Pharmacologic Treatment of Chorea in Huntington Disease

Case Presentation: Part I

A 50-year-old male with a history of hypertension is referred to the neurology clinic by his primary care office for management of Huntington disease (HD). The patient has a strong family history of HD with multiple maternal family members affected, including his mother. After his mother was diagnosed about 15 years ago, the patient underwent genetic counseling and elected to have genetic testing. The Huntington gene testing showed that he had a CAG triplet repeat expansion of 48 on one allele with a normal number of CAG triplet repeats on the other. Despite this, he had been largely asymptomatic until about 2 years previously, when coworkers told him that he was “fidgety.” Over time, these movements became more prominent and started interfering with daily life (e.g., causing him to drop items). The movements do not occur while he is sleeping. However, stressful situations can exacerbate them. The symptoms have been so bothersome recently that he has had some falls. He has noticed that working through complex problems now takes him a little longer, but he is still able to do it and has noticed no other cognitive symptoms. He also denies any other problems, including memory loss, agitation, hallucinations, depression, visual changes, anhedonia, headaches, swallowing problems, and weakness.

His past medical history is significant for hypertension.

His medications include lisinopril.

He has no known drug allergies.

He does not smoke, abuse alcohol, or use illicit substances. The patient is not married. He feels he has excellent family support.

He has a strong maternal family history of HD, including his mother, an aunt, an uncle, and his sister. Two of his brothers have not been tested and are asymptomatic. The patient has no children.

In addition to what is noted above, a complete 14-topic review of systems is obtained and is unremarkable.

On physical examination, he is a well-developed and well-nourished male in no acute distress. He is afebrile. His blood pressure is 120/70, pulse is 75, and respiratory rate is 12.
No bruits are heard over his neck. There are no murmurs or abnormal heart sounds.

He is alert and oriented to person, place, and date. Registration and 5-minute recall are normal. He has no problems with serial seven calculations or intersecting pentagons. He follows commands and names and repeats without difficulty. His speech is fluent.

Cranial nerve testing reveals PERRLA; optic discs are sharp, and visual fields are full to confrontation. Extraocular muscles are intact but he has a brief delay in initiating eye movements. Facial sensation and strength are normal. Hearing is intact bilaterally to finger rub. Palate, tongue, and uvula are midline. He can protrude his tongue for 20 seconds. Shoulder shrug strength is normal.

Motor strength is MRC grade 5/5 throughout. His tone is normal without any cogwheel rigidity. There is no bradykinesia. There is no dystonic posturing.

The patient has brief involuntary movements of his face, trunk, and limbs. On occasion, these movements interrupt what he is trying to do. He cannot reliably suppress them. The movements are frequent, occurring every 5–10 seconds. They are also worse earlier in the visit, when he admits he is more nervous.

He has normal pinprick, vibratory, and joint position sense in the extremities. Romberg is negative.

Reflexes are 2/4 throughout. Plantar responses are flexor bilaterally.

Coordination is normal on finger-nose-finger and heel-knee-shin testing bilaterally.

He has a broad-based gait. The involuntary movements continue during gait testing, and he appears to try to incorporate them into his walking. He lurches with some steps. He takes several steps to recover on the pull test but does not fall.

Review of the paperwork sent from his primary care physician’s office shows that he has unremarkable electrolytes and liver function testing. An EKG is normal.

You spend some time discussing the HD diagnosis with the patient. He understands that HD is a progressive hereditary neurodegenerative disorder that can lead to abnormal movements, cognitive problems, and psychiatric problems.

You explain that HD is an incurable disorder but that your clinic can attempt to treat his symptoms. His largest problem at the present time is chorea. You discuss nonpharmacologic strategies to treat chorea, such as relaxation techniques, and the availability of adaptive tools (e.g., protective padding, home equipment) that can make handling the extra movements easier. You also counsel him that the medication tetrabenazine has US Food and Drug Administration (FDA) approval for the treatment of chorea. Furthermore, the recent AAN evidence-based guideline “Pharmacologic Treatment of Chorea in Huntington Disease” suggests that this medication is likely
effective for treating chorea. You educate him that possible adverse effects include depression, thoughts of suicide, and parkinsonian symptoms such as slowing of his movements. After discussion about the potential risks and benefits, the patient agrees to try this medication. You initiate tetrabenazine 12.5 mg daily for 1 week followed by 12.5 mg twice daily. You finish by referring him to physical therapy for gait training.

Case Presentation: Part II

The patient returns to the neurology clinic in 1 month. He feels he is doing well. He thinks the tetrabenazine has helped the involuntary movements though he continues to have them. He is working with physical therapy and was given a cane. He has not subsequently fallen. He denies any new problems, including tremor, depression, thoughts of suicide, stiffness, or slowness.

His medical history is unchanged. His physical examination is largely unchanged though you note that the involuntary movements have decreased. Furthermore, his gait is steadier with his cane and with a decrease in the lurching seen previously.

You counsel him that you could increase the tetrabenazine if he feels the movements are still bothering him. You say that you would likely add a third tetrabenazine dose between the other two (for a total of tetrabenazine 12.5 mg three times a day). However, the patient is content with the current level of chorea control. You schedule a follow-up appointment for him to see you in 3 months and advise him to call you with any new problems in the meantime.

Questions

1. Regarding symptomatic treatment of HD, which of the following statements is correct?
A. Chorea is the most disabling symptom in HD and should be treated first.
B. Psychiatric problems are inevitable in HD and should be addressed preventatively if not present prior to intervention for other symptoms.
C. Cognitive impairment is common in HD, and medications should be started early for this to delay or slow its progression.
D. Given the variability of symptoms in HD even early in the disease course, physicians and patients must decide which if any symptoms require treatment.
E. None of the above

The correct answer is D. Motor symptoms such as chorea, psychiatric problems (including depression, apathy, delusions, and others), and cognitive impairment all occur in HD. However, particularly early in the disease, different patients may experience different symptoms. In some patients, psychiatric problems will be the most prominent early manifestation; in others, it will be chorea. Treatment should focus on the symptoms that are causing the person difficulty in daily life. In addition, even when they are present, not all symptoms require treatment. Patients with HD may not notice the chorea initially, and it may not warrant treatment at an early stage. Symptomatic treatment in HD requires a unique assessment for each patient in order to identify the most bothersome and
disabling symptoms. Physicians and patients must then decide if these symptoms are severe enough to warrant treatment when weighing the possible benefits and risks.

2. When chorea requires treatment, which medication has the most evidence for a meaningful effect?
A. A neuroleptic such as haloperidol
B. Amantadine
C. Tetrabenazine
D. Riluzole
E. Either A or C

The correct answer is C. Tetrabenazine is likely effective in achieving important antichoreic benefits (Level B). It is also the only drug approved by the FDA for treating chorea in HD. While typical and atypical neuroleptic agents are commonly used for the treatment of chorea in HD, particularly if a patient also has behavioral problems, there is no high-quality evidence to support this. The evidence is thus insufficient to recommend for or against the use of neuroleptic agents for chorea (Level U). Whereas amantadine is likely effective in improving chorea to some extent (Level B), the degree of improvement is unknown, and thus it is unclear whether amantadine treatment is clinically meaningful. Riluzole 200 mg/day is likely effective at producing moderate antichoreic benefits (Level B), but the 100-mg/day dose is likely ineffective (Level B). Riluzole is rarely used for chorea in clinical practice. Possible adverse effects and cost may limit the use of some treatments. There are no head-to-head comparisons of drugs used for chorea in HD.

3. When using tetrabenazine to treat chorea in HD, which of the following possible adverse effects should be considered?
A. Depression
B. Suicide
C. Parkinsonism
D. Prolongation of the corrected QT interval
E. Both A and B
F. All of the above

The correct answer is F. Tetrabenazine may cause new or worsened depression and can increase the risk of suicide in patients with HD (who are already at a higher risk of suicide than the general population). It can also cause or worsen parkinsonism. Tetrabenazine may prolong the corrected QT interval, though this was not seen in the 12-week study of tetrabenazine use in HD. In addition, though not mentioned in the options above, US tetrabenazine prescribing information recommends genotyping for CYP2D6, the enzyme responsible for metabolizing tetrabenazine, prior to use. Possible interactions with other medications metabolized by the CYP2D6 system, such as fluoxetine or paroxetine, should be considered during TBZ dosing.

4. What limitations exist when interpreting the evidence for treating chorea in HD?
A. Lack of high-quality studies regarding commonly used neuroleptic agents
B. The tendency for studies to enroll patients who are ambulatory, retain good functional capacity, and are free from disabling depression or cognitive decline
C. Lack of studies regarding the clinically important change on chorea scales
D. Both A and C
E. All of the above

The correct answer is E. HD studies typically enroll patients who are ambulatory, retain good functional capacity, and are free from disabling depression or cognitive decline. Thus, study results may not be generalizable to the entire HD population, particularly to patients with HD at a later point in the disease course. Additionally, the clinically meaningful change for chorea scales is not established. This makes interpreting study results difficult, as it is possible that studies show a statistically significant improvement in chorea that is not clinically important. Finally, neuroleptic agents are the most commonly used treatments in HD in certain parts of the world and are recommended in various consensus papers regarding HD treatment, but lack of high-quality evidence limits the development of evidenced-based guidelines for these drugs.

Diagnosis Coding
The stated diagnosis in both Part I and Part II is HD. Given all of the manifestations in this patient are typical of the disease, it is unnecessary to list them in addition to the diagnosis.

ICD-9-CM code:
333.4 Huntington’s chorea

ICD-10-CM code:
G10 Huntington’s disease
   Huntington’s chorea
   Huntington’s dementia

Evaluation and Management Coding
The patient is referred for continued care, so the visit would be billed as a new patient. The best code would be a new patient 99204, as the history and physical examination are comprehensive and the medical decision making is moderately complex. One could bill for a level 5 new patient if 60 minutes was spent with the patient and 30 minutes or more was expended in counseling and coordination of care. The second visit is more difficult to code, as we do not know how much time was spent with the patient in counseling. This coder would choose a level 3 established patient code, 99213, on the basis of the work done, or if time was spent in counseling and coordination of care, the level would be level 3 for 15 minutes total, level 4 for 25 minutes, and level 5 for 40 minutes. Keep in mind that 50% or more of the time must be spent in counseling or coordinating care.

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