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A rare case report of van der Knaap disease with Fahr's disease

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Abstract
Van der Knaap is an inherited demyelination disorder characterised by macrocephaly, leukoencephalopathy, and subcortical cysts showing early onset in life. Fahr's disease is characterised by calcification in globus pallidus, dentate nuclei of cerebellum, and white matter showing late onset in life. Both diseases are rare in occurrence. We aimed to provide a case report of a 25-year-old female patient who underwent CECT and CE-MRI and showed findings of both diseases.

Keywords: Van der knaap, fahr, megalencephaly, leukoencephalopathy, consanguinity

Introduction
Van der Knaap disease is a rare autosomal recessive disorder that is characterised by the demyelination/cystic degeneration of the white matter, thus also named vanishing white matter disease. It is characterised by the presence of macrocephaly (infantile onset), subcortical cerebral leukoencephalopathy, and a few neurological symptoms like motor function delay, seizures, spasticity, ataxia, and also mental deterioration [1, 2]. Usually, the age of presentation is from birth to 25 years of life with a median age of 6 months [3, 4]. In India, this disease is more common in Aggarwal community, thus giving it another name, i.e., Aggarwal's disease. Megalencephalic leukoencephalopathy with subcortical cysts (MLC) summarizes the main features in a single term [5].
Fahr's disease is a rare disorder that is characterised by B/L symmetrical coarse basal ganglia calcification and is thus also named idiopathic striopallidodentate calcinosis [6]. The most frequent site of the calcification is Globus Pallidus but deposits may be present in the putamen, dentate nucleus, thalamus, caudate nucleus, cerebellum, and cerebral white matter [7]. It is characterised by the presence of extrapyramidal and cerebellar symptoms, and movement disorders (like chorea, tremor, and dystonia) often accompanied by psychiatric symptoms (such as psychosis, mood disorders, and dementia) [8]. The usual age of presentation is 40-60 years but may also be seen in children in some instances. Some cases are also reported that had no neurological signs.

Case report
A 25-year-old female born from consanguineous marriage in a Muslim family from Shahjahanpur district of Uttar Pradesh, India with normal prenatal and postnatal development except for the macrocephaly. The patient presented to our Department of Radiodiagnosis with a recent episode of seizure with frothy discharge from the mouth. She had experienced a previous episode of seizure five years back and since then she has continued on antiepileptic medications. From early adolescence, intellectual disability progresses in the form of decreased scholastic performance, slowness of activities, decrease in communication skills, and increase in clumsiness while walking. She had very little control over her bladder and was suffering from urinary incontinence. On examination, the patient was conscious with decreased attention, gross incoordination, troublesome language skills, and difficulty in conveying her responses when any questions were asked.
She was advised to undergo CECT Brain and then later further advised to undergo CE-MRI Brain.

Investigations

CT scan

Multiple calcified lesions were noted in bilateral basal ganglia, thalami, bilateral frontal lobe, and bilateral cerebellar hemispheres. Multiple hypodense lesions with mild peripheral enhancement in bilateral cerebellar hemispheres. Ill-defined hypodensities in bilateral periventricular and subcortical white matter are visualised. Mild to moderate distortion of bilateral lateral ventricles is also observed.

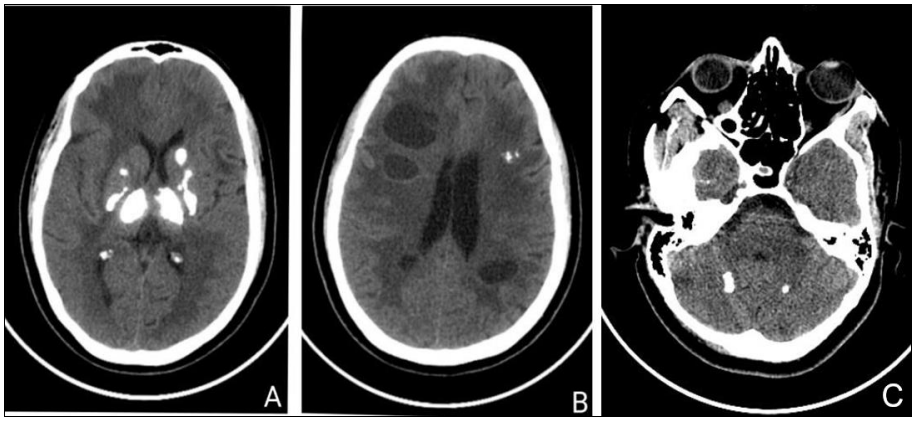

Fig 1: CT Axial sections (A) Image showing B/L calcifications involving Basal ganglia and Thalami. (B) Image showing ill-defined hypodensities and distorted lateral ventricles. (C) Image showing B/L calcifications involving Cerebellum

MRI

Multiple coarse areas of blooming (Suggestive of calcification) are seen in B/L basal ganglia, thalamus, cerebellum, and B/L high frontal and parietal lobe in the supra ventricular region. Diffuse confluent, symmetrical white matter hyperintensity is seen in B/L cerebral hemisphere extending up to sub-cortical U fibres but sparing those U fibres. Also, multiple well-defined cystic lesions are seen in B/L cerebral brain parenchyma largest measuring up to 2.7 x 2.6cm.

Few of the cyst shows incomplete wall enhancement and also multiple nodular areas of. enhancement is distributed symmetrically in B/L cerebral hemisphere Likely S/O Active demyelination.

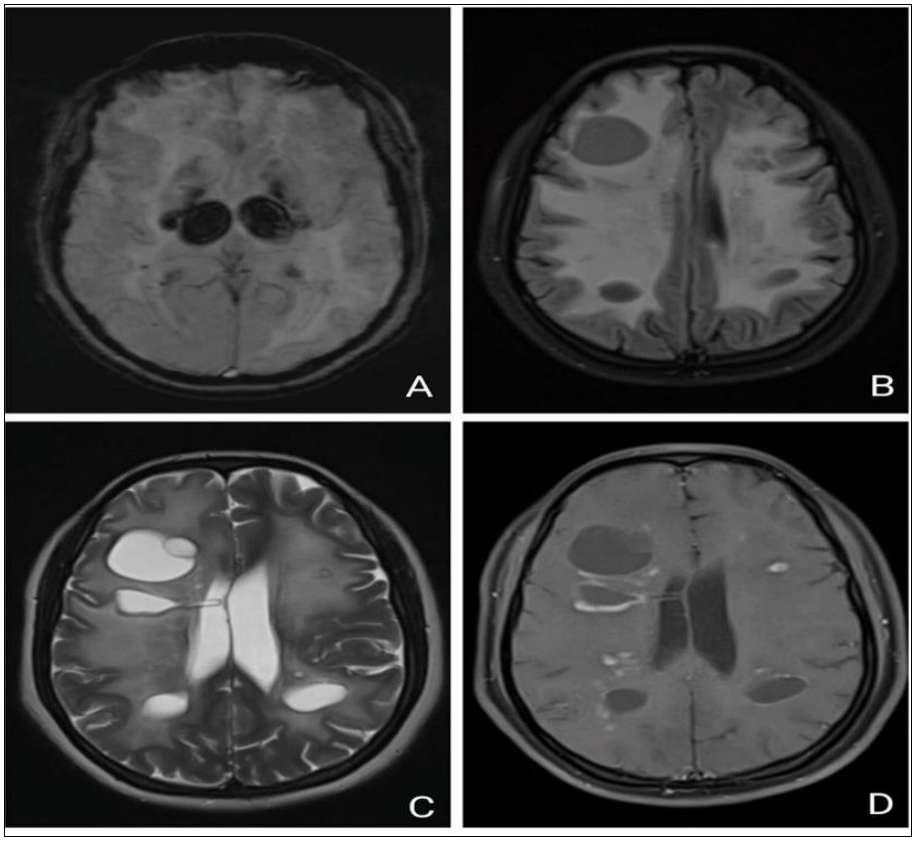

Fig 2: MRI axial section (A) SWI sequence showing area of blooming in B/L basal ganglia and thalami. (B) FLAIR sequence showing hypointense cystic areas with ill-defined diffuse white matter hyperintensity in B/L cerebral hemisphere (C) T2-W sequence showing hyperintense cystic areas with ill-defined diffuse white matter hyperintensity in B/L cerebral hemispheres (D) Post Gd contrast T1-W sequence showing multiple cystic areas with incomplete rim enhancement along with multiple nodular enhancing areas in the cerebral hemisphere.

Discussion

MLC was first reported by Singhal *et al* in 1991 from India in the Aggarwal community and was named and further studied by Knaap *et al* in 1995 by presenting a case series on eight children who had identical syndrome of cerebral leukoencephalopathy and megalencephaly with infantile-onset [1]. Although the median age of presentation for MLC is six months, it can present from birth to 25 years. In our case, the patient is being diagnosed at the age of 25 years although the symptoms were present and further progressing since adolescence. The most consistent feature with MLC in genetically proven cases is macrocephaly which is present in this case also. There are varying symptoms in cases of MLC. Clinical findings include slow- onset ataxia, seizures, late-onset mental deterioration, spasticity, sensory bladder, and even extrapyramidal symptoms are also evident in some cases [5]. MRI of the brain is usually the most useful diagnostic modality. Hallmark features of MLC in MRI Brain are diffuse white matter changes in the brain with the appearance of subcortical cysts in the temporal lobe and fronto- parietal subcortical area [4]. The number and size of these cysts can increase with time.

The differential diagnosis of the MLC is very limited, which includes Alexander Disease, Canavan's disease, Glutaric acid Type 1, infantile-onset GM2 gangliosides, and Tay Sachs disease [5, 9, 10]. Most of these conditions usually involve the basal ganglia, which is atypical for MLC. Moreover, most of the other leukoencephalopathies cause death early in childhood or adolescence, but MLC has a comparatively gradual course of progression, with life expectancy up to the 3rd-4th Decade of life [3]. Typical MRI findings with typical clinical presentation help us in clinching the diagnosis of MLC. There is no definitive available treatment for MLC. Patients are treated symptomatically with antiepileptics, acetazolamide, and physiotherapy.

Along with MLC, Bilateral striopallidodentate calcinosis also known as Fahr's disease (FD) is also observed in our case. Karl Theodor Fahr in 1930 reported the first case where a patient with neurodegenerative disorder presented with abnormal deposition of minerals (such as calcium) in brain parenchyma [11]. Benke *et al*. presented a case of Fahr's disease with severe neuropsychological manifestations and no movement disorders. After undergoing FDG-PET investigation, it is observed that there is a massive reduction of metabolism of glucose in bilateral basal ganglia, dentate nucleus, and also orbitofrontal and anterior cingulate gyrus which is correlating with the clinical picture and behavioural changes in that case [8]. Clinical symptoms in FD show heterogeneity. The typical clinical picture in the case of FD is neuropsychiatric symptoms along with movement disorders. But a case can present only with neuropsychiatric, i.e., behavioural changes, or can even be asymptomatic [6].

Fahr's disease usually presents in the elderly, however early onset presentation can occur, but with limited movement disorders [13]. CT scan of the brain is usually the most effective screening tool to observe brain calcifications. In our case, CT demonstrates extensive bilateral and symmetrical intracranial calcification at typical sites and MRI confirms those CT scan findings.

The differential diagnosis of FD includes hyperparathyroidism, hypoparathyroidism, pseudohypoparathyroidism, hypervitaminosis D, infections (tuberculosis, cytomegalovirus, toxoplasmosis, syphilis, influenza), systemic diseases (SLE, systemic Scleroderma) and calcified brain tumors [6, 7, 11]. Most of these diseases cause bilateral and asymmetric cerebral calcifications, mainly in the cerebellum and basal ganglia. Calcification in FD commonly occurs in the basal ganglia, dentate nucleus, cerebral cortex as well as cerebellar hemisphere, as was in our case. These deposits can be composed of calcium, phosphorus, carbonate, mucopolysaccharides, and metals including iron, copper, zinc, magnesium, and silver can also be found [14]. The diagnosis of Fahr's disease depends upon the neuroimaging (characteristic sites of calcification in the brain) and exclusion of other causes of intracranial calcification. There is no standard treatment available for FD. The goal of treatment is the management of symptoms. For Parkinson-like features, atypical antipsychotics are preferred over levodopa.

Conclusion

This is the rarest of the rare case of Van der Knaap disease in an ethnic group different from the usual Aggarwal community in Indian studies, in late adolescence (also not common) along with Fahr's disease (usual presentation is between 40 to 60 years of age) in a 25-year-old female. Characteristic MRI features, macrocephaly, cerebral symptoms, movement disorders, and psychotic symptoms, along with a clinical course of symptoms such as seizures and mental function deterioration are the key to diagnosis. So, Van der Knaap as well as Fahr's should be considered in the differential diagnosis of adolescents and adults with above mentioned features even when the patient is presenting only with neuropsychiatric symptoms and no neurological symptoms.

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Conflict of Interest

Not available

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