PLA2G6-Associated Dystonia Parkinsonism

Phospholipase-associated Neurodegeneration (PLAN) with *PLA2G6* mutation comprises a continuum of three phenotypes with overlapping clinical and radiological features. The spectrum comprises typical Infantile neuroaxonal dystrophy (INAD) also known as Seitelberger disease, atypical neuroaxonal dystrophy (ANAD) and more recently described entity *PLA2G6*-associated dystonia parkinsonism (PLAN-DP). We, herein, report an adolescent with PLAN-DP.

A 14-year-old boy, product of a non-consanguineous marriage and with a normal birth and developmental history, presented with difficulty in walking from last one year. Parents noticed dragging of the left leg while walking with short steps. This was followed by stiffness of both the legs and arms with frequent falls on left side while walking along with dystonic posturing of left leg. Patient developed generalized slowness with decreased arm swing, unable to close fist and poor interest in surroundings. Patient was unable to sit and stand after one year of onset of illness along with poor speech in form of decreased phonation and articulation. There were no psychiatric or behavioral changes. There were no other affected family members with a similar illness.

On examination, patient was conscious and oriented but lacking emotional expression on the face. Generalized bradykinesia was present involving trunk and all four limbs. Motor examination revealed cogwheel rigidity with exaggerated deep tendon reflexes and positive Babinski sign. Sensory, cranial nerve and cerebellar examination were normal. Kayser-Fleischer ring was not detected, and fundus evaluation was normal. Patient developed urgency and incontinence of urine during his course of illness. On the basis of clinical diagnosis of neurodegeneration with extra pyramidal symptoms a differential diagnosis of Wilson disease, dopa-responsive dystonia (Segawa disease), pantothenate kinase-associated neurodegeneration (PKAN), hypoparathyroidism and mitochondrial disorder were considered and evaluated for.

Brains magnetic resonance imaging MRI showed T2 hyper intense shadow in the insular cortex and some part of temporal lobe but no evidence of T2-weighted hypo-intensities in the basal ganglion and substantial nigra. There was no evidence of cerebellar atrophy or brainstem involvement. All laboratory tests including serum biochemistry, liver and thyroid function test, serum ceruloplasmin, and 24-hour urinary copper excretion were within normal limits. Direct gene sequencing revealed a homozygous missense variation in exon 16 of the *PLA2G6* gene (chr22:g.38508565C>T; Depth: 315x) which resulted in the amino acid substitution of Glutamine for Arginine at a codon 741(p.Arg741Gln; ENT00000332509.3). The mutation was previously described as pathogenic (rs121908686) and is present in ExAC database with very low frequency (0.0002277). Patient was put on levodopa which resulted in dramatic improvement in motor symptoms and speech. He is under follow-up and sustaining good response to drugs.

Paisan-Ruiz, et al. [4] described 23 patients of PLAN-DP from 16 pedigrees [3,4], with youngest age of onset of 4 years and the oldest 37 years. Dystonia and parkinsonism were seen uniformly but neuropsychiatric and cognitive decline were seen invariably as initial presentation in adult-onset disease. Autonomic dysfunction, specifically urinary symptoms have been observed frequently as in this case and may be an important clue in diagnosis. Kapoor, et al. [5] in a review discussed the genetic analysis of *PLA2G6* in 22 Indian families with phospholipase-2 associated neurodegeneration. This mutation was found in 12/22 (54.55%) families with INAD and ANAD which again suggest variable phenotypic expression of this disorder. Majority of families presented with INAD/ANAD and only one family presented with PLAN-DP, but was negative for this mutation.

In our patient, MRI showed no evidence of hypointensity in globus pallidus and substansia nigra; although, PLAN has been consistently reported to have neurodegeneration with brain iron accumulation. Iron accumulation was found in only eight patients (33%) in a previous review of 23 patients, which is less than what is reported in INAD (40-50%). The process of iron accumulation; however, is not well described.

The protein product of *PLA2G6*, phospholipase–A2 group VI (iPLA2-IVA) is an enzyme involved in the metabolism of glycerophospholipids and it plays an important role in inner mitochondrial membrane homeostasis [8].

In conclusion, PLAN-DP is characterized by remarkably heterogeneity in presentation and at present no specific clinical criteria are there to pinpoint the diagnosis but the early onset dystonia parkinsonism with psychiatric symptoms, speech deterioration, cognitive changes, autonomic dysfunction, iron deposition in MRI and response to levodopa is suggestive towards this differential diagnosis and these children should be evaluated for *PLA2G6* mutation.

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REFERENCES

1. Seitwelberger F. Neuroaxonal dystrophy: Its relation to aging and neurological disease. *In:* Vinke PJ, Bruyn GW, Klawans III, editors. Handbook of clinical neurology, Extrapyramidal disorders. Vol 5 (49), Elsevier Science, 1986. p. 391-415.
2. Paisan-Ruiz C, Bhatia KP, Li A, et al. Characterization of *PLA2G6* as a locus for dystonia-parkinsonism. Ann Neurol

2009; 65:19-23.
3. Karkherian S, Shahidi GA, Walker RH, Paisan-Ruiz. *PLA2G6*-associated dystonia-Parkinsonism: Case report and literature review. Tremor Other Hyperkinet Mov. 2015;5:317.
4. Bower MA, Bushara K, Dempsey MA, Das S, Tuite PJ. Novel mutation in siblings with late onset *PLA2G6*-aasociated neurodegeneration (PLAN). Mov Disord 2011; 26:1768-9.
5. Kapoor S, Shah MH, Singh N, et al. Genetic analysis of *PLA2G6* in 22 Indian families with infantile neuroaxonal dystrophy, atypical late onset neuroaxonal dystrophy and dystonia parkinsonism complex. PLoS One. 2016;19:11.
6. Kurain MA, Haylick SJ. Pantothenase kinase-associated neurodegeneration (PKAN) and *PLA2G6* associated neurodegeneration (PLAN). Review of two major neurodegeneration with brain iron accumulation (NBIA) phenotype. Int Rev Neurobiol. 2013;110:49-71.
7. Paisan-Ruiz C, Li A, Susanne A, et al. Widespread Lewy body and Tau accumulation in childhood and adult onset dystonia-parkinsonism cases with *PLA2G6* mutation. Neurobiol Aging. 2012;33:814-23.
8. Balsinde J, Balboa MA. Cellular regulation and proposed biological function of group VI A calcium independent phospholipase A2 in activated cells. Cell Signal. 2005; 17:1052-62.

Takotsubo Cardiomyopathy in Pediatric Scrub Typhus

Takotsubo Cardiomyopathy or stress cardiomyopathy is a heart failure syndrome characterized by transient left ventricular dysfunction with typical regional wall motion abnormalities [1]. The wall motion abnormalities are not confined to the vascular distribution of a single epicardial coronary artery; hence, non-ischemic mechanisms are considered responsible. Initially described in adult women with emotional stress as 'broken-heart syndrome', it was subsequently recognized in both males and females. Takotsubo cardiomyopathy has been reported rarely in children. We describe a case of Takotsubo cardiomyopathy associated with sepsis in a child.

A 10-year-old boy presented with complaints of high-grade fever since four days and fast breathing and poor oral intake since one day. On examination, he had tachycardia, hypotension, respiratory distress, generalized edema and hepatomegaly. High-flow oxygen, intravenous fluids and inotropes were started (noradrenaline followed by dobutamine). Laboratory investi-gations revealed a C-reactive protein of 101 mg/L. As clinical and laboratory features were suggestive of severe sepsis, intravenous antibiotics were started. Since hypotension persisted, 2D echocardiogram was done, which showed mid-ventricular regional wall motion abnormality (**Fig. 1a**), with normal contractility of cardiac apex (**Fig**. **1b**) and mild mitral regurgitation. ECG showed mild ST elevation in lead V2. Troponin level was mildly elevated (16.4 ng/L), and B-type natriuretic peptide (BNP) markedly elevated (15725 pg/mL). In view of a diagnosis of Takotsubo cardiomyopathy, noradrenaline was tapered and diuretic drugs were prescribed. A repeat echocardiogram after three days showed normalization of left ventricular function and resolution of mitral regurgitation. Repeat ECG showed T wave inversion in V2. Work-up for persistence of fever spikes and thrombocytopenia revealed negative dengue serology, and positive result for OX K antigen on Weil Felix test The child showed improvement on oral Doxycycline and was discharged without any cardiac medications by ninth day of hospitalization.

Takotsubo cardiomyopathy is a reversible heart failure syndrome. It derives its name from the shape of the left ventricle in the typical apical-ballooning form, which resembles a Japanese octopus-trap. Four common morphological variants have been described [1]. In younger patients, a high proportion of non-apical anatomical variants are seen [2]. Our case was of the mid-ventricular type, with hypokinesia of the mid-ventricle and sparing of the apex.

Distinguishing Takotsubo syndrome from acute infective myocarditis can be challenging. However, involvement in Takotsubo cardiomyopathy shows typical regional pattern whereas in myocarditis it tends to be diffuse, and it shows a low or moderate troponin rise while there is frequently a significant rise in troponin in myocarditis [1]. The differential diagnosis includes sepsis-induced cardiomyopathy, but in the latter too, there is global involvement and enlargement of the ventricle, as opposed to regional affection in the former [3].

Regional wall motion abnormality of Takotsubo cardio-myopathy requires differentiation from acute coronary syndrome, a less common entity in children. Characteristically laboratory evaluation shows an extremely elevated BNP and mild troponin elevation. In contrast, in coronary ischemia, the degree of BNP elevation is typically lesser than in Takotsubo cardiomyopathy, troponin is significantly elevated and ECG and echocardiographic wall motion abnormalities are confined to the vascular distribution of epicardial coronary arteries [4]. ECG in Takotsubo cardiomyopathy may show non-specific ST changes, with later development of T wave inversion, as seen in our case, or even QTc prolongation [1]. Cardiac magnetic resonance during the acute phase may help differentiate Takotsubo cardiomyopathy from both, myocarditis as well as acute myocardial infarction [2].

Sepsis has been widely described in adults as a cause for Takotsubo cardiomyopathy, with a causative organism identifiable in culture in up to 50% of admissions [5]. Our search of English language scientific literature did not reveal any report of this disorder in pediatric sepsis following scrub typhus infection. There is a possibility that scrub typhus as a cause is