty, and have indicated that the earlier the onset of narcolepsy-cataplexy in a child, the greater the risk of precocious puberty.[3] Weight loss can occur after treating narcolepsy-cataplexy in children, but the extent that treating narcolepsy-cataplexy can reverse precocious puberty has not been examined in depth.[4] Exactly how narcolepsy and precocious puberty are related is unclear but research studies have produced some interesting findings.

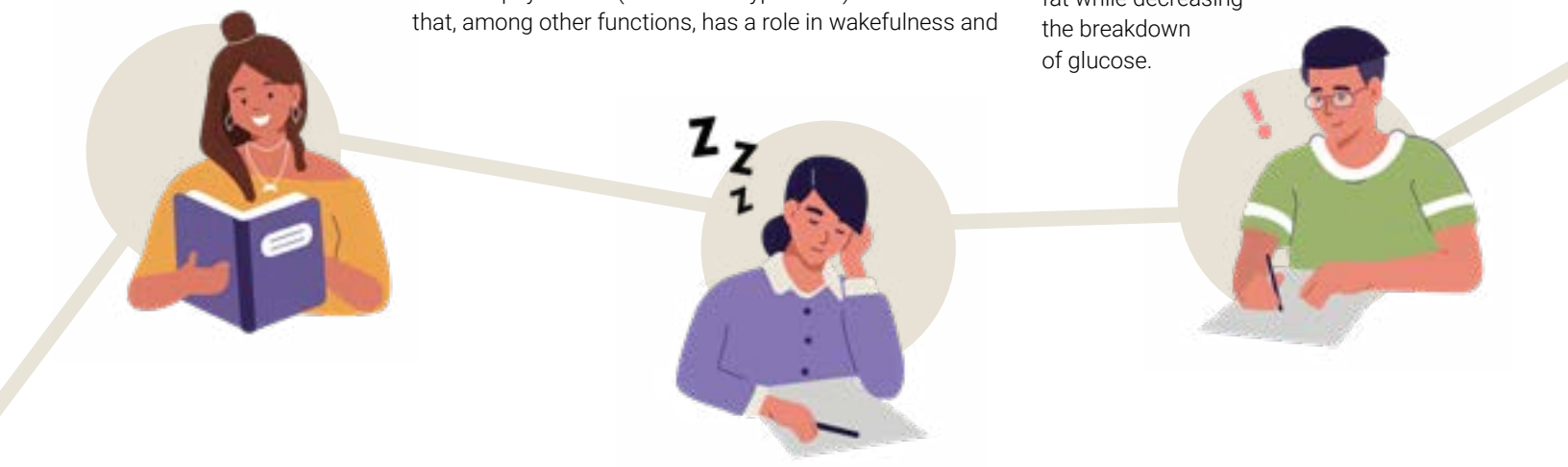
Approximately 25% to 74% of individuals with narcolepsy-cataplexy are overweight or obese, and precocious puberty occurs in 17% of children with narcolepsy-cataplexy.[3,5] Narcolepsy is a syndrome consisting of four symptoms: vivid realistic dream imagery on going to sleep (i.e., hypnagogic hallucination) or on awakening (i.e., hypnopompic hallucination); excessive daytime sleepiness; sleep paralysis (i.e., a temporary inability to move on awakening or going to sleep); and cataplexy (i.e., sudden skeletal muscle weakness that occurs with the expression of strong emotions such as mirth or anger). A person does not have to have all four symptoms to be diagnosed with narcolepsy. In recent years, a fifth symptom has been suggested: disrupted sleep.6 Narcolepsy can occur with cataplexy (i.e., "narcolepsy type I") or without cataplexy (i.e., "narcolepsy type II").

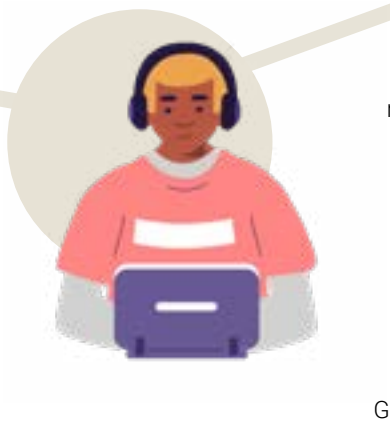
Exactly how narcolepsy develops is unknown. Some evidence indicates that narcolepsy has a genetic component. Some people with narcolepsy, especially people with narcolepsy-cataplexy, have the HLA-DQB1*06:02 gene, which is a variation (i.e., allele) of the HLA-DQB1 gene. The HLA-DQB1 gene is part of a family of genes called the human leukocyte antigen (HLA) complex. This complex is involved in immunity and allows the body to distinguish its own proteins from proteins produced by viruses and bacteria. The HLA genes encode for proteins that are on the surface of certain immune cells. These proteins then attach to protein fragments (i.e., peptides) outside of a cell. If the immune system recognizes the peptides as foreign (e.g., viral or bacterial peptides), the immune response is triggered to attack the invading viruses or bacteria.

Some research indicates that the loss of orexin-producing cells in the hypothalamus (a structure at the base of the brain) is a factor that is associated with narcolepsy. Orexin (also called hypocretin) is a hormone that, among other functions, has a role in wakefulness and increases appetite. Alterations in orexin genes or the loss of orexinergic neurons results in narcolepsy in rodents[7-9] and dogs[10] in animal models of narcolepsy. The loss of orexinergic cells may also contribute to increased weight in individuals with narcolepsy.

What causes the loss of orexin-producing cells in narcolepsy is unknown (i.e., idiopathic). However, some research indicates that this loss may be related to an improper immune response: in some instances, symptoms of narcolepsy start soon after a child has had a bacterial or viral infection.[11] Supporting the possibility of an improper immune response in narcolepsy, immunotherapy such as intravenous immunoglobulin therapy has been shown to reverse or reduce symptoms of narcolepsy, especially cataplexy, in some children.[12,13]

In addition to its role in sleep-wake, the hypothalamus is involved in growth. It releases growth hormone-releasing hormone, which stimulates the pituitary to release growth hormone. Growth hormone increases the movement of amino acids from blood into cells, which then use the amino acids to form tissue proteins, thereby enhancing growth. Growth hormone also enhances the breakdown of fat while decreasing the breakdown of glucose.





The hypothalamus also synthesizes somatostatin, which inhibits the release of growth hormone. The release of growth hormone-releasing hormone and somatostatin are regulated in a feedback manner by the blood levels of growth hormone and insulin-like growth factor I (a hormone that, along with growth hormone, promotes bone and tissue growth and development).

Certain neurons in the hypothalamus synthesize and release gonadotropin-releasing hormone (GnRH). The hormone travels through the bloodstream to the anterior pituitary gland where GnRH receptors stimulate the pituitary gland to synthesize and release the gonadal hormones luteinizing hormone and follicle-stimulating hormone. In males, luteinizing hormone binds to cells in the testicles to stimulate the production of sperm cells. In females, follicle-stimulating hormone stimulates the growth of eggs in the ovaries.

The onset of puberty (i.e., sexual maturity) normally begins at 8–13 years old in girls and at 9–14 years old in boys. Signs of puberty in both sexes are the development of pubic and underarm hair, a rapid increase in height (i.e., "growth spurt"), acne, and underarm odor. In addition to these signs, girls will develop breasts and experience the onset of menstrual periods, and boys will have growth of the penis and testes, deepening voice, and facial hair. Precocious puberty occurs when the onset of puberty occurs before eight years old in girls and nine years old in boys. Children with precocious puberty initially grow taller than their peers because of the growth spurt; however, because the growth spurt occurs earlier, these children stop growing earlier than their peers. Therefore, individuals who experience precocious puberty in childhood will often be smaller than their peers in adulthood.

Precocious puberty is classified as central (i.e., caused by a problem in the brain) or peripheral (i.e., caused by a problem outside the brain). The cause of central precocious puberty is usually idiopathic, but it can occur as a result of a tumor, brain abnormalities, or brain injury.

Some research indicates that precocious puberty may have a genetic component. For example, a mutation in the MKRN3 gene has been associated with precocious puberty.[14-16] The MKRN3 gene is involved in directing the onset of puberty.

Peripheral precocious puberty can result from exposure to certain chemicals in the environment or the consumption of foods that disrupt the activity of natural endocrine hormones. Endocrine-disrupting chemicals stimulate or inhibit the activity of natural hormones by binding to their receptors or by affecting their synthesis, transport, metabolism, and elimination. For example, bisphenol A (BPA), a chemical used in various plastic products, stimulates the actions of certain molecules (e.g., the protein kisspeptin 1) that have a role in the onset of puberty and inhibits the actions of certain molecules such as the yin yang 1 (YY1) protein and the enhanced at puberty 1 (EAP1) protein that inhibit the onset of puberty.[17] Some pesticides used to kill unwanted organisms in agriculture and in other settings (garden, medicine) are endocrine disruptors.[19] The pesticides dieldrin, endosulfan, methiocarb, and fenarimol have estrogen-agonist and androgen-antagonist activity. Humans can become exposed to these pesticides through dietary and environmental means (e.g., water and soil).

Potential risk factors for precocious puberty in children with narcolepsy-cataplexy was first examined by Poli et al.[3] In their study, the children underwent pubertal endocrine assessments, which involved gonadotropin-releasing hormone (GnRH) stimulation tests in which the GnRH agonist gonadorelin was intravenously administered; x-ray imaging of the nondominant wrist to determine the bone/chronological age ratio and pelvic ultrasound imaging for girls, and brain magnetic resonance imaging of the hypothalamic-pituitary region. They diagnosed precocious puberty when a child had secondary sexual characteristics before the age of 8 years (girls) or 9 years (boys); markedly elevated levels of plasma luteinizing hormone (i.e., >5 minus/mL after the GnRH stimulation tests); and no brain abnormalities on magnetic resonance images.

Poli compared the prevalence of precocious puberty among obese children with narcolepsy-cataplexy versus its prevalence among obese children without narcolepsy (i.e., the controls). The findings were that precocious puberty affected nearly 17% of children with narcolepsy-cataplexy, but it only affected 1.9% of the controls. In their study, most (74%) of the children with narcolepsy-cataplexy (i.e., with and without precocious puberty) had overweight/obesity. Poli suggests that precocious puberty and overweight/obesity among children with narcolepsy-cataplexy may indicate extended hypothalamic dysfunction.

The interplay between the orexinergic system and hypothalamic hormones involved in growth may be involved in the increased prevalence of precocious puberty in overweight/obese children with narcolepsy-cataplexy. Orexin is involved in feeding (i.e., increased hunger), promotes wakefulness, and is involved in the sleep-to-wake transition. It inhibits the secretion

Individuals who experience precocious puberty in childhood will often be smaller than their peers in adulthood.

of the growth hormone by modulating the activity of growth hormone-releasing hormone neurons and somatostatin neurons.

Fibers from orexin-producing neurons in the hypothalamus project to nuclei that control growth hormone secretion in the anterior pituitary. Therefore, orexin may be involved in growth hormone secretion resulting from growth hormone-releasing hormone stimulation. Some research suggests that the level of growth hormone is higher during sleep, and orexin may be involved in sleep-induced growth hormone secretion.[20]

In 1985, Chisholm and colleagues[21] reported their experience with a nearly 6-year-old girl with narcolepsy-cataplexy, breast development, and advanced bone age. Based on their findings, they proposed that the very early onset of narcolepsy-cataplexy could have attributed to the girl's precocious puberty. Other reports noting an association between narcolepsy-cataplexy and precocious puberty soon followed.[1,2,22] For now, the mechanisms that link narcolepsy and precocious puberty remain unclear. Future studies may clarify this link.

However, clinicians may need to consider having a child with narcolepsy-cataplexy undergo endocrine evaluations, especially if the child is overweight/obese and/or has signs of precocious puberty. This evaluation may allow a clinician to detect or confirm precocious puberty and treat it early to prevent complications such as growth problems and to reduce the risk of developing other problems such as breast cancer, teen pregnancy, heart disease, and diabetes.

References

1. Peraita-Adrados R, Garcia-Penas JJ, Ruiz-Falco L, et al. Clinical, polysomnographic and laboratory characteristics of narcolepsy-cataplexy in a sample of children and adolescents. *Sleep Medicine*. 2011;12:24-27.
2. Perriol MP, Cartigny M, Lamblin, MD, et al. Childhood-onset narcolepsy, obesity and puberty in four consecutive children: A close temporal link. *Journal of Pediatric Endocrinology and Metabolism*. 2010;23:257-265.
3. Poli F, Pizza F, Mignot E, et al. High prevalence of precocious puberty and obesity in childhood narcolepsy with cataplexy. *Sleep*. 2013;36(2):175-181.
4. Ponziani V, Gennari M, Pizza F et al. Growing up with type 1 narcolepsy: Its anthropometric and endocrine features. *Journal of Clinical Sleep Medicine*. 2016;12:1649-1657.
5. Maia Palhano AC, Kim LJ, Moreira GA. Narcolepsy, precocious puberty and obesity in the pediatric population: A literature review. *Pediatric Endocrinology Reviews*. 2018;16(2):266-274.
6. National Institute of Neurological Disorders and Stroke, National Institutes of Health. Narcolepsy Fact Sheet. National Institutes of Health: Bethesda, MD. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Narcolepsy-Fact-Sheet. Published 2020. Accessed April 17, 2020.
7. Chemelli RM, Willie JT, Sinton CM, et al. Narcolepsy in orexin knockout mice: Molecular genetics of sleep regulation. *Cell*. 1999;98:437-451.
8. Gerashchenko D, Kohls MD, Greco M, et al. Hypocretin-2-saporin lesions of the lateral hypothalamus produce narcoleptic-like sleep behavior in the rat. *Journal of Neuroscience*. 2001;21:7273-7283.
9. Hara J, Beuckmann CT, Nambu, T, Willie JT, et al. Genetic ablation of orexin neurons in mice results in narcolepsy, hypophagia, and obesity. *Neuron*. 2001;30:345-354.
10. Faraco J, Lin X, Li R, et al. Genetic studies in narcolepsy, a disorder affecting REM sleep. *Journal of Heredity*. 1999;90:129-132.
11. Seong MJ, Hong SB. Autoimmunity and immunotherapy in narcolepsy. *Sleep Medicine Research*. 2017;8:1-7.
12. Plazzi G, Poli F, Franceschini C, et al. Intravenous high-dose immunoglobulin treatment in recent onset childhood narcolepsy with cataplexy. *Journal of Neurology*. 2008;255:1549-1554.
13. Abad VC, Guilleminault C. New developments in the management of narcolepsy. *Nature and Science of Sleep*. 2017;9:39-57.
14. Abreu AP, Dauber A, Macedo DB, et al. Central precocious puberty caused by mutations in the imprinted gene MKRN3. *New England Journal of Medicine*. 2013;368:2467-2475.
15. Abreu AP, Macedo DB, Brito VN, et al. A new pathway in the control of the initiation of puberty: The MKRN3 gene. *Journal of Molecular Endocrinology*. 2015;54:R131-R139.
16. Fanis P, Skordis N, Toumba M, et al. Central Precocious Puberty Caused by Novel Mutations in the Promoter and 5'-UTR Region of the Imprinted MKRN3 Gene. *Frontiers in Endocrinology (Lausanne)*. 2019;10:677.
17. Leonardi A, Cofini M, Rigante D, et al. The effect of bisphenol A on puberty: A critical review of the medical literature. *International Journal of Environmental Research and Public Health*. 2017;14(9):1044-1063.
18. Engeli RT, Rohrer SR, Vuorinen A, et al. Interference of paraben compounds with estrogen metabolism by inhibition of 17beta-hydroxysteroid dehydrogenases. *International Journal of Molecular Sciences*. 2017;18(9): pii: E2007; doi: 2010.3390/ijms18092007.
19. Mnif W, Hassine A, Bouaziz A, et al. Effect of endocrine disruptor pesticides: A review. *International Journal of Environmental Research and Public Health*. 2011;8:2265-2303.
20. Lopez M, Seoane LM, Tovar S, et al. Orexin-A regulates growth hormone-releasing hormone mRNA content in a nucleus-specific manner and somatostatin mRNA content in a growth hormone-dependent fashion in the rat hypothalamus. *European Journal of Neuroscience*. 2004;19:2080-2088.
21. Chisholm RC, Brook CJ, Harrison GF, et al. Prepubescent narcolepsy in a six year old girl. *Sleep Research*. 1985;15:113.
22. Plazzi G, Parmeggiani A, Mignot E, et al. Narcolepsy-cataplexy associated with precocious puberty. *Neurology*. 2006;66:1577-1579.

REGINA PATRICK, RPSGT, RST, *has been in the sleep field for more than 20 years and works as a sleep technologist at the Wolverine Sleep Disorders Center in Tecumseh, Michigan.*