Melatonin’s Potential Side Effects: It May Be in Your Genes

To the Editor: According to a recent study using data from the 1999-2000 through 2017-2018 cycles of the National Health and Nutrition Examination Survey (NHANES), the prevalence of melatonin supplement consumption, including self-reported use of more than 5 mg/d of melatonin, significantly increased over time. More specifically, the overall reported prevalence of melatonin use increased from 0.4% in 1999-2000 to 2.1% in 2017-2018. Furthermore, the prevalence of melatonin use of more than 5 mg/d rose from 0.08% in 2005-2006 to 0.28% in 2017-2018. These NHANES findings received a great deal of public attention (Altmetric score on March 31, 2022: 1014), including a discussion of possible safety concerns about melatonin. But what are the potential adverse effects of melatonin? According to a recent meta-analysis including data from 79 studies with 3861 participants, melatonin, even when taken in a higher dose (≥10 mg/d) and for 3 months or longer, was not associated with an increased risk of serious adverse effects events. However, a 40% increase in adverse events was found, but these were primarily limited to headache, dizziness, and drowsiness.

Surprisingly, in the discussion of melatonin’s safety profile, little attention has been paid to the genetic polymorphism rs10830963 in the melatonin receptor 1B (MTNR1B) gene carried by about 30% of the general population. Carriers of the risk G allele of single-nucleotide polymorphism rs10830963 show higher expression of MTNR1B in β cells in pancreatic islets compared with noncarriers. Through binding to MTNR1B, melatonin acutely blocks glucose-induced insulin secretion by β cells. Thus, those carrying copies of the G allele where pancreatic islets expressed more MTNR1B may show impaired postprandial glucose disposal under the impact of melatonin. In line with this assumption, a randomized crossover study of 845 participants found that an oral glucose tolerance test scheduled 1 hour before habitual bedtime (ie, a time of the day when endogenous melatonin rises in the blood) resulted in lower insulin release and higher plasma glucose concentration. Notably, the effect of late eating impairing glucose tolerance was stronger in carriers of the G allele than in noncarriers. These findings could also explain why the G allele of MTNR1B rs10830963 confers an increased risk of type 2 diabetes.

Findings that adverse effects of exogenous melatonin supplements appear to be limited to headache, dizziness, and drowsiness may mislead the patients to believe that melatonin supplements are generally safe. However, as pointed out in this Letter to the Editor, users of melatonin supplements should undergo periodic glycated hemoglobin (HbA1c) monitoring. In this context, physicians and researchers should pay particular attention to those carrying the G allele of MTNR1B rs10830963.

POTENTIAL COMPETING INTERESTS

Between 2020 and 2021, Christian Benedict served as a scientific consultant for Repha GmbH, Langen, Germany. No other disclosures related to the content of this commentary were reported.

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Malignant Histiocytosis With PD-L1 Expression—Dramatic Response to Nivolumab

To the Editor: A woman in her 60s was admitted to the hospital for exploration of erythema nodosum, lower limb edema, and asthenia. Clinical examination revealed no other abnormalities, and autoimmune and
infections results were normal. 18F-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) was performed and showed upper mediastinal, peritracheal, hilar, and left paracardiac adenopathies with strong hypermetabolism (maximum standard uptake value of 18). Surgical biopsy specimens of a mediastinal lymphadenopathy were obtained by cervicotomy and revealed abundant histiocytes. Immunostaining was positive for CD45, CD123, CD14, CD4, and CD33 and negative for CD56, ALK, CD34, CD117, S100, CD1a, and CD68. Almost 90% of tumor cells displayed positive staining for programmed cell death ligand 1 (PD-L1), and phospho-ERK expression was strong. Next-generation sequencing targeting was performed for 75 genes principally involved in the MAP kinase cell signaling pathway; a CALR mutation was identified but no BRAF mutation. The diagnosis was consistent with malignant histiocytosis according to the revised classification of the Histiocyte Society.

Monochemotherapy with 60 mg/m² of doxorubicin was initiated. After 7 cycles, the clinical disorders had resolved, and FDG PET/CT revealed a general improvement of all lesions. However, 4 months later, disease progression was observed. In light of the phospho-ERK overexpression, targeted anti-MEK therapy was initiated. After 7 months of treatment with trametinib, FDG PET/CT showed disease progression. Compassionate treatment with 3 mg/kg of nivolumab was therefore initiated. After 3 courses of treatment, FDG PET/CT showed a substantial response, with a clear decrease in the number and intensity of hypermetabolic lymphadenopathies (Figure).
Malignant histiocytosis (or histiocytic sarcoma) is a rare disease characterized by a malignant proliferation of cells resembling mature tissue histiocytes. Median age at diagnosis is 63 years; the prognosis is usually poor, with a median overall survival of 6 months, because no standard treatment has yet been established and responses to conventional chemotherapy at advanced stages are generally poor. Mutations affecting the RAS-MAPK signaling pathway are detected in most cases, and the off-label use of targeted therapies has been reported to yield clinical responses in several cases. It has been suggested that PD-L1 expression is detectable in most cases, but the utility of PD-L1/PD-1 blockade in histiocytic neoplasms remains unclear. We report here the first case of a response to nivolumab in an adult with malignant histiocytosis. Next-generation sequencing appears to be essential for the diagnosis of this rare histiocytic condition, given the therapeutic options available. However, immune checkpoint inhibition may also be a valuable therapeutic option for patients with malignant histiocytosis expressing PD-L1.

Potentially Competing Interests

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Primary Sarcoïdosis of the Adipose Tissue: A New Variant of Sarcoïdosis

To the Editor: Although sarcoïdosis predominantly targets the lungs, almost every organ can be affected. This occasionally renders the diagnosis a difficult task. We describe a patient with isolated adipose tissue sarcoïd granulomas, constituting the first ever report on this unique manifestation.

A woman in her mid-50s presented to the emergency department complaining of fatigue. The patient had been in her usual state of health until 3 months before this admission, when she first noticed a feeling of asthenia that gradually deteriorated. Her past medical history was unremarkable, and the physical examination disclosed no abnormalities. Laboratory tests revealed severe hypercalcemia (13.8 mg/dL; to convert to mmol/L, multiply by 0.25) and acute kidney injury (serum creatinine concentration, 1.7 mg/dL; to convert to μmol/L, multiply by 88.4). Additional laboratory test results included excessive urine calcium excretion, low serum parathormone (PTH) level, low serum 25-hydroxyvitamin D level (12.3 ng/mL; to convert to nmol/L, multiply by 2.496), increased activity of serum angiotensin-converting enzyme (211 U/L; to convert to nkat/L, multiply by 16.667), and normal serum level of 1,25-dihydroxyvitamin D (25.8 pg/mL; to convert to pmol/L, multiply by 2.4). Interferon-γ release assay and a tuberculin test response were negative.

The diagnostic process was focused on the dangerously high serum calcium concentration. Suppressed PTH levels narrowed the differential diagnosis to malignant disease–related hypercalcemia and ectopic calcitriol production. Thoracic computed tomography (CT) showed no signs of mediastinal or hilar lymphadenopathy, bone scintigraphy excluded osteolytic metastases, and normal PTH-related protein levels (<1 pmol/L) ruled out PTH-related protein–secreting malignant neoplasm. Serum and urine protein electrophoresis and immunofixation excluded classic secretory multiple myeloma; nonsecretory multiple myeloma was ruled out by a bone marrow biopsy.

The more likely conditions having been eliminated, the probability of a granulomatous disease refocused the diagnostic work-up. Low 25-hydroxyvitamin D levels coupled with inappropriate normal levels of 1,25-dihydroxyvitamin...