Case Report

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Huntington's Disease - Challenges in Early Diagnosis and Screening

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ABSTRACT

Background: *Huntington's disease (HD) is a rare neurodegenerative disorder with a global prevalence of 2.7 per 100,000, though this rate can vary significantly across different regions [1]. These variations are often due to differences in diagnostic criteria and methods of case identification. Genetic counseling and predictive testing are available for asymptomatic adults at risk of HD, allowing them to make informed decisions regarding caregiving, financial planning, and reproduction. Early identification of genetic risk also opens the door to participation in clinical trials. Ideally, discussions around genetic risk and prenatal testing should occur before pregnancy to optimize planning and decision-making.*

In developing countries like the Republic of Moldova, genetic testing for HD is accessible; however, the lack of a population-wide screening program and clinical guidelines hinders the early identification and diagnosis of at-risk families. Without such a systematic approach, many individuals carrying the genetic mutation may remain undiagnosed until symptoms appear, limiting their options for early intervention and participation in preventive measures.

Purpose: *This study aims to highlight the need for a population-wide screening program and comprehensive management guidelines for Huntington's disease to improve early diagnosis and patient care in developing countries.*

Method: *We present a case report of a 40-year-old female who initially consulted a neurologist due to fatigue, uncontrolled hand movements, difficulty walking, and speech impairment. Her paternal grandmother and uncle both passed away from Huntington's disease, though the diagnosis was based on clinical symptoms rather than confirmed through genetic testing. After genetic counseling and HTT gene testing, Huntington's disease was confirmed.*

Results: *Patient's diagnosis was confirmed only after the symptoms onset at the age of 40 due to the lack of a screening database of her HD family history.*

Conclusion: *The delay in diagnosing Huntington's disease in this patient highlights the critical need for a comprehensive screening program and a centralized database for family histories of genetic conditions. Early identification and intervention could be significantly improved if systematic approaches and resources were in place to facilitate timely diagnosis based on family history.*

Keywords
Huntington Disease, Population-wide screening program, Comprehensive management guidelines, HTT gene, Genetic counseling.

Introduction
Huntington disease (HD), a neurodegenerative autosomal dominant disorder, is characterized by involuntary choreatic movements with cognitive and behavioral disturbances. It occurs as a result of cytosine, adenine, and guanine (CAG) trinucleotide repeats on the short arm of chromosome 4p16.3 in the Huntingtin (HTT) gene. This mutation leads to an abnormally long expansion of the polyglutamine in the HTT protein, which leads to neurodegeneration. The expansion also causes the HTT protein to be more prone to aggregation and accumulation that mitigates protein folding. HD commonly affects patients between the ages of 30 to 50 years. However, the longer the CAG repeats, the earlier the onset of symptoms.

Huntington's disease (HD) is a dominantly transmitted neurodegenerative disorder with wide variation in onset age but with an average age at onset of 40 years. Children of HD gene carriers have a 50% chance of inheriting the disease. The characteristic symptoms of HD are involuntary choreiform movements, cognitive impairment, mood disorders, and behavioral changes which are chronic and progressive over the course of the illness [1].

HD is a "trinucleotide repeat" disorder, which is caused by an increase in the number of CAG repeats in the HD gene. Repeats of 40 or larger are associated with disease expression, whereas repeats of 26 and smaller are normal. Intermediate numbers of repeats, between 27 and 35, are not associated with disease expression but may expand in paternal transmission, resulting in the disease in descendents. Repeats of 36-39 are associated with reduced penetrance whereby some develop HD and others do not.

The identification of the genetic defect in HD permits direct genetic testing for the presence of the gene alteration responsible for the disease. Tests may be performed in three circumstances: (1) confirmation of diagnosis, (2) predictive testing of persons at genetic risk for inheriting HD, and (3) prenatal testing [2].

The goals of genetic counseling are: (1) to inform the individual of his or her options about testing or other alternatives, depending upon personal circumstances, (2) to ensure that the individual is aware of the risks and possible adverse consequences of his or her specific testing circumstances, and (3) to inform the individual of the limitations and level of accuracy of the procedure. Counseling does not try to exclude or discourage persons but tries to ensure that the individual is making an informed choice [3].

Case Presentation
A 40-year-old female consulted a neurologist with symptoms of fatigue, uncontrolled hand movements, difficulty walking, and speech impairment. She has two sons, aged 5 years and 1 year and 5 months. Her paternal grandmother and uncle exhibited similar neurological symptoms. The grandmother passed away at 62 years old, and the uncle at 52, both due to pneumonia-related complications. Although neither had undergone genetic testing for Huntington's disease (HD), they were clinically diagnosed based on their symptoms and received symptomatic treatment, though the specific medications used remain unknown. The patient's father went missing at the age of 32, and his clinical and genetic status is unknown, as he had not yet exhibited any symptoms of HD.

After reviewing her family history and clinical signs, the neurologist referred her for genetic counseling. Following the counseling session, she decided to proceed with genetic testing for the HTT gene. Both she and her two children underwent genetic testing to determine their risk for HD. Genetic testing for the number of CAG repeats in the HTT gene confirmed that the patient is positive for Huntington's disease, with 46 CAG repeats on the second allele.

Table 1: Huntington's Disease. Determination of the number of CAG repeats in the HTT gene.

The investigated parameter	The allele number	Number of CAG repeats on each allele	Reference value
***HTT* Gene, exon 1**	Allele 1	17	**<27 CAG repeats**
	Allele 2	46	

Classification of CAG repeats in relation to Huntington's Disease:
1. <27 CAG repeats - normal genotype with no risk for HD.
2. 27-35 CAG repeats - normal genotype, but with a risk of developing HD in the next generation.
3. 36-39 CAG repeats - alleles associated with HD with reduced penetrance.
4. >39 CAG repeats - alleles associated with HD.

Fortunately, genetic testing of the number of CAG repeats in the HTT gene for both of her children, who each had only 17 CAG repeats, revealed a normal genotype with no risk of developing Huntington's Disease (HD).

Table 2: Huntington's Disease. Determination of the number of CAG repeats in the HTT gene (5 y.o. boy).

The investigated parameter	The allele number	Number of CAG repeats on each allele	Reference value
***HTT* Gene, exon 1**	Allele 1	17	**<27 CAG repeats**
	Allele 2	17	

Table 3: Huntington's Disease. Determination of the number of CAG repeats in the HTT gene (1,5 y.o. boy).

The investigated parameter	The allele number	Number of CAG repeats on each allele	Reference value
***HTT* Gene, exon 1**	Allele 1	17	**<27 CAG repeats**
	Allele 2	17	

In summary, if the patient's uncle or grandmother had undergone genetic testing before her symptoms appeared, and if her family

history had been properly considered, she could have been tested for Huntington's Disease (HD) earlier, allowing for proactive management. While there is no cure for HD, she can still benefit from counseling and symptomatic treatment to enhance her quality of life. Despite the challenges, she is relieved and happy that her children did not inherit the gene, ensuring they are not at risk of developing the disease.

Discussions

A precisely taken family history remains the basis of the diagnosis of Huntington's disease, which can be nowadays confirmed by DNA analysis. The presence of motor signs was until recently the gold standard for diagnosis, but we have learned from the systematic follow-up of pre-manifest mutation carriers that cognitive as well as psychiatric symptoms or signs can also be the first manifestations of the disease. The motor signs, mainly unwanted movements, remain, however, the most characteristic and specific for a clinical diagnosis [4].

As the disease progresses, patients become entirely dependent on their caregivers, requiring constant support to manage both motor and cognitive symptoms. Although genetic testing is available in Moldova, the absence of a systematic screening program for at-risk individuals presents a significant barrier to early diagnosis and intervention.

Early identification of patients at risk for HD is critical. It provides the opportunity to participate in clinical trials, explore experimental treatments, and receive essential counseling. Moreover, early diagnosis allows patients and their families to prepare for the future, offering a chance to better cope with the inevitable progression of the disease.

In the U.S., the clinical protocol for managing Huntington's disease (HD) includes a comprehensive approach involving several key steps. These include a telephone intake, two genetic counseling visits, a thorough neurological examination, and in-person delivery of genetic test results. This ensures that patients and their families are fully informed and supported throughout the diagnostic process. The protocol reflects a high standard of care and patient-centered approach, emphasizing genetic counseling, risk assessment, and emotional preparation for the results [5].

In contrast, in the Republic of Moldova, clinical protocols for HD are more limited. While genetic testing is accessible, there is no established nationwide screening program or comprehensive clinical guidelines like in the U.S. Moldova's protocols largely focus on palliative care for those already diagnosed, addressing symptom management and improving quality of life, but lack structured steps for early diagnosis, genetic counseling, and ongoing support [6].

This comparison highlights the gap in care, where Moldovan protocols prioritize end-stage care rather than early detection and intervention, limiting the ability for preventive measures or early treatment planning. To address these issues, there is an urgent need for a comprehensive approach that includes screening programs for at-risk individuals and organizational programs potentially in collaboration with international institutions [7]. That offer counseling, education, and a framework for managing the disease. Such initiatives would empower patients and caregivers to better understand Huntington's disease, improve quality of life, and potentially slow disease progression through early interventions.

The clinical assessment of the symptoms and signs of HD is important for patient, family and care-givers. To follow the patient systematically, mainly for research purposes, several scales have been developed. The best known are the Shoulson and Fahn capability scale and the Unified Huntington Disease Rating Scale (UHDRS) [8]. The UHDRS consists of a motor, behaviour, cognitive and functional part, preceded by a history and medication scheme. For the behaviour signs a new scale was developed by Craufurd: the Problem Behaviour Scale (PBS). Other scales, for instance for the quality of life, are also in use. In the European Network for Huntington disease a whole set of assessment scales has been devised, which are now in use for over 6,000 patients in Europe.

Goals of the genetic counseling process may include providing information about test options, assessing psychological well-being, helping patients and families communicate about genetic risk, facilitating adaptation to grief and loss, interpreting results, assisting with decision-making and referrals, or some combination of these things [9].

Because of the genetic nature of Huntington disease, the physician confirms a diagnosis, not only for an individual, but for a family. Furthermore, all members of the family, regardless of the risk, are affected psychologically by the knowledge that a family member has HD [10].

Differential Diagnosis

Huntington disease falls into a differential diagnosis for dementia, chorea, and psychiatric disturbances.

Non inherited Conditions

Tardive dyskinesia, thyrotoxicosis, cerebral lupus, Levodopa-induced dyskinesia, Group A beta-hemolytic streptococcus.

Inherited Conditions

1) Chorea-acanthocytosis: Autosomal recessive. Due to mutations in the VPS13A gene, that codes for chorein, a protein involved in intracellular protein sorting.
   A. Clinical features include facio-bucco-linguo-masticatory chorea, dystonia, and dyskinesia that are aggravated by feeding, accompanied by tongue protrusion and self-mutilating tongue. Patients might also present with violent neck spasms with sudden flexion/extension.
   B. The progressive movement disorder, along with cognitive and behavioral changes are similar to HD. However, unlike HD, the presence of myopathy, acanthocytosis, as well as the mean age of onset of 30 years, are differentiating features.

2) McLeod syndrome: X-linked recessive. It is caused by mutations in the XK gene. It affects the basal ganglia, muscles, myocardium, and peripheral nerves. Chorea may involve the facio-buccal region, but tongue or lip biting, dysphagia, or parkinsonism is rarely seen. Cognitive and psychiatric disturbances overlap with HD while the presence of acanthocytosis, compensated hemolysis, as well as McLeod blood group phenotype (absence of expression of Kell antigen on erythrocytes) help to distinguish it from HD.
3) Pantothenate kinase-associated neurodegeneration: Autosomal recessive. It is caused by mutations of the PANK2 gene, which codes for pantothenate kinase. This enzyme plays a role in the synthesis of coenzyme A from vitamin B5 and is associated with lipid metabolism. The age of onset is before 6 years and presents with generalized dystonia with bucco-facial and lingual involvement. Parkinsonism, choreoathetosis, and pyramidal signs might also be observed. A later onset of symptoms with lesser severe presentation might also be seen with rigidity, focal arm dystonia, or cognitive and behavioral problems.
4) Wilson disease: Presents with orofacial dystonia associated with parkinsonism in the setting of generalized dystonia that could pose a diagnostic challenge.
5) Huntington disease-like 1: Autosomal dominant. Range of clinical features that overlap with Huntington disease. Earlier onset of action, as well as slower progression, can be used as differentiating features.
6) Huntington disease-like 2: Autosomal dominant. These are clinically indistinguishable from HD.
   Prevalence is highest among and exclusive to patients of African descent
7) Spinocerebellar ataxia type 17: Autosomal dominant.
   Overlapping features with HD include chorea, dementia, and psychiatric disturbances. Cerebellar ataxia is a prominent movement disorder.
8) Dentatorubral-pallidoluysian atrophy: Autosomal dominant. Also presents with progressive movement disorders and dementia, psychiatric disturbances are common. Ataxia and myoclonus are more prominent movement disorders [11].

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