INTRODUCTION
Vanishing white matter (VWM) or childhood ataxia with central hypomyelination (CACH) disease was first described by Eickle in 1962 in a 36-year lady who presented with ataxia and amenorrhea. This was later identified as a clinico-MRI entity and is perhaps the most prevalent form of leucoencephalopathy in children with autosomal recessive pattern of inheritance. Pathophysiologically, VWM disease is associated with different mutations in e-IF2B, a gene which is responsible for protein synthesis, especially under stressful conditions. The disease has a bad prognosis and treatment is usually supportive especially during the times of cellular stress. The condition presented hereby has not been reported from Pakistan, previously.

CASE REPORT
A 19-year girl presented with one-month history of increasing quadriparesis, predominantly affecting the lower limbs, ataxia, headaches, behavioural problems, and failure to achieve menarche. She had a flu-like pyrexial illness in her early teens with subsequent gait abnormalities which were initially mild. Moreover, she never consulted a physician before. She denied any trauma, recent infection, illicit drug use or surgery. She had normal development as a child and achieved all the developmental milestones in time. She was good at academics.

On physical examination, she was in good health overall and all the vital signs were within normal limits. She had normal height and weight for her age. She had underdeveloped secondary sexual characteristics including small breasts and scarce pubic hair. She had limb weakness in pyramidal distribution with predominant involvement of the lower extremities and cerebellar signs. Her sensory and spinal examination was unremarkable. Fundoscopy was consistent with crescent formation around the temporal halves of both the discs (Figure 1). Rest of her history and clinical examination was normal.

Vanishing White Matter (VWM) Disease Presenting As Neuro-Ovarian Failure
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ABSTRACT
A 19-year girl was admitted with a one-month history of worsening spastic paraparesis, cerebellar ataxia, visual decline and worsening headaches on a background of walking difficulty, progressive quadriparesis and migraine since the age of 10 years. She had no sensory loss, and cranial nerves examination was notable for optic atrophy with crescent formation only. She had primary amenorrhea and underdeveloped secondary sexual characteristics. Ultrasonographic studies of the pelvis confirmed small ovaries, and uterus. The magnetic resonance imaging (MRI) of the brain showed diffuse leukodystrophy. A diagnosis of leuko-ovarian syndrome or vanishing white matter (VWM) disease was made on the basis of Van der Knaap criteria. To the best of their knowledge, the authors are most probably reporting the first ever case of this rare clinical entity from Pakistan with special focus on its diagnostic and management challenges in the light of limited retrospective case reviews.

Key Words: Vanishing white matter. Leukodystrophy. Primary amenorrhea. Leuko ovarian syndrome. Van der knaap criteria. Optic atrophy.

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Figure 1: Slit lamp photograph of the left optic disc showing grey crescent formation at the temporal half (taken with permission of the patient).
She was extensively investigated for her neuro-ovarian features and an MRI brain/spine was notable for diffuse and extensive loss of cerebral white matter primarily affecting the frontal lobes and thinning of the corpus callosum. The pituitary gland was reported to be normal (Figure 2). The ultrasound abdomen and pelvis showed very small ovaries and uterus for age. The hormonal assay showed elevated FSH (60.4 mIU/ml) and LH (17.1 mIU/L) and very low estrogen, findings consistent with primary ovarian failure. Rest of the anterior pituitary hormones and biochemical studies including liver and renal function tests, blood sugar and thyroid function tests were perfectly normal. So considering the clinical evidence of her neurological and gynecological features coupled with an MRI brain consistent with diffuse leukodystrophy and biochemical proof of primary ovarian failure, a cumulative diagnosis of vanishing white matter (VWM) disease was made on the basis of clinical and radiological criteria suggested by Van der Knaap. The genetic tests for eukaryotic initiation factor 2-B (e-IF2B) were not carried out due to lack of facility in our setup and the affordability issues on the part of the patient. The patient received a short course of intravenous steroids with minimal improvement. She was advised regular follow-ups.

**DISCUSSION**

Childhood ataxia with central nervous system hypomyelination/vanishing white matter disease (CACH/VWM) can present with ataxia, spasticity, and variable optic atrophy in combination with primary ovarian failure; hence, also called as leuko-ovarian dystrophy. The disease spectrum ranges from an aggressive prenatal, infantile and an early childhood onset forms (onset age 1 - 5 years) to a relatively more insidious late childhood/juvenile onset (onset age 5 - 15 years) and adult onset phenotypes. This patient had a diagnosis of adult onset variant of VWM disease.

Adult onset variant of VWM disease is mildest amongst the different phenotypes of the disease. This presents with a combination of neurological features, especially spasticity and ovarian failure with preserved cognitive function at least initially. The treatment is usually supportive and there is some controversy regarding the use of steroids in such patients. This patient had both focal neurology and primary ovarian failure at presentation and she received a short course of intravenous steroids with minimal improvement.

VWM disease is caused by mutations in a gene called eukaryotic initiation factor 2B (e-IF2B), which is thought to be responsible for protein synthesis, especially under the conditions of cellular stress. This explains why this disease is triggered or flared up by infections, surgery or head trauma. In this patient, we did not have the genetic confirmation due to lack of the facility of the genetic diagnosis in our setup.

Abnormalities on MRI brain may precede the neurological features of the disease. A typical MRI shows diffuse and extensive loss of cerebral white matter, thinning out of the corpus callosum, internal capsule, and pyramidal tract. Cerebral and cerebellar atrophy is common but brainstem is rarely involved. The MRI brain in this patient showed all these findings and the authors plan to follow this patient clinically and with serial MRIs brain to know more about this rare clinical entity.

**REFERENCES**