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Case Report

NEURO-IMAGING IN "HUNTINGTON DISEASE (HD)" "A RARE PROGRESSIVE NEURO-DEGENERATIVE DISORDER"

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ABSTRACT
Huntington Disease (HD) is an autosomal dominant, progressive neuro-degenerative disorder with a distinct phenotype characterized by chorea & dystonia, progressive dementia, incoordination, cognitive decline and behavioral difficulties. Magnetic Resonance Imaging (MRI) in moderate to severe Huntington disease show loss of striatal volume with concomitant enlargement of the frontal horns of the lateral ventricles giving caudate lobes a 'box-like' configuration.Clinical andneuro-radiological abnormalities can be demonstrated in gene-positive individuals before the onset of manifest Huntington's disease, even as far as 15 years before the disease onset (Ha and Fung, 2012). Here, we present a Case of Huntington Disease with characteristic clinical and imaging findings- a thirty-eight years old right handed male who presented to the Department of General Medicine with signs of progressive chorea, rigidity and dementia associated with seizures. Chorea was initially mild but progressed to severe and caused uncontrollable limb movements. Dysarthria, dysphagia and abnormal eye movements werepresent. It was associated with increasing depression, bradykinesia, cognitive impairment and aggression over the period of time.

Keywords: *Autosomal Dominant, Huntington's Chorea, HD – Huntington Disease, M.R.I. -Magnetic Resonance Imaging, Neuro-Degenerative Disorder*

INTRODUCTION
Huntington Disease (HD) is rare, progressive,dominantly inherited,neuro-degenerative disease of the central nervous system (CNS) caused by expansion of a CGA triplet in the gene *IT15* of chromosome 4, which encodes a protein of unknown function called *huntingtin*. It was first described by American physician George Huntington in 1872 (Martin, 1980).
The diagnosis of Huntington Disease is based on clinical, imaging and genotypic findings.Clinical presentation is typically with progressive rigidity, choreo-athetosis (Huntington's Chorea), dementia, psychosis and emotional lability. Morphologically, it is characterized by diffuse atrophy, with the greatest loss of neurons seen in the caudate nucleus and putamen. The basal ganglia at death weigh about 50% of normal (Bird, 1978) and also demonstrate neuronal loss and gliosis. Receptor binding studies of postmortem specimens suggest that certain intrinsic striatal neurons and their efferent pathways to globuspallidus and substantia nigra are the majorsites of pathologic disruption (Shoulson, 1984). However, in the initial cases, the diagnosis is challenging.
Magnetic Resonance Imaging (MRI), because of its greatest spatial and contrast resolution, is the preferred neuro-imaging modality for the establishment of diagnosis and assessing the type of lesion.

CASES
A thirty-eight years old right handed male presented to the Department of General Medicine, Mahatma Gandhi Medical College and Hospital, Jaipur (Rajasthan) with the history of progressive chorea, rigidity and dementia associated with seizures. Chorea was initially mild but progressed to severe and caused uncontrollable limb movements. Dysarthria, dysphagia and abnormal eye movements were present. It was associated with increasing depression, bradykinesia, cognitive impairment and aggression over the period of time. The patient was a known case of Huntington diseasesince 5 years and had taken no medication.
Patient's birth history and developmental history was uneventful.
There was no h/o any serious childhood infections, neuro-infection or any trauma.

Case Report

Physical and Clinical Examination

Patient was a middle aged male, moderately built and nourished & disoriented to time, place and person with abnormal and incoordinated limb movements and rigidity.

His general physical examination and vitals were normal. Central Nervous System examination revealed profound dementia with severe dystonia and chorea of head, trunk and limbs with exaggerated deep tendon reflexes and bilateral extensor plantar response. Examination of other systems was unremarkable.

Radiological Examination

M.R.I. Brain: MRI of Brainrevealedprominence of ventricular system and cisterns suggestive of diffuse cerebral atrophy. Mild atrophy of caudate nucleus was noted with altered frontal horn width to inter-caudate distance ratio (*FH/CC* ratio = 1.84) and inter-caudate distance to inner table width ratio (*CC/IT* ratio = 0.166).

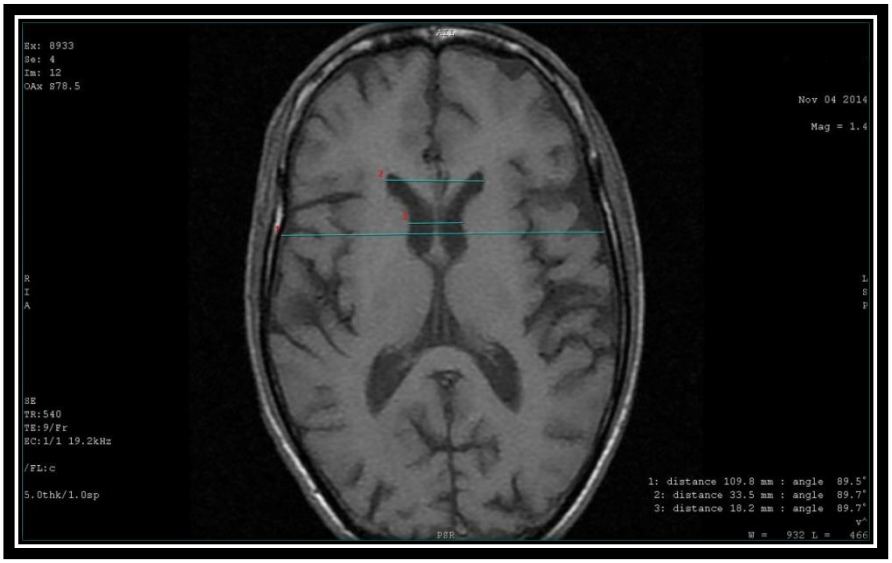

Figure 1: T1-weighted M.R.I. Axial Image showing Frontal Horn width (FH)-*marking 2*-(=33.5 mm), Inner Table width (IT)-*marking1*-(=109.8mm) and Intercaudate distance (CC)-*marking 3*-(=18.2mm) [FH/CC ratio = 1.84; CC/IT ratio = 0.166]

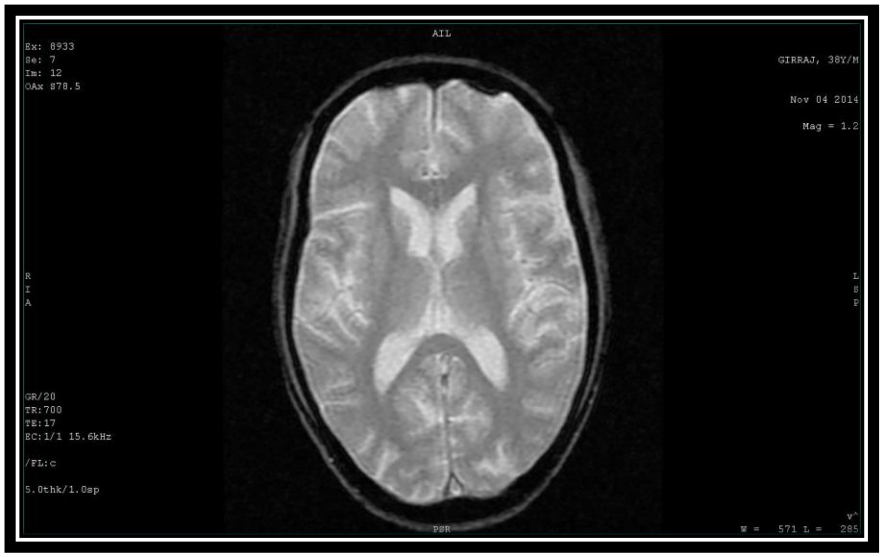

Figure 2: T2-weighted M.R.I. Axial Image showing bilateral caudate head atrophy with enlargement of frontal horns of lateral ventricles (*Box-like configuration*)

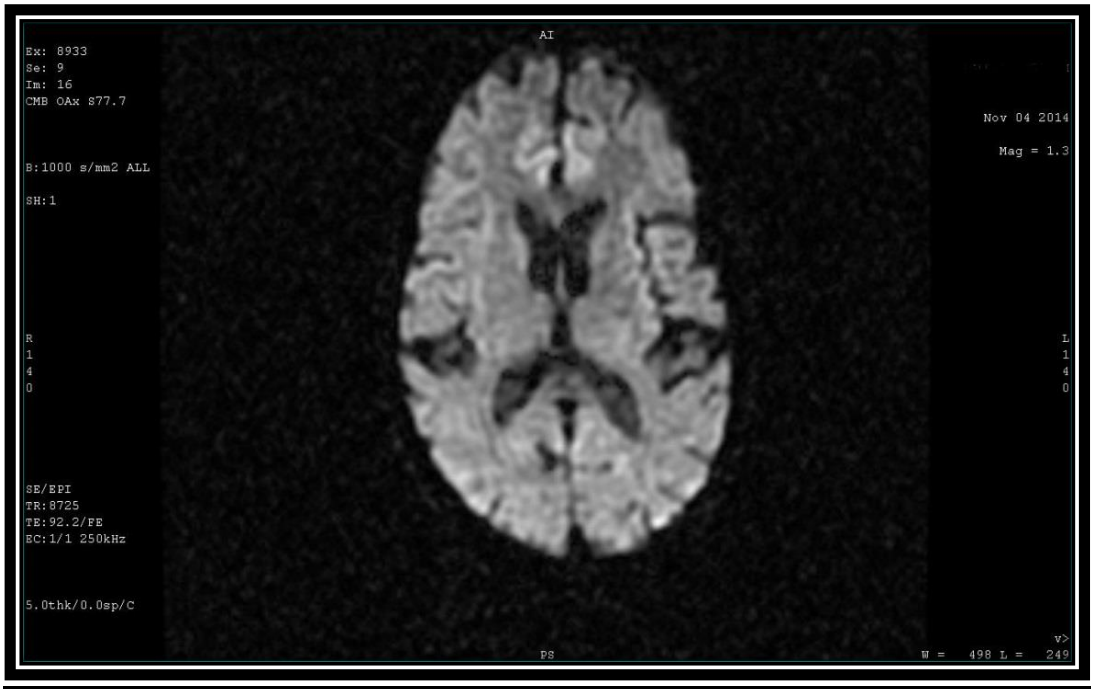

Figure 3: Diffusion-Weighted (DWI) M.R.I. Axial Image showing no evidence of any diffusion restriction in periventricular regions

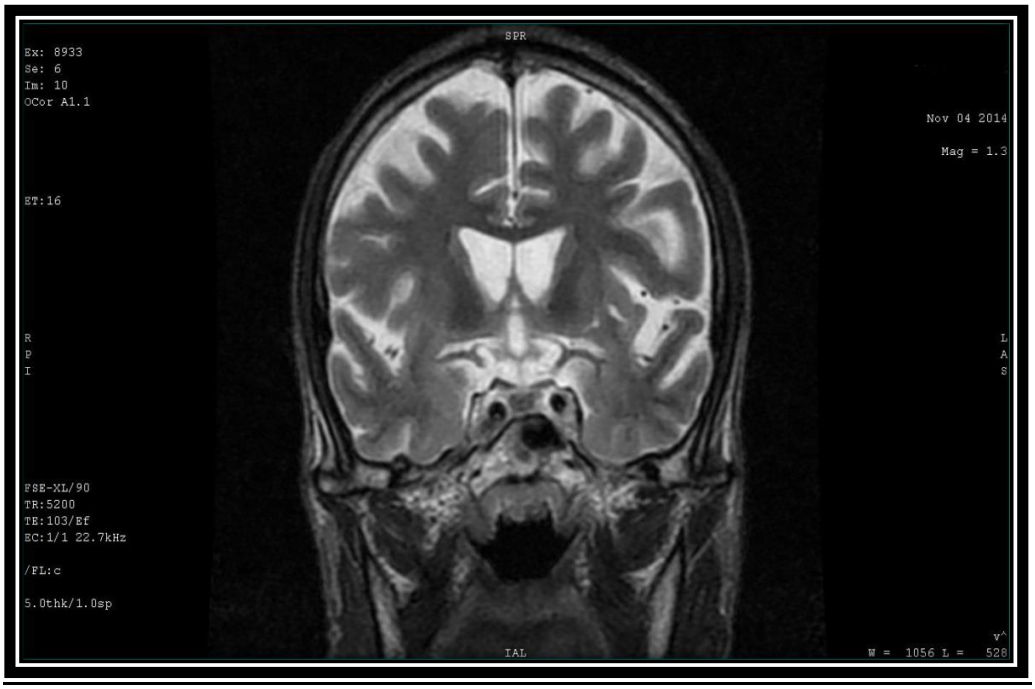

Figure 4: T2-weighted M.R.I. Coronal Image showing diffuse cerebral atrophy and generalized age inappropriate cortical volume loss

Coronal and axial scans demonstrated moderate thinning of the putamen and caudate nuclei. In addition, there was moderate diffuse cortical atrophy.Brain stem and cerebellar hemispheres appeared normal. On Magnetic Resonance Spectroscopy (MRS), Lactate peak was noted with decrease in NAA/Creatinine ratio.

DISCUSSION

Huntington disease is an inheritable disorder that is autosomaldominant with complete penetrance caused by a loss of GABAergic neurons of the basal ganglia, especially of caudate nucleus and putamen (Imarisio *et al.,* 2008). The characteristic caudate and cortical atrophy was first described radio graphically using pneumoencephalography (Blinderman *et al.,* 1964).

It has a worldwide prevalence rate of 5-10/100,000 with areas of increased prevalence in western Scotland and Venezuela, where prevalence reaches 7000/100,000. It is typically diagnosed between 30 and 50 years of age.

Incidence is equal in both genders, although there appears to be an effect depending on the gender of the parent from whom the defect was inherited: if inherited from the father, presentation is earlier. The cause for this effect is as yet uncertain (Ho *et al.,* 1995).

In approximately 1-6% symptoms occur before the age of 20, so-called 'juvenile' form, which appears to be a variant of the usual adult form, with a different pattern of symptoms. In juvenile cases having inherited the disease from the father is far more common (Ho *et al.,* 1995).

Clinical presentation is typically with progressive rigidity, choreoathetosis, dementia, psychosis and emotional lability. The juvenile form has a different presentation, with cerebellar symptoms, rigidity and hypokinesia being prominent (Dormont and Seidenwurm, 2008).

It is an autosomal dominant disorder with genetic anticipation (i.e. next generation will have more repeats of CAG and a more severe course of the disease or show symptoms earlier) particularly if the inherited mutated allele is paternal. The mutation responsible is on chromosome 4p16:3, and consists of a CAG trineucleotide repeat. The usual 10-30 copies are amplified to > 36, and the greater the number of repeats the earlier the age of onset (Ho *et al.,* 1995).

Microscopically, there are Huntington nuclear inclusion bodies. Both deep grey matter and to a lesser degree white matter are involved in HD (Sieradzan *et al.,* 1999).

Neuroimaging

Although all modalities capable of structural brain imaging will demonstrate morphological changes of Huntington disease, MRI has the greatest spatial and contrast resolution and is thus preferred.

On MRI, the most striking, and best known, feature is that of caudate head atrophy resulting in enlargement of the frontal horns, often giving them a "box" like configuration (Dormont and Seidenwurm, 2008; Ho *et al.,* 1995; Paulsen *et al.,* 2004). This can be quantified by a number of measurements:

- frontal horn width to intercaudate distance ratio (FH/CC)
- intercaudate distance to inner table width ratio (CC/IT)

Terrence *et al.,* (1977) and Barr *et al.,* (1978) described these ratios as reliable criteria for Huntington disease.

On the same axial plane obtained on the ACPC line (anterior commissure- posterior commissure) the ratio between the distance between the caudate heads (where they are closest) and the lateral margins of the frontal horns is obtained known as Frontal horn width to intercaudate distance ratio (FH/CC). The normal mean FH/CC ratio range is 2.2 to 2.6. As the caudate heads reduce in volume the CC distance will approach the FH distance, and the ratio will approach 1.

On the same axial plane obtained on the ACPC (anterior commissure and posterior commissure) line, the ratio between the distance between the caudate heads (where they are closest) and the distance between inner-table of the skull (measured along the same line as the intercaudate distance) is obtained known as Intercaudate distance to inner table width ratio (CC/IT). The normal CC/IT ratio range 0.09 to 0.12. As the caudate heads reduce in size, the CC distance will increase and as such the CC/IT ratio will increase.

MR spectroscopymay demonstrate elevation of lactate in the occipital cortex and basal ganglia which correlates with duration of symptoms. There is also decrease in NAA/creatinine ratio in keeping with neuronal loss in basal ganglia.

Basal ganglia may show decreased T2 signal and blooming on SWI in keeping with iron deposition (Macerollo *et al.,* 2014).

PET scan demonstrates hypometabolism by decrease FDG uptake in basal ganglia and frontal cortex even before noticeable caudate nucleus volume loss (Ahmad *et al.,* 2014).

Management

Current drug therapy has no effect on the progression of disability. Hyperkinesias and psychiatric symptoms may respond well to pharmacotherapy, but neuropsychological deficits and dementia remain untreatable. Patients, their families and carriers require a great deal of physical and emotional support. Neural and stem cell transplantation is a potential future treatment (Bonelli and Hofmann, 2007).

Prognosis

This is a relentlessly neurodegenerative disorder. The clinical features develop progressively with severe increase in choreic movements and dementia. Death is usually from an intercurrent illness e.g. respiratory tract infection (Bonelli and Hofmann, 2007).

Differential Diagnosis

Differential Diagnoses for HD includes- Wilson Disease (WD), Leigh Disease (LD), Hallervorden-Spatz Syndrome (HSS), Acute hypoxic encephalopathy, Carbon monoxide poisoning and hypoglycemic encephalopathy.

Wilson Disease (WD), also known as hepato-lenticular degeneration, is a rare autosomal recessive disorder of copper metabolism, affecting multiple organ systems. Clinical presentation is varied and includes weakening of hands and dysarthria, dystonia, cerebellar and psychiatric symptoms. Kayser-Fleischer rings are seen in cornea and are characteristic feature. Neuroimaging may demonstrate atrophic changes in basal ganglia, cortical and cerebellar regions with hyperintensity in lentiform nuclei and mesencephalic regions on T1-weighted sequences and T2 hyperintensity involving basal ganglia and ventrolateral aspect of thalamus with or without diffusion restriction on DWI. Axial T2-weighted sequence show 'face of giant panda sign' at midbrain level – a characteristic of this disease (Wilson, 1912).

Leigh Disease (LD), also known assubacute necrotizing encephalomyelopathy (SNEM), is a progressive neurodegenerative disorder and invariably leads to death in childhood. Clinical symptoms include psychomotor delay/regression and superimpose signs of basal ganglia and brain stem dysfunction such as ataxia, ophthalmoplegia, dystonia, respiratory rhythm disturbance and cranial nerve palsies. Neuroimaging may demonstrate T2 hyperintensities in brainstem, periaqueductal gray matter, medulla, midbrain and putamen with reduced signal on T1-weighted sequences in these areas with or without some diffusion restriction on DWI. MRS may show elevated choline, lactate and reduced NAA levels (Leigh, 1951).

Hallervorden-Spatz Syndrome (HSS), also known aspantothenate kinase-associated neurodegeneration (PKAN), is an autosomal recessive disorder causing involuntary spasticity and progressive dementia with brain iron accumulation. Clinical presentation is varied and includes rigidity, dysarthria, dystonia, retinitis pigmentosa, progressive mental retardation, cognitive impairment, spasticity and tremors. Neuroimaging may demonstrate central T2 hyperintensity in antero-medial part of globuspallidus withhypointense lateral part of globuspalliudus referred to as 'eye of tiger sign' and decreased NAA peak on MRS (Asumal *et al.,* 2003).

The above differential diagnoses were easily ruled out in our patients based on MRI findings.

Conclusion

Clinically, HD is characterized chorea & dystonia, progressive dementia, incoordination, cognitive decline and behavioral difficulties.

MRI abnormalities of HD includeloss of striatal volume and increased size of frontal horns of lateral ventricles giving caudate lobes a 'box-like' configuration with elevation of lactate levels in occipital cortex.

HD should be considered in the differential diagnosis, especially if there is atrophy of caudate head, putamen with generalized age inappropriate cortical volume loss. The radiologist plays a key pivotal role as neuro-imaging is an important tool for early diagnosis and excluding differential diagnoses, which can modify the progression of disease with timely intervention and management.

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