THE KOREAN SOCIETY OF NEPHROLOGY
APCN & KSN 2024
June 13(Thu) - 16(Sun), 2024 Coex, Seoul, Korea
Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

Abstract Submission No.: A-0366

Thrombotic microangiopathy in a child with coenzyme q10 deficiency associated glomerulopathy

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Case Study : Background Thrombotic microangiopathy (TMA) defines a group of disorders characterised by microangiopathic haemolytic anaemia, thrombocytopenia, and organ dysfunction, commonly acute kidney injury. Injury of the vascular endothelium is central to the pathogenesis of TMA. We hereby report a case of familial TMA in a Chinese boy with primary CoQ10 deficiency and confirmed COQ6 mutation. Case presentation A Chinese boy presented with steroid-resistant nephrotic syndrome at 8-month-old and went into end-stage kidney disease requiring peritoneal dialysis 7 months later. Whole-exome sequencing revealed compound heterozygous mutations in COQ6 (NM_182476.3) gene c.427G>A p.(Val143Met) and c.1335G>T p.(Arg445Ser), and primary CoQ10 deficiency was subsequently confirmed in skin fibroblasts. At 25 months, he presented with acute onset of respiratory failure and hypertensive encephalopathy, together with the triad of microangiopathic haemolytic anaemia, thrombocytopenia, and acute kidney injury. TMA was diagnosed and he was initiated on therapeutic plasma exchange and bridged to eculizumab. While on eculizumab for one year with full complement suppression, he had a TMA relapse at four. Eculizumab was taken off at 4-year-old for questionable efficacy, and the patient remained relapse-free for more than 3 years. The older sister of our index patient succumbed to multi-organ failure with histological evidence of TMA when she was four. Retrospective genetic analysis revealed the same compound heterozygous mutation in the COQ6 gene. Discussion This is the first report of familial TMA in a patient with primary CoQ10 deficiency caused by COQ6 genetic variant. The exact mechanism of mitochondrial cytopathy leading to TMA remains unknown. We postulated that mitochondrial dysfunction and severe hypertension contributed to endothelial cell injury, followed by complement activation which contributed to TMA. It should be noted that although C5 inhibitors are recommended as the first line therapy for suspected complement-mediated TMA, patients with C5 inhibitor resistant TMA should be re-evaluated with alternative pathogenic causes.

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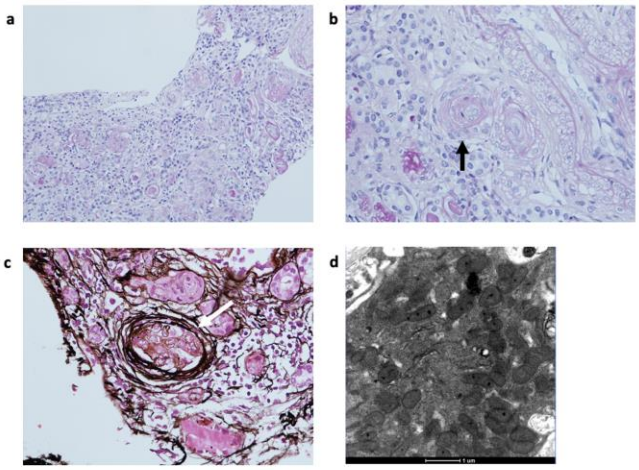
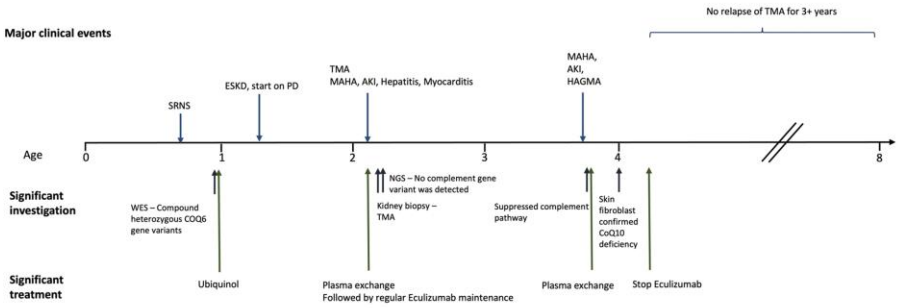


a) PAS stain showing chronic changes with global glomerulosclerosis and marked tubular atrophy
b) Arteriolar narrowing with swollen endothelial cells and lamination (black arrow)
c) Silver stain shows segmental tramlines and an arteriole with edematous wall and swollen endothelial cells (white arrow)
d) Electron micrograph showing a few dense core materials in mitochondria
PAS = Periodic acid-Schiff staining

Family History –
Elder sister – aHUS with multi-organ failure
Deceased at age of 4
Retrospective genetic evaluation – Shared same compound heterozygous variants in COQ6 genes



AKI = Acute kidney injury; CoQ10 = Coenzyme Q10; ESKD = End-stage kidney disease; NGS = Next generation sequencing; MAHA = Microangiopathic haemolytic anaemia; PD = Peritoneal dialysis; SRNS = Steroid-resistant nephrotic syndrome; TMA = Thrombotic microangiopathy ; WES = Whole exome sequencing

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Laboratory variables (unit)	Result	Reference values
Haemoglobin (g/dL)	7.1	11.0 – 14.0
White blood cell (10^9/L)	7.2	5.0 – 15.0
Platelet (10^9/L)	84	200 – 490
Neutrophil (10^9/L)	6.1 (84.1%)	1.5 – 8
Lymphocyte (10^9/L)	0.7 (9.8%)	6.0 – 9.0
Monocyte(10^9/L)	0.3 (0.3%)	0.2 – 1.0
Peripheral blood film	Schistocytes presents	
LDH (U/L)	2376	198 – 327
Na (mmol/L)	136	134 – 144
K (mmol/L)	4.6	3.4 – 4.6
Urea (mmol/L)	29.0	3.2 – 7.9
Creatinine (μmol/L)	616	15 – 31
Calcium (mmol/L)	2.20	2.22 – 2.53
Phosphate (mmol/L)	3.67	0.96 – 1.86
ALT (U/L)	5372	11 – 30
ALP (U/L)	126	104 – 345
Bilirubin (μmol/L)	30	5 -21
pH	7.22	7.35 – 7.45
HCO3- (mmol/L)	10.4	22.0 – 26.0
Lactate (mmol/L)	3.5	0.5 – 2.2
CK (U/L)	11443	4 – 190
hsTnI (ng/L)	23976	<= 21
Prothrombin time (sec)	22.2	9.7 – 12.1
APTT (sec)	30.4	27.0 – 38.0
Haptoglobin (g/L)	< 0.04	0.07 – 1.63
CRP mg/L	12	< 5.0
Complement 3 (g/L)	0.43	0.83 – 1.52
Complement 4 (g/L)	0.07	0.13 – 0.37
ADAMT13 activity (%)	44%	70 – 160%
ADAMT13 antigen (ng/ml)	240	430 - 979
ADAMTS13 Autoantibody	0.7	< 15 units/ml
Complement function analysis		
Classical pathway (%)	15	74 – 151
Alternative pathway (%)	Unquantifiable low activity	
C3d (mU/L)	86	< 40
sC5b-9 (ng/ml)	284	58 – 239
Factor H (μg/ml)	245	284 – 528
Factor I (μg/ml)	18	18 - 48
Anti-factor H1 U/ml	< 10	<10
Microbiological work-up		
Blood culture	No growth	
Nasopharyngeal aspirate Nucleic acid testing	Common respiratory viruses not detected	
Stool	No usual enteric pathogen isolated	
Urine pneumococcal antigen	Negative	
Metabolic work-up		
Dried blood spot metabolic test	Normal plasma amino acids and homocysteine levels	
Urine metabolic profile	No hyperexcretion of methylmalonic acid Detected moderate hyper-excretion of 3-Methylglutaric acid and 3-Methylgluaconic acid	
Genetic work-up (subsequent analysis)		
Complement gene	Negative for C3, C4BPA, C5, CD46, CD55, CD59, CFB, CFD, CFH, CFHR1, CFHR3, CFHR4, CFHR5, CFI, CFP, DGKE, MMACHC gene	