Central Nervous System

Symptoms

Cognitive impairment

Intellectual disability is expected in individuals with clinically evident myotonic dystrophy at birth. In less severe forms of the disease, cognitive and behavioral abnormalities can involve IQ, executive function, visual-spatial construction, arithmetic ability, attention, and personality to variable degrees. Intellectual disability is a static abnormality associated with brain maldevelopment, but whether DM can also cause a progressive, degenerative, or even dementing disorder remains controversial. In addition to the primary alteration in brain function caused directly by the myotonic dystrophy mutation, hormonal or other systemic abnormalities in myotonic dystrophy might cause or exacerbate intellectual dysfunction by secondarily affecting the central nervous system (CNS).

Excessive daytime sleepiness

Excessive daytime sleepiness (hypersomnia) is common in myotonic dystrophy and can develop at any age. As opposed to generalized fatigue, which is also common in myotonic dystrophy, hypersomnia causes patients to sleep frequently, and often unpredictably, throughout the day despite having normal or greater than normal duration of sleep at night. Hypersomnia in myotonic dystrophy can result from several distinct mechanisms, including:

- Behavioral abnormalities with an erratic sleep schedule and poor sleep hygiene
- Ventilatory muscle weakness with sleep-related hypoventilation and non-restorative sleep
- Airway obstruction due to pharyngeal weakness and obstructive sleep apnea
- CNS causes of central alveolar hypoventilation
- CNS causes of central hypersomnia due to disordered arousal

Behavioral, emotional, and socialization difficulties

- Behavioral phenotypes such as avoidant personality are more common in patients with low cognitive ability and advanced physical handicap, but have also been described in DM1 and DM2 patients with normal IQ.
- Physical disabilities in severely affected individuals (such as craniofacial abnormalities, dysarthria and abnormal facial appearance) also influence behavior, emotional state, and socialization.
- Substance abuse is common in a subset of myotonic dystrophy subjects, but requires additional investigation to determine its cause.
- Frequency and severity of depression in myotonic dystrophy is often difficult to assess due to the concurrence of apparently unrelated apathetic or avoidant personality, sleep and eating dysfunction, and inexpressive facial appearance due to facial muscle involvement.

Peripheral Neuropathy

Minimal abnormalities in peripheral nerve function have been confirmed by nerve conduction studies, but significant peripheral nerve abnormalities, previously suggested by muscle biopsy features, have not been confirmed. Symptoms attributable to peripheral nerve involvement are uncommon and rarely clinically significant.

Patterns of CNS Problems

Congenital DM1
Childhood/Adolescence • Intellectual impairment due to potentially severe intellectual disability. Speech abnormalities, dysmorphic facial appearance, and lack of facial expression can make mild or normal cognitive impairment appear more marked. • Developmental delays and learning disabilities related to the cognitive impairment and exacerbated by craniofacial abnormalities (dysarthria, lack of facial expression), and distal weakness (lack of dexterity, generalized fatigue) • Apparent apathy and inertia can be exacerbated by multiple causes, including cognitive impairment, avoidant personality, daytime hypersomnia, neuromuscular fatigue, and inexpressive facial appearance due to facial muscle weakness • Psychiatric disorders (including attention deficit, socialization difficulties, anxiety, substance abuse, and depression) • Visual-spatial and constructional difficulties due to cognitive deficits are exacerbated by motor impairment
Adulthood • Executive function abnormalities, daytime sleepiness and psychiatric disorders frequently become more evident with age
Childhood Onset DM1
Childhood/Adolescence • Variable cognitive impairment. Patients who come to medical attention during childhood but after the neonatal period may have congenital defects including intellectual disability, which is mild compared to those with overt congenital disabilities. Dysarthria, dysmorphic facial appearance, and lack of facial expression can result in subjects with mild cognitive impairment appearing more markedly affected than is accurate. These mistaken impressions can occur both during casual interactions and on formal neuropsychological testing unless the evaluator appropriately corrects for the patient's physical disabilities. • Apparent apathy and inertia resulting from and exacerbated by multiple causes, including cognitive impairment, avoidant personality, daytime hypersomnia, neuromuscular fatigue, and inexpressive facial appearance due to muscle weakness • Developmental delay and learning disabilities • Psychiatric disorders including attention deficit, socialization difficulties, anxiety, substance abuse and depression • Visual-spatial and constructional difficulties due to cognitive deficits which are exacerbated by motor impairment
Adulthood • Increasing age is associated with more evident executive function abnormalities, daytime sleepiness and psychiatric disorders.
Adult Onset DM1
Classic form • Intellectual impairment or static cognitive impairment is NOT expected in patients without clinical features of myotonic dystrophy until adulthood (as opposed to those with early onset symptoms who are not correctly diagnosed until adulthood). • Progressive cognitive loss can occur in true adult onset DM1, typically in association with multisystemic deterioration, though the relationship of this apparent dementing process with executive function loss and psychiatric disorders that both increase with age requires further investigation. • Psychiatric disorders including attention deficit, avoidant personality, socialization difficulties, anxiety, and depression increase with age, and are exacerbated by hypersomnia and multisystemic disease. • Excessive daytime sleepiness can be the primary and presenting symptom in some individuals with adult onset disease. • Visual-spatial constructional difficulties may be present in true adult onset DM1 but have not yet been thoroughly investigated. • Executive function deteriorates with age in adult onset DM1 subjects, leading to greater difficulty in organizing and responsibly performing routine lifetime activities (paying bills, keeping appointments, arranging schedules, etc.)

DM2
• Overall less is known about CNS effects of DM2, and additional research in needed. • As in true adult-onset DM1 patients, intellectual impairment or static cognitive impairment is NOT expected in DM2. • As in true adult-onset DM1 patients, progressive cognitive loss can occur in DM2, typically in association with multisystemic deterioration, executive function loss and psychiatric disorders. • Psychiatric disorders including attention deficit, avoidant personality, and depression become more common with age, and are exacerbated by hypersomnia and multisystemic disease. • Executive function deteriorates with age in adult onset DM2 subjects, leading to greater difficulty in organizing and responsibly performing routine lifetime activities (paying bills, keeping appointments, arranging schedules, etc.).

Diagnosis

Evaluation of excessive daytime sleepiness (EDS)

Excessive daytime sleepiness results in significant morbidity and mortality due to accidents while driving, at work or at home, therefore it is important to recognize the problem and determine the underlying cause. In situations requiring quantification, the degree of excessive sleepiness can be formally evaluated by sleepiness scales. (A subset of the Stanford Sleepiness Scale has been validated in DM1.) The following set of questions can be used for simple identification of hypersomnia in clinic patients:

- When do you go to sleep each night and how many hours do you sleep?
- Do you take one or more naps during the day?
- Do you at times experience a sudden need to sleep during the day?
- Do you often fall asleep while watching TV or at the movies or a show?
- Do you have difficulty being inactive for prolonged periods?
- Are you generally in great shape and alert during the day?

The following screening measures can be used to help determine whether intervention or referral to a sleep laboratory is indicated:

- Sleep diaries: Help patients and physicians objectify a sense of sleepiness
- Actigraphy: Provides a quantitative measure of sleep habits, recording movements and documenting hours of inactivity and sleep over periods of days
- Nocturnal oxymetry: Performed at home to measure nocturnal hypoventilation and help determine if ventilatory failure, sleep apnea or central hypoventilation are responsible for impaired sleep and excessive daytime sleepiness

Evaluation methods available at comprehensive sleep centers include:

- Polysomnagram: Test that monitors electroencephalographic activity to determine sleep stage and duration, and compare it to ventilatory effort and oxygenation. This information can help define causes of hypoxia during sleep. Due to the multiple potential causes of daytime sleepiness in myotonic dystrophy, qualified comprehensive sleep laboratory evaluation is required to determine presence of any parasomnias, sleep apnea, central or neuromuscular hypoventilation or central hypersomnia, each of which has specific significance and treatment. Unfortunately, many sleep laboratories focus only on sleep apnea, being unaware of the complexities of sleep disturbance in myotonic dystrophy. Standard treatment of sleep apnea in non-myotonic dystrophy patients (CPAP) is often contra-indicated in DM patients, so knowledge of the multiple causes of sleep disturbance in myotonic dystrophy is essential.

- Multiple Sleep Latency Test [MSLT]: Measures the time it takes to repeatedly fall asleep. To assure comparable sleep history, this test is best performed after a standard night's sleep monitored with polysomnography. MSLT is often essential for the diagnosis of central hypersomnia in myotonic dystrophy.

- Structural assessment. Magnetic resonance imaging (MRI) can be used to identify the high-T2 signal abnormalities that are common in DM1 and DM2 cerebral white matter. The pathophysiological significance of these abnormalities is controversial, so at present the primary importance is to recognize that they are common in myotonic dystrophy in order to avoid misdiagnosis. Congenital and childhood forms of DM1 are associated with generalized atrophy on MRI studies, and initial studies have shown cerebral volume loss in adults with DM1 and DM2 compared to age-matched controls. In patients with DM1 and DM2, positron emission tomography (PET) studies can identify reduced frontal and temporal lobe blood flow, though the causal relationship of this finding to cognitive or executive dysfunction is yet to be determined.

- Neuropsychological assessment: Evaluation performed to assess cognitive strengths and weaknesses. In particular, testing in DM1 children should be considered routinely when early signs of cognitive or developmental issues are present. Any evaluation should accommodate the physical impairments that may be present (such as hearing loss or speech deficits) and differentiate between physical and mental issues that may be perceived as cognitive dysfunction. Tests include:

  Cognitive skills tests

  - Age appropriate IQ (eg. WPPSI and WISC)
  - Executive function and higher cognition skills
  - Visual-spatial ordering skills
  - Visual perception/construction/memory skills
  - Attention skills
  - Verbal abstract reasoning skills
  - Temporal-sequential ordering skills

Tests for other neuropsychological functions

- Attention-deficit/hyperactivity disorder (ADHD)
- Energy levels
- Social skills and general behavior
- Emotional facility (such as evaluation of anxiety, withdrawal, depression, conduct disorders)

Treatment

Excessive Daytime Sleepiness (EDS)
Wakefulness-promoting agents for narcolepsy, such as modafinil, are sometimes prescribed off-label for attention-deficit hyperactivity disorder (ADHD) and excessive daytime sleepiness. These agents have shown modest benefit as assessed by the Epworth sleepiness scale.

Cognitive Dysfunction
Identification of cognitive dysfunction is crucial to providing appropriate individualized interventions and behavioral therapy. Early intervention for cognitive weaknesses, academic achievement problems, and behavior, attention, or social issues can have significant impact on a child's success in later life. The knowledge of specific deficits may also inform staff as to how medical problems may affect schoolwork, and therefore aid in behavior management.