A typical episode of BRIC usually starts with pruritus which increases in intensity and impairs the quality of life followed by jaundice as seen in our series [4]. The symptoms may persist from 2 weeks to 18 months before spontaneous resolution and asymptomatic period may vary from 1 month - 33 years [3]. Low GGT, a hallmark biochemical finding in this metabolic disorder in spite of clinical and biochemical stasis excludes all the intra- and extra- hepatic causes of cholestasis except bile acid synthesis defect (BASD). However, in BASD, itching is not common and low GGT occurs with normal level of bile acids. The characteristic changes seen in liver biopsy in BRIC are the intracanalicular cholestasis with lobular inflammation without fibrosis, which was seen in all the 6 patients, thus satisfying the diagnostic criteria [5]. PFIC1 and BRIC 1 share the same genotype but have different phenotypes, the former being universally progressive. *ATP8B1* gene is a translocator present on canalicular membrane of hepatocytes and mutation leads to membrane instability and decreased function of bile salt export pump thereby resulting in cholestasis. Missense mutations are most common in BRIC type 1 [6] (seen in patient 1 and 2) and can either be homozygous (patient 2) or compound heterozygous mutations (patient 1). However, Lee, et al. [7] have reported a similar phenomenon of heterozygous frame shift mutation only on one allele of *ATP8B1* gene. Cholestyramine, UDCA and rifampicin have been used in various combinations for the treatment of pruritus and in our experience, neither cholestyramine nor UDCA worked well while rifampicin alone gave a sustained relief in one patient. Rifampicin, though considered as hepatotoxic, works well in BRIC by activating transcription of CYP3A4, thereby stimulating hydroxylation of bile salts and excretion at the basolateral membrane, thereby relieving pruritus [8]. Endo-scopic nasobiliary drainage [9], biliary diversion procedures [10], plasmapheresis and liver transplant have been suggested for refractory pruritus.

This case series highlights the paradoxical perceptions in diagnosis and management of BRIC, namely low GGT in spite of cholestasis and use of rifampicin-a hepatotoxic drug, inspite of underlying liver disease.

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Diabetes Mellitus Due to Wolfram Syndrome Type 1 (DIDMOAD)

Wolfram syndrome (WFS) type 1 is a monogenic disorder with autosomal recessive inheritance caused by mutations in *WFS1*, a gene (location 4p16.1) associated with endoplasmic reticulum function in neuronal and endocrine cells [1]. WFS is also known as DIDMOAD syndrome and is characterised by Diabetes insidipus (DI), Diabetes mellitus (DM), Optic atrophy (OA), and Deafness (D). Here, we report 5 unrelated Indian children presenting to us over the last 2 years with a referral diagnosis of type 1 diabetes mellitus (T1DM), subsequently diagnosed to have DIDMOAD syndrome. We also highlight atypical presentations and early pointers to the disease.

A 9-year-old girl was diagnosed to have T1DM 2 years back and was on insulin therapy. She presented with decreased visual acuity and polyuria (urine output 4 L/day) that persisted despite good glycemic control. On evaluation, urine osmolality was 158 mosmol/L and serum osmolality was 302 mosmol /L. Urine osmolality increased to 280 mOsm/L with intravenous vasopressin suggestive of central DI. Magnetic resonance imaging (MRI) brain revealed an absent pituitary bright spot. Detailed evaluation revealed hydroureteronephrosis, neurogenic bladder, bilateral optic atrophy and bilateral moderate sensorineural hearing loss. Direct sequencing of *WFS1* gene by Sanger method, revealed a novel homozygous variant frame shift mutation c.2486_2489dupTGGA (p.Glu830Asp*111) in exon 8. She was managed with oral desmopressin tablets, clean intermittent urinary catherization and continued on insulin therapy.

Five patients (3 males) with WFS type 1 were identified with the mean (SD) age of 11 (2) years. There was no family history or consanguinity in the parents. All patients had DM and OA. DI was present in 4 patients and hearing impairment and urological abnormalities in 3 patients each. All cases had normal stature except one, and all were pre-pubertal except case 3. Case 3 presented at 13 years with DM since 4 years, polyuria (despite adequate glycemia) and visual problems. Eye examination revealed optic atrophy and glaucoma. She was diagnosed to have central DI and started on desmopressin. On follow-up, she had delayed puberty (absent menarche till 16 years with SMR stage 3). The baseline gonadotropin levels were LH 1.09 mIU/mL and FSH 6.37 mIU/mL, and levels post-GnRH stimulation LH 20.6 mIU/mL and FSH 28.6 mIU/mL.

Thyroid function tests were done in all children and were found to be within normal limits. Case 3 reported compound heterozygous missense/frameshift mutation in exons 4/8 c.397G>A/c.1234_1237delGTCT (p.A133T/p.V412Sfs29). Case 2 revealed a homozygous deletion Exon 8 c.1525_1539 del15 (p.V509_Y513del) on genetic analysis by Sanger method and Case 4 revealed a novel homozygous variant missense mutation Exon 8 c.1372G>A (p.A458T). No mutation was identified in Case 5.

WFS is a rare neuro-degenerative autosomal recessive disease that was first described in 1938 [2]. Its prevalence was estimated to be 1 in 68,000 to 1 in 770,000 [2,3]. Apart from these common manifestations, screening for urological and psychological abnormalities, and endocrine disorders is paramount, as they often remain unnoticed, adding to disease morbidity. The minimum diagnostic criteria of WFS are the coincidence of early-onset DM and OA [2]. There is no effective treatment for this neurodegenerative disease with reports suggesting a median life expectancy of 30 years [2]. Death usually occurs from respiratory failure as a result of brain stem atrophy.

DM is usually the first manifestation of the disease. A multicentric study conducted by Rohayem, et al. [4] described notable differences between the diabetes of WFS and TIDM including earlier median age of onset of diabetes, less incidence of diabetic ketoacidosis at onset, a much lower insulin requirement, rare micro-vascular complications, and absence of autoantibodies in the former. The mean (SD) age of diagnosis of DM in our study was 8.2 years (2) with none of patients having diabetic ketoacidosis at presentation.

Diabetes insipidus appears at an average age of 14 years and affects approximately 70% of patients [3]. About 80% of the patients in our study had DI, which is consistent with the literature. The diagnosis is often delayed as polyuria and polydipsia are overlapping symptoms of both DI and DM.

Patients with WFS demonstrate progressive optic atrophy that usually occurs after diagnosis of DM. Other ophthalmological findings reported are colour vision deficits, cataract and pigmentary retinopathy [5]. All patients in our case series had optic atrophy, whereas glaucoma and cataract were present in two and one patient, respectively.

Bladder dysfunction in children and young adults with WFS is common and easily missed (only 30% symptomatic), and can be initial presenting feature as was seen with two of our cases. Structural and functional urinary tract abnormalities are commonly seen including atonic bladder, bladder-sphincter dyssynergia, hydro-ureteronephrosis, and recurrent urinary tract infections [6].

Patients with DIDMOAD have been reported to have growth failure due to defects in hypothalamic pituitary function [6] and hypogonadism, therefore follow-up of these patients is essential. Neurological complications generally appear in later life at a median age of 30 yrs (range 5-44yrs) and include truncal ataxia, loss of gag reflex, myoclonus, epilepsy, peripheral neuropathy and central apnea [1]. Psychiatric manifestations including depression, psychosis and aggression are also common and should be screened for.

In conclusion, our case series highlights a lack of awareness among physicians about this entity, culminating into under and delayed diagnosis of this disorder. There is a need to have a high index of suspicion for the diagnosis of DIDMOAD syndrome in patients with T1DM presenting with other systemic involvement. Patients with DIDMOAD should be screened for other associated problems and require multi-disciplinary care [6]. Since this is a neurodegenerative disorder with poor prognosis, it is prudent to provide appropriate genetic counselling and offer prenatal diagnosis for prevention in future pregnancies.

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