Kabuki syndrome and Metachromatic Leukodystrophy, dual diagnosis in a female patient: a case report

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BACKGROUND

"Kabuki make-up" (Niikawa) Syndrome (NS) is a rare multisystem disorder caused by heterozygous pathogenic variants in the KMT2D (OMIM #602113) gene for type 1 (OMIM #146920) and KDM6A (OMIM #300128) gene for type 2 (OMIM #300867). Characteristic features include: microcephaly, intellectual disability, distinctive facies, short stature, cardiovascular, skeletal, genitourinary, and gastrointestinal anomalies.

Arylsulfatase A deficiency, or metachromatic leukodystrophy, (MLD; OMIM #250100) is an autosomal recessive condition caused by homozygous or compound heterozygous pathogenic variants in the ARSA (OMIM #607574) gene. The condition may present in several forms delineated by age of onset. In late-infantile onset MLD (before 30 months), infants present with early developmental and milestone abnormalities followed by major progressive neurologic deterioration. Adult onset MLD (after 16 years) presents with declining academic performance, emotional instability, psychosis, and other neurologic features.

FEATURES	NS TYPE 1	LATE INFANTILE MLD	ADULT MLD	PATIENT
Postnatal growth deficiency	+			
Global delays	+			+
Mild-moderate intellectual disability	+			
Dysmorphic facies	+			+
Large cupped ears	+			+
Weakness/hypotonia		+	+	+
Falls/toe-walking		+		
Dysarthria		+		
Cognitive/motor complications		+	+	+
Personality/emotional changes			+	
Neurological abnormalities		+	+	+
Performance changes			+	
Skeletal anomalies	+			+
Persistence of fetal fingertip pads	+			
Congenital heart defects	+			+
GU/GI anomalies	+			+
Renal aberrations	+			+
Ophthalmologic abnormalities	+	+		
Cleft and/or lip palate	+			
Orthodontic anomaly	+			+
Susceptibility to infections and autoimmune disorders	+			+
Seizures	+	+	+	
Endocrinologic abnormalities	+			
Hearing loss	+	+		
Feeding problems	+			+

CASE PRESENTATION

A female patient was born at 39 weeks to a 27-year-old G2P1>2 mother and 27-year-old father, after an uncomplicated pregnancy. Family history is significant for developmental delay and ADHD in her brother, and bipolar disorder in her mother.

At 8 weeks of age, she presented for evaluation of microcephaly, dysmorphic features, scoliosis, bilateral clinodactyly V, hypotonia, bicuspid aortic valve, and feeding difficulties requiring G-tube placement.

Karyotype was normal. SNP microarray revealed two variants of uncertain significance: a 75 kbp microduplication at 8p22 and a 510 kbp microduplication at 9q32. She returned at 27 months with global developmental delays added to the phenotype. Whole exome sequencing revealed a heterozygous pathogenic variant in KMT2D p.R1757* (c.5269C>T), with compound heterozygous pathogenic variants in ARSA: p.I181S (c.542T>G) and intronic c.465+1G>A, consistent with a diagnosis of both Niikawa (Kabuki) syndrome type 1 and MLD.

While already presenting with a depressed level of enzyme activity, as predicted in MLD, the patient had no associated symptoms at 8 years old.

CONCLUSION

While both Kabuki syndrome and metachromatic leukodystrophy are well established within the literature independently, a combination of these two distinct and unrelated abnormalities has never been reported.

Molecular testing and genetic counseling are essential as a consideration for patients and their families in cases entailing severe neurodevelopmental phenotype, characteristic facial features, and congenital anomalies, especially in cases where a complex phenotype may be attributed to more than one genetic condition with differing prognoses.

REFERENCES

Adam MP, Hudgins L, Hannibal M. Kabuki Syndrome. 2011 Sep 1 [Updated 2022 Sep 15]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022.

Gomez-Ospina N. Arylsulfatase A Deficiency. 2006 May 30 [Updated 2020 Apr 30]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022