EXOSOMES AS NOVEL BIOMARKERS FOR EARLY DIAGNOSIS OF HUNTINGTON'S DISEASE

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Received: Jun 25, 2026 Accepted: Jul 22, 2026 Published: Jul 24, 2026

ABSTRACT:

Huntington's disease (HD) is a hereditary, progressive neurodegenerative disorder caused by CAG repeat expansion in the huntingtin (HTT) gene, leading to mutant huntingtin (mHTT) aggregation, neuronal dysfunction, and widespread neurodegeneration. Despite well-established genetic etiology, early diagnosis and effective disease-modifying therapies remain significant challenges. This review critically examines current advances in biomarkers and highlights the emerging role of exosomes in the diagnosis and management of HD. Conventional biomarkers, including neuropsychological assessments and structural neuroimaging, provide important clinical insights but are limited in sensitivity, particularly during the premanifest stage. Functional imaging modalities such as FDG-PET offer improved detection of early metabolic alterations; however, their clinical applicability is constrained by cost and accessibility. Among wet biomarkers, cerebrospinal fluid (CSF) remains the most reliable source, with mHTT serving as a key biomarker for disease progression and therapeutic monitoring. Nevertheless, the invasive nature of CSF collection restricts its routine use, prompting the exploration of peripheral biofluids. Recent studies have identified blood-based biomarkers, particularly neurofilament light chain (NFL), as indicators of neuronal damage, though their lack of disease specificity limits diagnostic precision. In this context, exosomes have emerged as promising candidates due to their ability to cross the blood–brain barrier and carry disease-specific molecular cargo, including proteins and nucleic acids reflective of neuronal status. This review discusses the dual role of exosomes in HD pathogenesis and therapy, including their involvement in mHTT propagation and their potential as vehicles for targeted delivery of therapeutic molecules such as miRNAs. Overall, exosome-based strategies represent a transformative approach for non-invasive diagnosis, disease monitoring, and targeted therapy in HD. Future research should focus on standardization, validation, and clinical translation to fully realize their potential in precision medicine.

INTRODUCTION:

Huntington's disease (HD) is a progressive, hereditary neurodegenerative disorder characterized by motor dysfunction, cognitive decline, and psychiatric disturbances. It is caused by an abnormal expansion of the cytosine–adenine–guanine (CAG) trinucleotide repeat in the *Huntingtin (HTT)* gene located on chromosome 4. This mutation leads to an expanded polyglutamine (polyQ) sequence in the huntingtin protein, resulting in protein misfolding, aggregation, and neuronal toxicity. HD follows an autosomal dominant inheritance pattern, meaning that an affected individual has a 50% chance of passing the mutated gene to their offspring. The disease typically manifests in mid-adulthood, although the age of onset may vary widely [1]. The pathological changes in HD primarily affect the basal ganglia, particularly the

caudate nucleus and putamen, where degeneration of GABAergic medium spiny neurons occurs. As the disease progresses, neurodegeneration also extends to the cerebral cortex and other brain regions [2]. These neuronal changes lead to the classical triad of symptoms in HD: motor disturbances, cognitive impairment, and psychiatric abnormalities. Among these, psychiatric and behavioral symptoms often appear before motor symptoms and can significantly impact the patient's quality of life and family relationships. Psychiatric manifestations in HD are common and may occur in approximately 33–76% of patients. Depression is the most frequently reported symptom and is often accompanied by anxiety, guilt, low self-esteem, and apathy. Irritability, aggression, obsessive–compulsive behaviors, and emotional instability may also occur at various stages of the disease. In advanced stages, some patients develop psychosis characterized by paranoid thinking and auditory hallucinations. Suicide risk is significantly elevated in individuals with HD, particularly around the time of genetic testing or when patients begin to lose independence. These psychiatric symptoms may appear several years before the onset of motor abnormalities, suggesting that early pathological changes occur in brain regions responsible for emotional and cognitive regulation. [3,4]. Diagnosis of Huntington's disease has evolved significantly with advances in genetic testing. The identification of the HTT gene mutation has enabled predictive and prenatal genetic testing, allowing individuals with a family history of HD to determine their risk before the onset of clinical symptoms. Neuroimaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) can reveal structural and metabolic changes in the brain, particularly striatal atrophy and reduced glucose metabolism. However, ethical and psychological concerns are important considerations in predictive genetic testing, as individuals must cope with the possibility of developing an incurable disorder. [5,6]

Currently, there is no cure for Huntington's disease, and treatment focuses primarily on managing symptoms and improving quality of life. Pharmacological therapies are used to control motor symptoms such as chorea, commonly using dopamine-depleting agents like tetrabenazine or dopamine receptor-blocking drugs. Psychiatric symptoms such as depression, aggression, and anxiety are treated with antidepressants and atypical antipsychotic medications including olanzapine and clozapine. In addition to medication, non-pharmacological interventions such as physiotherapy, occupational therapy, speech therapy, psychological support, and nutritional management play an essential role in patient care. A multidisciplinary approach involving healthcare professionals, caregivers, and support organizations is crucial in managing the complex symptoms of HD and providing long-term support for patients and their families [7,8].

EXOSOMES

Extracellular vesicles (EVs), initially discovered to aid cells in waste disposal, are classified as exosomes. By carrying nucleic acids, proteins, and metabolites to other cells, they play a critical role in intercellular communication. Exosomes are little vesicles that develop from endosomes, which are cell compartments. Among the numerous bioactive ingredients found in them are lipids, proteins, growth hormones, nucleic acids, and other metabolites. Exosomes are little vesicles with a size of 30 to 150 nm that are produced by a variety of cells and may be seen in a number of bodily fluids, including tears, blood, and more. In 1983, they ere first found in sheep reticulocytes and initially associated to the absence of transferrin receptors during cell differentiation.[9]

EXOSOMES BIOGENESIS:

Exosomes, ectosomes, and apoptotic blebs are the three primary vesicle types. The sizes of ectosomes from 50 to 1000 nm, and apoptotic blebs, which released by dying cells, from 50 to 5000 nm. Exosomes are the most researched of these. In bodily fluids, they are widespread and are tiny, spherical vesicles secretes by almost every cell type. When endosomal membranes fold inward, they create multivesicular bodies (MVBs) with smaller vesicles inside. Exosomes are produced as a result of this process as shown in fig:1. Depending on whether they fuse with lysosomes for destruction or with the plasma membrane to produce exosomes into environment, MVBs may either merge with lysosomes or the plasma membrane. [10]

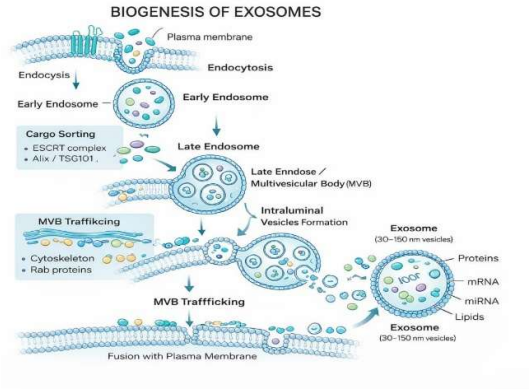

Fig: 1 Biogenesis of Exosomes

CONTENT OF EXOSOMES:

The content of exosomes vary widely depending on their environment and cell of origin. Waste management, intercellular communication, inflammation and immune system regulation, and assistance with regeneration and repair are among the vital functions the carry out. The lipid composition of exosomes is essential to their stability because it shields their contents from hazardous enzymes and chemicals. Exosomes are minute particles released by cells that include a variety of biological components. Depending on the kind of cell from which they originate and the environment in which they are activated, their contents might differ significantly. Lipids, proteins, nucleic acids such as (mRNAs and miRNAs), and tiny molecules make up the majority of exosomes. There are more than 2,400 distinct types of RNA and over 4,000 different proteins that researchers have found in exosomes. The function of EVs varies across biological processes. Exosomes are essential for communication between cells under both healthy and pathological circumstances, microvesicles aid in cell signaling, and apoptotic bodies transfer materials from dying cells to healthier ones.[11]

UPTAKE OF EXOSOMES:

Exosomes are produced into bodily fluids and aid in cell communication. Receiving cells can absorb them in one of three primary ways. Exosomes can initially deliver their contents by directly fusing with the cell membrane. They may also communicate with the target cell via receptor interactions. Finally, exosomes may enter the target cell through various forms of endocytosis, such as micropinocytosis, phagocytosis, raft-regulated endocytosis, and clathrin- and caveolin-regulated endocytosis.[12]

COMPONENTS OF EXOSOMES:

Exosomes are made up of a variety of molecules, such as nucleic acids, proteins, and lipids as shown in fig:3. Exosomes mirror the cell that created them in terms of their composition, hich includes both membrane bound and soluble components.[13]

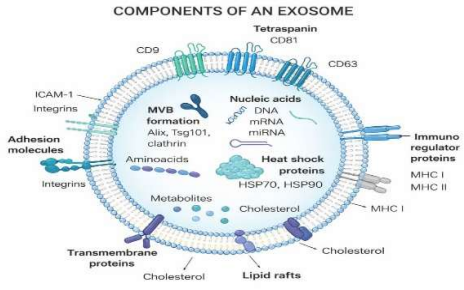

Fig: 2 Components of an Exosome

HUNTINGTON'S DISEASES

INTRODUCTION

The most prevalent hereditary neurodegenerative disease, Huntington's disease (HD), is typified by excessive, uncontrollable motor movements as well as emotional and cognitive impairments [14] as shown in the fig:3. It is brought on by repeats of the cytosine, adenine, and guanine (CAG) trinucleotide in the Huntingtin (HTT) gene on the short arm of chromosome 4. Neurodegeneration results from this mutation, which causes an unusually lengthy polyglutamine expansion in the N-terminal region of the HTT protein. Additionally, the enlargement increases the HTT protein's susceptibility to accumulation and aggregation, which reduces protein folding [15]. Cognitive, motor, and mental disturbances are its defining characteristics. Multiple processes, such as disruption of transcription, proteostasis, and mitochondrial function, as well as direct toxicity of the mutant protein, cause neuronal malfunction and death at the cellular level when huntingtin is mutant [16]. HD affects the extrapyramidal motor system and is typified by chorea, progressive dementia, and other mental symptoms. GABAergic medium spiny striatal neurons are the most damaged in terms of brain disease, which leads to atrophy of the putamen, globus pallidus, and caudate nucleus. The cerebral cortex also exhibits noticeable atrophy. The thalamus, superior olive, lateral tuberal nucleus of the hypothalamus, zona reticulata of the substantia nigra, and deep cerebellar nuclei may also lose neurons [17]. Mutant huntingtin causes neuronal malfunction and death at the cellular level via a variety of pathways, such as direct toxicity of the mutant protein, disruption of transcription, proteostasis, and mitochondrial function [18] . HD is a dominantly transmitted neurodegenerative disease that affects the cerebral cortex and basal ganglia. It usually manifests around midlife, but it can also strike at any age, from as young as two or three to as old as eighty or older. The usual lifespan from onset to death is 17–20 years, while there is some evidence that slower advancement is linked to later onset. There is a 50% likelihood that children of HD gene carriers will inherit the gene [19]. Although HD cannot be cured, its symptoms can be managed with medication. HD is diagnosed using the most recent methods and technologies [20], Because of this gene mutation, HD is now one of the uncommon neurodegenerative diseases for which people with a known family history can undergo predictive genetic testing. [21] Since HD is caused by a single mutation, illness models have been created by introducing the defective gene into non-human primates, mice, fish, worms, and fish. Huntington's single mutation is the catalyst that gives the protein additional harmful properties that are detrimental to brain cells. Additionally, it impairs the normal huntingtin protein's capacity to carry out molecular actions essential to the survival and proper operation of the neurons that mostly degenerate in the disorder.[22]

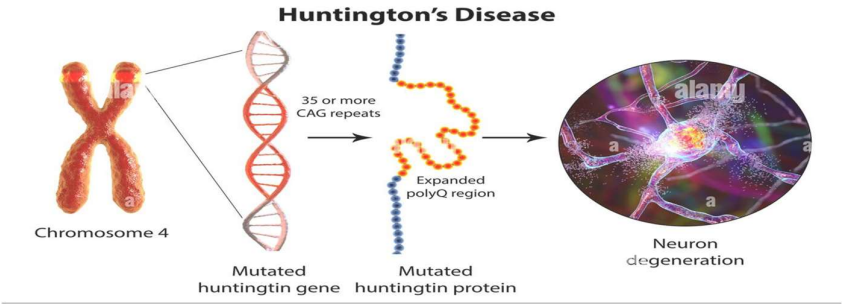

Fig: 3 Huntington's Disease

HUNTINGTON'S PROTEIN

The debilitating neurodegenerative disease Huntington's disease (HD) is caused by an aberrant growth of a glutamine stretch (polyQ) in the N-terminal sequence of huntingtin (HTT), which has made it a well-known protein as shown in the fig:4**.** At the tissue and subcellular levels, HTT is widely distributed[23]. Human development and healthy brain function depend on the huntingtin protein. [24] The huntingtin protein has a complicated and dynamic distribution inside cells and is widely expressed during

development [25]. HTT protein complexes play a role in preserving synaptic transmission efficiency. PolyQ-HTT, a pathogenic type of HTT, likely affects the kinetics of molecular processes in the synapsis by disrupting protein–protein interactions [26]. A stretch of the letters C-A-G in HTT repeating itself too frequently—CAGCAGCAGCAGCAG—is what causes HD. We refer to this as the "CAG repeat expansion." The average person has 20 CAG repeats, but HD patients have 40 or more. Any individual with this CAG repeat expansion in the HD gene will eventually have the condition, and their offspring have a 50% chance of getting it as well [27]. It is anticipated to be a pleiotropic protein that mediates a wide range of physiological activities by interacting with several effector proteins [28]. It has been suggested that Htt is an extended super-helical solenoid with a diameter of about 200 ˚[29].

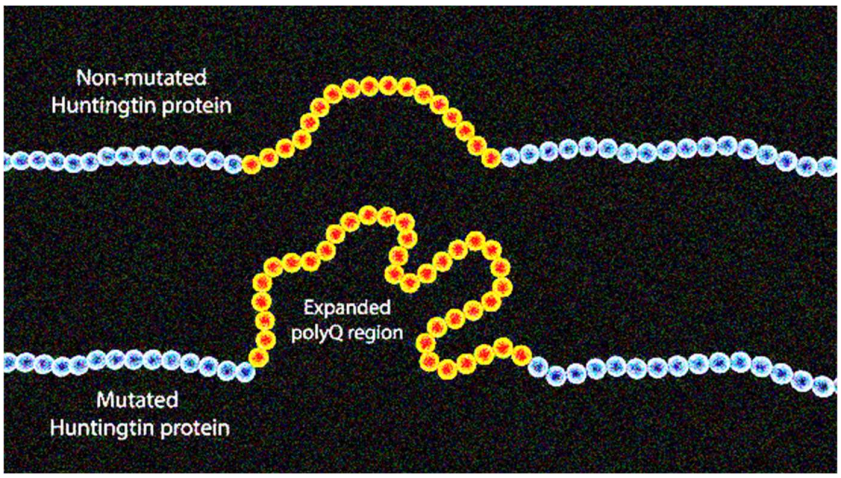

Fig: 4 Huntington's Protein

HUNTINGTON'S PROTEIN ETIOLOGY

The prevalence of Huntington disease, a rare neurological condition, is 2.7 per 100,000 people globally. The population has a high prevalence of 10.6 to 13.7 per 100,000. For Asian and African countries, the prevalence is far lower [30]. A single gene that is passed down from a parent is different in HD. A person only needs one copy of the nontypical gene to develop the condition since it follows an autosomal dominant inheritance (ADI) pattern as shown in table:1. Every gene, with the exception of those on the sex chromosomes, is inherited in two copies, one from each parent [31].

Repeat count	Classification	Disease status	Risk to offspring
< /=26	Normal	Will not be affected	None
27-35	Intermediate	Will not be affected	Elevated, but <50%
36-39	Reduced penetrance	May or may not be affected	50%
40+	Full penetrance	Will be affected	50%

Table no: 1 Huntington's Protien Etiology

The disruption of cell metabolism is another important subject in the etiology of HD studies. Biochemical analyses of post-mortem HD brain and HD patient lymphoblast cell lines have revealed disturbed metabolic pathways. The fact that impaired energetics were detected in HD adult skeletal muscles as well

as neural tissues suggests that huntingtin plays a crucial function in mitochondrial energy metabolism. Clinical research has connected this metabolic disruption to HD patients' symptoms of decreased body mass index (BMI) and weight. More significantly, preHD individuals had low BMI, which suggests an energy imbalance that could be the main cause of the illness [32].

HUNTINGTON'S EPIDERMIOLOGY

The prevalence of Huntington disease, a rare neurological condition, is 2.7 per 100,000 people globally. The frequency among populations of Caucasian descent is considerable, ranging from 10.6 to 13.7 per 100,000. For Asian and African countries, the prevalence is far lower. Geographically, the incidence ranges by more than ten times. Ethnic variations in the length of the CAG repeat are mostly responsible for these discrepancies. It has been observed that individuals of Caucasian heritage have an average CAG repeat length of 18.4 to 18.7, while those of East Asian descent have an average of 17.5 to 17.7. Longer lifespans and more precise genetic testing over the past few decades have also contributed to a rise in overall prevalence [33]. In 1872, George Huntington, a doctor on Long Island, New York, published "On chorea," which led to the first widespread recognition of Huntington's disease (HD) as a unique and genetic type of movement disorder. With chorea as the initial symptom, the disease often manifests in midlife and includes a range of choreiform movements, stiffness, cognitive deficits, and behavioral abnormalities. All human populations carry the HD mutation, however the prevalence of HD varies greatly among populations with different ancestries, with populations of European origin having the highest prevalence [34]. In HD, heart disease is typically the leading cause of death. Pneumonia is the second most frequent cause. Reed and Chandler discovered that 6.4% of female patients and 7.8% of male patients killed themselves among nonhospitalized patients. According to Hayden et al., 3.35% of all affected people's deaths in South Africa were due to suicide.[35].

BEHAVIORAL AND PSYCHIATRIC SYMPTOMS:

Psychiatric symptoms typically manifest before motor symptoms in the early stages of the illness. The percentage of individuals with mental symptoms varies from 33% to 76%, depending on the study's methodology. Because they interfere with daily life, these symptoms and signs usually have a highly negative impact on functioning and the family. The most prevalent symptom is depression. The diagnosis is difficult because HD also causes lethargy, apathy, and weight loss. Low self-esteem, anxiety, and guilt are prevalent. Apathy is correlated with the disease stage, although anxiety and depression are not. Suicide is more common in early symptomatic people and premanifest gene carriers. Suicide risk is highest during the period surrounding the gene test and when independence starts to wane. Additionally, anxiety is common (34–61%), sometimes in connection with ambiguity over the onset and/or progression of the illness. In addition to upsetting the patient's life, obsessions and compulsions can cause agitation and hostility. In retrospect, irritability is frequently the first symptom, but it actually happens at every stage of the illness. Irritability manifests itself in a wide range of ways, from physical aggressiveness to major arguments. The apathy syndrome is said to include a decline in interest and an increase in passive behaviour. Differentiating between depression and apathy can be challenging. Psychosis may manifest, primarily in the later phases of the illness. This is typically accompanied with cognitive deterioration. The entire clinical picture is similar to paranoid and auditory hallucinations in schizophrenia. Early on, hypersexuality can lead to serious issues in a partnership. Hypo-sexuality is the norm in the latter stages [36]. Three symptoms—motor disturbance, cognitive impairment, and psychiatric features—are indicative of Huntington's disease. Research and therapeutic focus have been on the motor and cognitive elements of Huntington's disease, despite the fact that it is widely known that psychiatric symptoms are prevalent. It is necessary to reevaluate the disease's psychological symptoms. First, stress, disability, and placement choices are the factors most closely linked to psychiatric disorders. Second, there is proof that brain alterations occur before the conventional clinical diagnosis, and psychological symptoms may appear ten years before motor symptoms. Lastly, there are intentions to treat "preclinical" people soon, and clinical studies are being conducted to delay the progression of Huntington's disease in clinically affected patients. To differentiate characteristics that are pathognomonic from behaviours that are sensitive but not illness-specific, a thorough examination of the neuropsychiatric symptoms linked to Huntington's

disease is crucial. Over the past few decades, models highlighting the significance of the basal ganglia in neuropsychiatric diseases have been published. According to a recent review, Huntington's disease may initially impair cognitive and mental behaviours rather than motor ones since the associative areas of the striatum experience the earliest pathological alterations. According to evaluations of psychiatric symptoms associated with Huntington's disease, suicide rates are more than four times higher than those of the general population, and depression, apathy, aggressiveness, and disinhibition are widespread.[37]

DIAGNOSIS AND TREATMENT:

DIAGNOSIS:

The hunt for a preclinical diagnostic method has consistently taken on a crucial role in both pathogenetic research and genetic counselling. Those who are at risk are uncertain about whether or not they will pass the condition on to their offspring because diagnostic procedures have generally been unable to identify the disease until after the prime childbearing years. Finding a pathogenetic mechanism for the illness is further hindered in the absence of a preclinical diagnosis. While cognitive impairment and emotional disruption may be present before overt movement disorder manifests, these indicators have not proven very helpful in the preclinical diagnosis of the illness. For instance, subtle preclinical neuropsychological abnormalities have shown cognitive alterations before overt disruption of motor function. but the predictive utility of these procedures has yet to be supported. Emotional and personality alterations have also been noted prior to the other symptoms. However, the frequency of these diseases in nongene-carrying children of affected individuals has cast doubt on the specificity of these findings. Although abnormalities have been found using electroencephalography, neuroimaging studies of cortical function have so far shown minimal diagnostic use. Even in patients with more advanced disease, early positron emission tomography investigations did not show signs of abnormal cortical glucose metabolism. However, a more recent study has shown cortical impairments, with the frontal lobes being particularly affected. The prospective utility of this approach has not yet been thoroughly investigated, despite the fact that the preclinical diagnostic relevance of PET anomalies in the cortex is currently unknown. Although striatal atrophy in patients with clinical evidence of Huntington's disease has been successfully documented by neuroimaging studies of subcortical structures, such as computed axial tomography (CT) and magnetic resonance imaging (MRI), striatal damage has not been identified before the overt manifestation of cognitive and motor deficits. Examining subcortical structures in preclinical diagnosis has not proven very successful, with the exception of positron emission tomography. PET can identify hypometabolism of glucose in the striatum prior to any clinical indications of the disease, cognitive impairment, or structural damage on computed axial tomography. Although it hasn't been used to examine Huntington's disease yet, magnetic resonance high-speed echo planar imaging, which has some advantages over PET in terms of spatial and temporal resolution, is undoubtedly very promising for future preclinical testing. The preclinical diagnostic options for Huntington's disease have changed dramatically as a result of two outstanding discoveries made in the last ten years has been available in clinical practice for approximately five years using the marker polymorphism. The method was restrictive and cumbersome in that it could only be used for patients with living relatives who were willing to undergo extensive screening procedures and who were heterozygous for the necessary polymorphism. With the isolation of IT- 15, it will now be possible to provide preclinical, including prenatal, screening for the Huntington's disease gene without extensive genetic testing of suitable family members. In the five years since the original genetic testing procedure was introduced to clinical practice, clinicians and researchers have begun to approach the ethical, social and personal consequences of the disease. Genetic counselling programs are being developed and evaluated, with particular relevance to prenatal prediction. The possibility of a preclinical test has caused a great deal of excitement among practicing clinicians.[38]

Those who are at danger or who suffer from the condition might not necessarily share this enthusiasm. Just 13% of those who are at risk have taken part in predictive testing programs since testing became accessible. The president of the Huntington's Society of America, who was tested for the Huntington's marker herself, may have said it best.The prospect of a positive test is terrifying when the time comes to find out. Prenatal testing presents a unique set of difficult moral dilemmas.

The availability of a prenatal test would still provide a significant personal barrier to the Huntington's patient making a decision about having children, even if we could put aside the bipolarity of the freedom to choose discussion. Numerous publications that worth consultation regarding ethics and testing provide a thorough analysis of these topics. genetic counselling and suggestions for carrying out testing procedures.Patient screening has been advised with caution, especially in view of a potential but inconsistently documented increase in the risk of suicide following testing.

TREATMENT:

Although there is **no cure or disease-modifying therapy** for Huntington's disease (HD), treatment focuses on **symptom management** and improving the patient's quality of life. Therapy is individualized based on symptom severity and functional impairment, combining **pharmacological treatment** with **non-pharmacological support**.

- **Chorea (hyperkinetic movements):** Primarily treated with **tetrabenazine**, a dopamine-depleting agent, and **typical or atypical antipsychotics** (e.g., **olanzapine**, **clozapine**). Olanzapine is often preferred because clozapine requires regular blood monitoring. Common adverse effects include **sedation, weight gain, and depression**.
- **Psychiatric symptoms:** Depression, aggression, and psychosis are managed with **antidepressants** and **atypical antipsychotics** such as olanzapine. Other agents like **risperidone** and **ziprasidone** have limited supporting evidence.
- **Hypokinesia: Dopaminergic drugs** have generally shown poor efficacy and are **not routinely recommended**.
- **Other therapies:** Numerous agents, including **amantadine, baclofen, cannabidiol, clonazepam, creatine, fluoxetine, minocycline, riluzole, and omega-3 fatty acids (PUFAs)**, have demonstrated **limited or no consistent clinical benefit**.
- **Surgical approaches: Deep brain stimulation (DBS)** has been explored in a few cases for severe chorea but remains **experimental**.
- **Neuroprotection:** Currently, **no approved therapy has been proven to slow or halt disease progression**. Disease-modifying drugs and **cell-based therapies** are still under investigation.
- **Cognitive symptoms:** Trials of **donepezil** and **rivastigmine** have **not shown significant clinical benefit** in patients with HD.

Overall, current HD management is **symptomatic and supportive**, with treatment tailored to each patient's motor, psychiatric, and cognitive manifestations. [39]

PSYCHIATRIC SIGNS:

Most medications are administered for depression and violent conduct since these symptoms are the most detrimental to family life. Open research and professional judgement serve as the foundation for all recommendations. There are numerous more care options available in addition to medication. Finding the appropriate therapy for the right individual at the right time is crucial. Physiotherapy, occupational therapy, speech therapy, dietetics, psychology, social work, and nursing are examples of non-medical therapies. The patient needs additional care as the illness progresses, which can benefit his or her partner as well. For instance, having a nurse at home to assist with showering could be beneficial. When a caregiver's workload becomes too much, daycare centers—which are typically attached to nursing homes—must provide assistance. After then, the patient enters a transitional phase and ultimately a 24-hour care scenario. The carer, who must manage growing responsibilities while losing contact with their former partner, frequently requires psychological assistance during the entire process of rising dependency. Partner groups can be quite helpful. Lay organisations are generally very helpful in educating patients, families, and carers. Since each person's symptoms and indicators vary greatly over time, both medical

and non-medical treatment must be customised. A multidisciplinary team should ideally oversee the treatment of patients and their families. The goal of treatment is to enhance quality of life. Unfortunately, there is currently no treatment. [40].

DIAGNOSTIC POTENTIAL OF EXOSOMES

Exosomes have a complicated and dual function in Huntington's disease (HD), contributing to the illness's development as well as serving as possible treatment agents. The mutant huntingtin protein (mHTT), which builds up in neurons and creates harmful aggregates, is the cause of HD. mHTT can be transported between cells by exosomes, which are microscopic vesicles involved in cell-to-cell communication. This can spread toxicity and hasten the illness.

However, exosomes can also offer defense. Astrocytes create beneficial exosomes (ASC-EXO) containing heat shock proteins and other supportive chemicals to help neurons deal with protein misfolding and reduce damage caused by mHTT. An essential protein in this process is αB-crystallin, a glial heat shock protein that promotes exosome production. However, mHTT disrupts this defensive mechanism by reducing αB-crystallin levels and forming aggregates in the nucleus. Astrocytes release less protective exosomes, making neurons more vulnerable.

Promising outcomes have been observed in experimental therapy utilizing ASC-EXO. Direct injection of these exosomes into the striatum in models of Huntington's disease reduces mHTT aggregation, enhances mitochondrial function, raises levels of phosphorylated CREB (a protein associated with cell survival) and PGC-1α (a crucial regulator of mitochondrial biogenesis), and ultimately reduces cell death. Exosomes can be created for targeted therapy in addition to their natural function. For instance, they can deliver siRNA to silence the HTT gene or transport miR-124 to suppress REST, a transcriptional repressor that is abnormally active in HD and inhibits neuronal gene expression. Additionally, studies such as parabiosis experiments suggest that exosomes derived from young blood can provide neuroprotective benefits, including reduced mHTT pathology, enhanced mitochondrial function, and decreased apoptosis. [41]

CURRENT BIOMARKERS IN HUNTINGTONS DISEASE

Dry Markers

In recent years, alternative molecular and behavioral measures have been explored as potential biomarkers for Huntington's disease

1. **Symbol Digit Modalities Test**

In the premanifest stage of Huntington's disease (HD), cognitive impairment may start even before the typical motor symptoms manifest. Neuropsychological testing can already identify subtle issues with visual attention and psychomotor speed, such as slower information processing, delayed reaction times, or diminished focus. However, conventional clinical evaluations frequently lack the sensitivity required to detect minute, slow changes over time, particularly in the early stages of the disease, making it difficult to precisely follow development or assess the effectiveness of early therapies. Structural brain imaging techniques, particularly MRI-based measurements of brain volume, have shown greater reliability as biomarkers in premanifest HD and are widely used in clinical trials because they can objectively detect changes in brain regions such as the striatum. Despite this advantage, structural brain atrophy in HD develops slowly, which limits its usefulness as a short-term outcome measure when testing new treatments. As a result, while both cognitive testing and structural imaging provide valuable information, each has limitations in detecting subtle, early, and rapid changes in disease progression. [42]

2. Fluorodeoxyglucose positron emission tomography

Compared to structural scans, which only display anatomical alterations, functional and metabolic imaging methods offer a more dynamic means of understanding disease activity in Huntington's disease (HD). Fluorodeoxyglucose positron emission tomography (FDG-PET) is a crucial technique that assesses how actively brain cells use glucose, the brain's primary energy source. FDG-PET can identify early metabolic failure even prior to considerable brain shrinkage because neurons with diminished function utilize less glucose. Riluzole-treated HD patients showed lower FDG uptake in the parietal lobe as compared to placebo-treated patients, suggesting lower metabolic activity in that area of the brain. Crucially, this decrease in glucose metabolism had a strong linear relationship with deteriorating motor symptoms and behavioral abnormalities, indicating that clinical symptoms worsened as metabolic activity decreased. This robust correlation implies that metabolic imaging, which provides a more rapid depiction of neuronal dysfunction than structural imaging alone, may work as a sensitive and trustworthy biomarker for monitoring disease progression and assessing therapy response in HD. [43]

3. **Neurofilament light chain**

Cerebrospinal fluid (CSF), which gathers waste products from the central nervous system (CNS) and reflects brain dysfunction, is thought to be the most dependable source of wet biomarkers in Huntington's disease. The primary biomarker of HD, mutant huntingtin (mHTT), is frequently measured in CSF, particularly in huntingtin-lowering treatments. CSF mHTT levels differ between premanifest and early-stage HD and correlate with motor and cognitive symptoms in early and mid-stages, making it both a prognostic and predictive biomarker; however, this correlation weakens in late-stage disease. One significant drawback is that lumbar puncture is necessary for CSF collection, which is an intrusive process with potential risks. Since the HTT gene is expressed throughout the body, mHTT cannot be verified as brain-specific even if it may be found in blood. Therefore, researchers are exploring more accessible biofluids such as blood, urine, saliva, feces, and even hair. For example, blood biomarkers like Neurofilament light chain (NfL) reflect neuronal damage due to BBB leakage, urine has shown elevated p75NTR in HD models, saliva contains detectable total HTT correlated with clinical features, feces may reveal microbiome changes, and hair cortisol levels have been proposed as potential prognostic markers. Consequently, current research focuses on identifying reliable biomarkers in easily accessible biofluids to reduce the need for invasive CSF sampling. [44]

3-1, Neurofilament light protein

Blood is a less invasive and accessible source of brain-derived biomarkers than cerebrospinal fluid (CSF) because impairment of the blood–brain barrier (BBB) allows molecules from the central nervous system to leak into the bloodstream in a number of neurodegenerative diseases, including Huntington's disease. Neurofilament light chain (NfL), a structural protein released into serum or plasma when neurons are injured, is one such biomarker. Research, such as the TRACK-HD cohort, has demonstrated that plasma NfL levels are markedly increased in carriers of HTT mutations at all stages of the disease, strongly correlate with CSF NfL (confirming brain origin), and are linked to cognitive decline and decreased brain volumes, especially in the caudate and putamen. Even while NfL is a useful prognostic indicator of neuronal degeneration, it may not be sensitive for identifying very early or prodromal disease alterations, nor is its quick response to therapy well established. Instead, it represents generic neuronal damage rather than HD-specific pathology. [45]

EXOSOMES IN HUNTINGTONS DISEASE

The aberrant amplification of CAG repeats in the Huntington's gene causes Huntington's disease, which progressively damages the brain, particularly the striatum. Abnormal activation of the transcription factor REST is one significant mechanism. Normally, mutant huntington’s controls REST activity, but in HD this control is lost, causing REST to suppress important genes like Brain-derived neurotrophic factor

(BDNF) which is essential for neuron survival. MicroRNA-124 (miR-124) is normally reduced in HD. Since miR-124 suppresses REST, its decrease leads to increased REST levels and further gene repression. Because miR-124 also supports neurogenesis and regulates neuronal cell cycles, delivering miR-124 could help restore brain function. However, free (naked) miR-124 is unstable and easily degraded, making it ineffective as a therapy. MiRNAs may be securely transported to target cells by exosomes, which are microscopic vesicles secreted by cells. Exosomes are being researched as therapeutic delivery vehicles because they naturally move genetic material across brain cells. Therefore, delivering miR-124 via exosomes offers a viable approach to treating HD by encouraging brain regeneration and restoring normal gene regulation.

Application	Relevance
Early Detection	Identifies molecular changes before MRI abnormalities
Disease Monitoring	Tracks progression longitudinally
Therapy Evaluation	Measures response to HTT-lowering therapies
Personalized Medicine	Biomarker-guided treatment adjustments

Table no:2 Clinical Implications

Exosome analysis offers a minimally invasive alternative compared to CSF collection.

CASE STUDY FOR HUNGTINTON DISEASES:

Case study 1:

T., age 10, was admitted due to strange behavior and increasing social disengagement that started at age 7. He authored strange, violent, and sexualized articles, spoke very little, and secluded himself at school by hiding beneath bushes, for example. Except for separation anxiety at age 4, early development was typical. Huntington's disease was not present in the family history, although there was a noteworthy two-generational history of severe depression. His father, 34, had been admitted to the hospital due to cognitive impairments, anxiety, depression with psychotic symptoms, and recent clumsiness, melancholy, and impatience. Upon evaluation, T. displayed intact orientation and attention, but also elective mutism, low energy, poor eating, minimal speaking, limited eye contact, and a gloomy mood. With the exception of mild rigidity and tongue weakness, the neurological examination was essentially normal; the EEG was nonspecific.

Case study 2:

T. was readmitted four years later with near-complete social isolation, depression, and mutism. Exaggerated reflexes, modest rigidity, aberrant tongue motility (not fully tested), micrographia, and a tense, hunched appearance were all present, along with minimal facial expression and slight mouth fasciculations. His mutism an jof paranoia, cognitive deterioration, and chorea. Huntington's disease (HD) was confirmed by genetic testing with a (CAG)48 expansion. The paternal grandmother had severe neurological and psychological symptoms that were suggestive with HD, according to additional family history. The differential diagnosis for T. was expanded to include HD. Juvenile HD was confirmed by genetic testing that revealed a (CAG)71 expansion. Typical striatal alterations (abnormalities of the putamen and caudate with ventricular enlargement) were seen on MRI. T. consented to testing following counseling, but while awaiting the findings, he displayed ambivalence and aggressive and suicidal actions. Following diagnosis, his suicidality and impulsivity gradually decreased. Antidepressant therapy for symptoms was the mainstay of treatment. After being moved to a supervised group home, he has stopped acting suicidally, is socially accepted, and frequently attends school. [47,48,49].

Case study 3:

Two case reports highlight the communication deficits associated with Huntington's disease (HD). Anne, a middle-aged Swedish woman with advanced HD, experienced severe chorea affecting speech, including poor articulation, impaired pitch and loudness control, and occasional echolalia. She also showed word-finding difficulties, reduced conversational initiative, delayed responses, minimal verbal output, and impaired discourse despite relatively preserved object and action naming. Difficulties in picture description, inference, and abstract language were also observed, although her hearing and vision remained intact. Joseph, a man in his mid-40s with recently diagnosed HD, exhibited social withdrawal, memory impairment, slurred and repetitive speech, ataxia, and delusions. During 16 months of improvisation-based music therapy, he gradually improved in musical coordination, rhythm, and emotional expression. Although verbal communication remained limited, music appeared to serve as an effective alternative means of emotional expression and social engagement [52,53,54]. An 80-year-old woman with a family history of Huntington's disease (HD) presented with a 5-year history of progressive gait impairment and chorea. Neurological examination showed mild orofacial and limb chorea, asymmetric bradykinesia, mild rigidity, and a shuffling gait without cognitive or sensory deficits. She was clinically diagnosed with HD and initially improved with tetrabenazine, later switching to reserpine due to cost. Neuropathological examination after her death confirmed typical HD changes (caudate atrophy and neuronal loss with gliosis) along with coexisting Alzheimer-type pathology. [55,56].

Case study 4:

In 2017, a 16-year-old child was referred due to deteriorating emotional symptoms and persistent tics. Despite treatment, tics started at age 11 with coughing and throat clearing before spreading to head and neck motions. His cognitive decline (IQ 64, poor focus, scholastic failure), motor impairment (rigidity, tremor, ataxia, dysarthria, handwriting trouble), social disengagement, and irritability all increased with time. Emotional instability, anger, anxiety, psychosis with visual and auditory hallucinations, and depression with suicide thoughts were among the mental symptoms. Routine labs were normal, but a neurological examination revealed tremor and a disturbed gait. Genetic testing confirmed juvenile Huntington's disease (JHD) by identifying 17 and 52 CAG repeats in the HTT gene. Huntington's illness was later shown to run in the paternal family. Psychological support and interdisciplinary care were provided to him. Sertraline was used to treat depression, whereas levomepromazine, aripiprazole, olanzapine, and haloperidol (later switched because of side effects) were used to treat psychosis and violence. Over the course of two years, angry outbursts diminished with treatment, despite ongoing motor and cognitive impairment. [57,58] depression with suicide thoughts were among the mental symptoms.

Case study 5:

In 2014, a 13-year-old boy with two known paternal family instances was referred for testing for Huntington's disease (HD). He gradually experienced motor symptoms, such as hand tremors, distal limb rigidity, unstable gait, speech difficulty, and hip and chest twitches during sleep. His vital signs and test findings were normal, and the neurological examination revealed that he was focused and aware. Genetic testing confirmed juvenile Huntington's disease (JHD) by identifying 17 and 69 CAG repeats in the HTT gene. His cognitive decline (IQ 50 in 2019), handwriting issues, social disengagement, impulsivity, emotional sensitivity, and motor impairment—particularly instability on stairs—all deteriorated with time. He soon needed ongoing assistance with everyday tasks due to dysphagia, eating disorder symptoms, and parkinsonism. Motor problems were the main factor affecting his quality of life. Levodopa, benserazide, and trihexyphenidyl in conjunction with tiapride treatment decreased rigidity and prolonged physical independence.[59]

Case study 6:

In October 2023, a 40-year-old woman who is illiterate, Ms. S.M., was admitted to a Moroccan hospital under mandatory admission due to her hetero-aggressive behavior. Schizophrenia ran in her family (brother affected). A psychiatric evaluation revealed chronic auditory and visual hallucinations, persecutory and

witchcraft delusions, instability, poor focus and memory, and non-spontaneous speaking. Lab results, brain imaging, and physical examination were all normal. After receiving treatment with injectable haloperidol (10 mg/day) for her short psychotic disorder diagnosis, her symptoms improved after three weeks. On oral haloperidol, she was released. She experienced dysarthria and aberrant upper limb motions during follow-up that did not improve with antiparkinsonian medication. The trio of chorea, mental symptoms, and cognitive deterioration triggered a neurological evaluation that resulted in the suspicion and genetic confirmation of Huntington's disease (HD). She was referred for genetic counseling and began on 200 mg of quetiapine per day. Poor treatment adherence and erratic follow-up have been seen.

CONCLUSION:

Huntington's disease (HD) is a complex, inherited neurodegenerative disorder marked by progressive motor dysfunction, cognitive decline, and profound psychiatric disturbances. The disease arises from a mutation in the HTT gene, leading to abnormal protein aggregation, neuronal toxicity, and widespread brain degeneration, particularly in the basal ganglia and cortex. Despite significant advances in understanding its genetic basis and pathophysiology, HD remains incurable, with current treatments focusing primarily on symptomatic relief and improving patient quality of life through a multidisciplinary approach. The growing body of research on exosomes has opened promising new avenues in both the diagnosis and treatment of HD. Exosomes serve as important mediators of intercellular communication and have demonstrated dual roles—both in propagating mutant huntingtin toxicity and in offering neuroprotective effects. Their ability to cross the blood–brain barrier, carry disease-specific biomarkers, and reflect the physiological state of neurons makes them highly valuable as non-invasive diagnostic tools. Moreover, their potential as therapeutic delivery vehicles, particularly for RNA-based interventions such as miRNA and siRNA, highlights their future significance in targeted and personalized medicine. Advancements in biomarker research, including neurofilament light chain and imaging techniques, further enhance early detection and disease monitoring. Case studies also emphasize the variability in clinical presentation, especially the early onset of psychiatric symptoms and the importance of timely diagnosis and genetic counseling. In conclusion, while Huntington's disease continues to pose major clinical and social challenges, emerging research—especially in the field of exosomes and molecular biomarkers—offers hope for earlier diagnosis, improved disease monitoring, and the development of innovative, disease-modifying therapies in the future.

REFERENCE:

1. Vonsattel JP, DiFiglia M. Huntington disease.
2. Waldvogel HJ, Kim EH, Tippett LJ, Vonsattel JP, Faull RL. The neuropathology of Huntington's disease. Behavioral neurobiology of Huntington's disease and Parkinson's disease. 2014 Oct 10:33-80.
3. Duff K, Paulsen JS, Beglinger LJ, Langbehn DR, Stout JC, Predict-HD Investigators of the Huntington Study Group. Psychiatric symptoms in Huntington's disease before diagnosis: the predict-HD study. Biological psychiatry. 2007 Dec 15;62(12):1341-6.
4. Ellis N, Tee A, McAllister B, Massey T, McLauchlan D, Stone T, Correia K, Loupe J, Kim KH, Barker D, Hong EP. Genetic risk underlying psychiatric and cognitive symptoms in Huntington's disease. Biological psychiatry. 2020 May 1;87(9):857-65.
5. Margolis RL, Ross CA. Diagnosis of Huntington disease. Clinical chemistry. 2003 Oct 1;49(10):1726-32.
6. Folstein SE, Leigh RJ, Parhad IM, Folstein MF. The diagnosis of Huntington's disease. Neurology. 1986 Oct;36(10):1279-.
7. Frank S. Treatment of Huntington's disease. Neurotherapeutics. 2014 Jan 1;11(1):153-60.
8. Ross CA, Tabrizi SJ. Huntington's disease: from molecular pathogenesis to clinical treatment. The Lancet Neurology. 2011 Jan 1;10(1):83-98.
9. Research progress of exosomes in pathogenesis, diagnosis, and treatment of ocular diseases Xinting Feng1,2, Zhen Peng1,3†, Lingyi Yuan1†, Ming Jin1, Haijian Hu1, Xin Peng4, Yaohua Wang1, Chun Zhang5, Zhiwen Luo2 * and Hongfei Liao1 * 24 January 2023

10. oria FN, Pampliega O, Bourdenx M, Meissner WG, Bezard E and Dehay B (2017) Exosomes, an Unmasked Culprit in Neurodegenerative Diseases. Front. Neurosci. 11:26.
11. Ananbeh H, Vodicka P, Kupcova Skalnikova H. Emerging Roles of Exosomes in Huntington's Disease. Int J Mol Sci. 2021 Apr 15;22(8):4085.
12. Exosome Processing and Characterization Approaches for Research and Technology Development
13. James J. Lai, Zoe L. Chau, Sheng-You Chen, John J. Hill, Katalin V. Korpany, Nai-Wen Liang, Li-Han Lin, Yi-Hsuan Lin, Joanne K. Liu, Yu-Chung Liu, Ruby Lunde, Wei-Ting Shen, First published: 25 March 2022
14. Singh, S., Paul, D., Nath, V., & A, R. (2024). Exosomes: current knowledge and future perspectives. Tissue Barriers, 12(2).
15. Exosomes in Liquid Biopsy: The Nanometric World in the Pursuit of Precision Oncology Karmele Valencia 1,2,3,4, * and Luis M. Montuenga 1,2,3,5, *
16. Huntington's Disease Steven Finkbeiner Gladstone Institute of Neurological Disease, Taube-Koret Center for Huntington's Disease Research, Departments of Neurology and Physiology, University of California, San Francisco, San Francisco, California 94158.
17. Huntington Disease, Anitha Ajitkumar; Forshing Lui; Orlando De Jesus.
18. Huntington's disease: a clinical reviewP. McColgana and S. J. Tabrizi a,baHuntington's Disease Centre, Department of Neurodegenerative Disease, UCL Institute of Neurology, London; and bNational Hospitalfor Neurology and Neurosurgery, Queen Square, London, UK.
19. Huntington's disease S Davies, D B Ramsden, J Clin Pathol: Mol Pathol 2001;54:409–413.
20. McColgan P, Tabrizi SJ. Huntington's disease: a clinical review. Eur J Neurol. 2018 Jan;25(1):24-34. doi: 10.1111/ene.13413. Epub 2017 Sep 22. PMID: 28817209.
21. Huntington's Disease Genetics Richard H. Myers Department of Neurology, Boston University School of Medicine, Boston, Massachusetts 02118.
22. HUNTINGTON'S DISEASE (HD): A BRIEF REVIEW, Fayyaz Hussain Qureshi, Sajjad Hussain Qureshi, Tayyaba Zia, Fajr Khawaja.
23. Biomarkers for Huntington's disease: A brief overview Annie Killoran1* and Kevin Biglan2 1Department of Neurology, University of Iowa, IA, USA 2Department of Neurology, University of Rochester, New York, USA.
24. Molecular Mechanisms and Potential Therapeutical Targetsin Huntington's DiseaseCHIARA ZUCCATO, MARTA VALENZA, AND ELENA CATTANEODepartment of Pharmacological Sciences and Centre for Stem Cell Research, Universita` degli Studi di Milano,Milan, Italy.
25. The Biology of Huntingtin Fre´ de´ric Saudou1,2,3, * and Sandrine Humbert1,2.
26. Huntington Disease and the Huntingtin Protein, panel Zhiqiang Zheng, Marc I. Diamond.
27. The biological function of the Huntingtin protein and its relevance to Huntington's Disease pathology, Joost Schulte [1,*], J Troy Littleton.
28. Proskura, A.L., Vechkapova, S.O., Zapara, T.A. et al. Protein–protein interactions of huntingtin in the hippocampus. Mol Biol 51, 647–653 (2017)
29. Huntington's disease – I. Symptomatology, Etiology, and action Mechanisms Dr. Alain L. Fymat* Professor, International Institute of Medicine & Science, California, USA.
30. The biological function of the Huntingtin protein and its relevance to Huntington's Disease pathology, Joost Schulte [1,*], J Troy Littleton.
31. Structural aspects of the Huntingtin protein investigated by biocomputing methods, Untersuchung struktureller Aspekte des Huntingtin-Proteins mit Biocomputing-Methoden, Rossetti, Giulia
32. Huntington Disease, Anitha Ajitkumar; Forshing Lui; Orlando De Jesus.
33. Huntington's disease – I. Symptomatology, Etiology, and action Mechanisms Dr. Alain L. Fymat* Professor, International Institute of Medicine & Science, California, USA.
34. Huntington disease: a single-genedegenerative disorder of the striatumPeggy C. Nopoulos, MD.
35. Huntington Disease, Anitha Ajitkumar; Forshing Lui; Orlando De Jesus.
36. Raymund AC Roos, Huntington's disease: a clinical review, Roos Orphanet Journal of Rare Diseases, 2010, 5(40): 1-8.

37. J S Paulsen, R E Ready, J M Hamilton, M S Mega, J L Cummings, Neuropsychiatric aspects of Huntington's disease, J Neurol Neurosurg Psychiatry, 2001, 71: 310–314
38. Scot E. Purdon, Ph. D, Erich Mohr, Ph. D, Vadim Ilivitsky, M.D, Barry D.W. Jones, M.D, Huntington's Disease: Pathogenesis, Diagnosis and Treatment, J Psychiatr Neurosci, 1994, 19(5): 359-367.
39. Exosomes in Liquid Biopsy: The Nanometric World in the Pursuit of Precision Oncology Karmele Valencia 1,2,3,4, * and Luis M. Montuenga 1,2,3,5, *
40. Wild EJ, Tabrizi SJ: Huntington's disease phenocopy syndromes. Curr Opin Neurol 2007, 20:681-7.
41. Gao P, Li X, Du X, Liu S, Xu Y. Diagnostic and therapeutic potential of exosomes in neurodegenerative diseases. Frontiers in Aging Neuroscience. 2021 Dec 16;13: 790863.
42. Pellegrini M, Bergonzoni G, Perrone F, Squitieri F, Biagioli M. Current Diagnostic Methods and Non-Coding RNAs as Possible Biomarkers in Huntington's Disease. *Genes*. 2022; 13(11):2017.
43. Squitieri F, Orobello S, Cannella M, Martino T, Romanelli P, Giovacchini G, Frati L, Mansi L, Ciarmiello A. Riluzole protects Huntington disease patients from brain glucose hypometabolism and grey matter volume loss and increases production of neurotrophins. European journal of nuclear medicine and molecular imaging. 2009 Jul; 36(7):1113-20.
44. Byrne LM, Rodrigues FB, Johnson EB, Wijeratne PA, De Vita E, Alexander DC, Palermo G, Czech C, Schobel S, Scahill RI, Heslegrave A. Evaluation of mutant huntingtin and neurofilament proteins as potential markers in Huntington's disease. Science translational medicine. 2018 Sep 12;10(458): eaat7108.
45. Shahim P, Zetterberg H, Tegner Y, Blennow K. Serum neurofilament light as a biomarker for mild traumatic brain injury in contact sports. Neurology. 2017 May 9; 88(19):1788-94.
46. Lee ST, Im W, Ban JJ, et al. Exosome-Based Delivery of miR-124 in a Huntington's Disease Model. J Mov Disord. 2017;10(1):45-52.
47. Gusella JF, Wexler NS, Conneally PM (1983), A polymorphic DNA marker genetically linked to Huntington's disease. Nature 306:234–238
48. Huntington G (1872), On chorea. Med Surg Rep 26:320–321 Lenti C, Bianchini E (1993), Neuropsychological and neuroradiological study of a case of early-onset Huntington's chorea. Dev Med Child Neurol 35:1007–1014
49. Meierkord H, Pfeiffer L, Ludolph A (1994), The aetiology and pathogenesis of Huntington's disease: recent advances. Nervenarzt 65:519–526
50. Saldert C, Eriksson E, Petersson K, Hartelius L. Interaction in conversation in Huntington's disease: an activity-based analysis and the conversation partner's view of change. J Interaction Res Commun Disord, in press.
51. Lindstrom E, Werner C. A-ning, Neurolingvistisk Afasiunderso¨kning. Stockholm: Ersta utbildning sinstitut; 1995.
52. Curtis, S. (1987) 'Music Therapy: A Positive Approachs In Huntington's Disease'. Proceedings of the 13th National Conference of the Australian Music Therapy Association Incorporated. Dawes, S. (1985a)
53. 'The Role of Music Therapy in Caring in Huntingtons Disease'. In Chiu & Teltscher (eds.) Handbook for Caring in Huntington's Disease. Melbourne: Huntington's Disease Clinic. Dawes, S. (1985 b)
54. 'Case study: Advanced Stage Huntington's Disease'. Proceedings of the 11th National Conference of the Australian Music Therapy Association Incorporated. 87-92.
55. Squitieri F, Jankovic J. Huntington's disease: how intermediate are intermediate repeat lengths? Mov Disord 2012;27: 1714–7.
56. 8 Andrich J, Arning L, Wieczorek S, et al. Huntington's disease as caused by 34 CAG repeats. Mov Disord 2008;23: 879–81
57. van Duijn E, Craufurd D, Hubers AAM, Giltay EJ, Bonelli R, Rickards H, et al. Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). J Neurol Neurosurg Psychiatry. 2014;85: 1411–8.
58. Quigley J. Juvenile Huntington's disease: diagnostic and treatment considerations for the psychiatrist. Curr Psychiatry Rep. 2017;19(2):17–20.
59. Ross CA, Aylward EH, Wild EJ, Langbehn DR, Long JD, Warner JH, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol. 2014;10(4):204–16.