Bilateral Sensorineural Hearing Loss in AKT3 Mutation: A Case Report and Brief Review of the Literature

Dear Editor,

Strengthening knowledge in neurogenetic field has led to increased use of high-throughput sequencing methods allowing scientists to identify the molecular etiologies of many megalencephaly syndromes, of which the phosphatidylinositol-3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) signaling pathway has been a topic of serious interest.[1] The genes *PIK3R2*, *AKT3*, and *PIK3CA* are main regulators of this pathway. To date, megalencephaly associated with *AKT3* gene mutation has been described in 21 cases; five of whom were reported to have 'non-syndromic' megalencephaly, a condition without the distinctive hallmarks of defined megalencephaly syndromes but only non-specific neurodevelopmental features including autism and intellectual disability.[1,2] We report a case of non-syndromic megalencephaly due to the *AKT3* mutation with sensorineural hearing loss (SNHL), a feature which was never reported before, with a brief review of the literature.

A 19-month-old male patient was presented with large occipitofrontal head circumference (OFHC). The patient was born at the 40th gestational week with a weight of 4110 grams and OFHC of 38.9 cm (99.74th percentile, SDs: +2.79) and had no postnatal adaptation problems. No regression but marked delay in neuromotor developmental stages was reported; head control and sitting without support were achieved at 11 and 17 months, respectively. Canonical babbling was reported to start at the age of 18 months. There were no meaningful words. Neurological examination revealed a large head (OFHC: 54 cm, >99.98th percentile, SDs: +3.6), prominent forehead, axial hypotonicity, and hyperlaxity. There were venous lines on the bilateral forehead, more prominent on the right. Head circumferences of both parents were within normal limits. The left ear failed in the transient evoked otoacoustic emission test, leading to further investigation with click-stimulating auditory brainstem response test at 70 dBnHL intensity which revealed that I., III., and V. absolute wave latencies and interwave latency differences were compatible with

normative data and I/V amplitude ratio was >1 in both ears. A click stimulus from the right ear revealed a V wave within the normal intensity-latency curve up to 20 dBnHL intensity, consistent with very mild sensorineural hearing loss. The V wave in the left ear within the normal intensity-latency curve was up to 35 dBnHL with click stimulus, while 55 dBnHL at 500 and 1000 Hz with tonal burst stimuli, demonstrating mild sensorineural hearing loss. Brain and spinal MRIs were normal except for a Rathke's cleft cyst [Figure 1]. Chromosome analysis, array-based comparative genomic hybridization, and 579 gene-inherited panel analysis genes were inconclusive. At age of four, independent walking started, but the patient was still unable to use meaningful words. Head circumference was 57.5 cm (>99.98th percentile, SDs: +3.99). Hyperlaxity in the first examination was not observed in this evaluation. Denver II developmental screening test revealed global developmental delay with each domain below -3 standard deviations. Whole exome sequencing revealed previously reported pathogenic c.237G>3 (p.Trp79Cys, W79C) change in the fourth exon of the *AKT3* gene which is associated with megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 2 (MPPH 2; OMIM#615937). Confirmation of this change was made by Sanger sequencing. Segregation analysis with parental DNA samples indicated that the variant occurred *de novo*. The patient who had only megalencephaly and global developmental delay (GDD) without other clinical and radiological distinguishing features of MPPH 2 was diagnosed with non-syndromic megalencephaly. Parental consent for publication was obtained.

The PI3K-AKT-mTOR signaling pathway consisting of 254 components with 478 links regulates a wide range of cellular functions including growth, neuroplasticity, and neurodevelopment via the functions of four genes: *PIK3R2*, *AKT3*, *CCND2,* and *PIK3CA*.[3] The *AKT3* gene encodes AKT3 protein, the well-known major downstream mediator of PI3K signaling. MPPH types 1, 2, and 3, all of which are inherited in an autosomal dominant pattern, are caused by the *PIK3R2*, *AKT3*, and *CCND2* mutations, respectively. To our knowledge, only 63 patients with MPPH were reported to date.[2] Besides its rarity, another feature complicating the diagnosis is substantial variation in clinical findings; such that megalencephaly and polymicrogyria are proposed to be basic diagnostic necessities.[2] Polydactyly and hydrocephalus, nonetheless, are complementary findings. In our patient, although the combination of megalencephaly, GDD, and transient hyperlaxity made the MPPH a suitable candidate, this diagnosis was excluded since megalencephaly and pituitary cyst were only radiological findings.

In a study to prove the association of SNHL with the auditory hair cells (HC) degeneration, PI3K signaling was demonstrated to mediate HC survival.[4] Furthermore, inhibition of nuclear factor-kappa B, the major downstream effector of AKT, leads to HC loss with changes in PI3K signaling.[5,6] To support the claim of these indirect links between AKT and hearing loss, activated AKT was detected in cochlea of guinea pigs, demonstrating the role of AKT3 in inner ear physiology.[7] However, the precise physiological mechanism of AKT, particularly at the level of individual contribution of isoforms, is still unknown. To enucleate this issue, Brand *et al*.[8] analyzed the mRNA expression of the three AKT isoforms in the inner ear of wild-type mice, and significant hearing loss was observed in *AKT3*-knockout mice, although the underlying pathomechanism

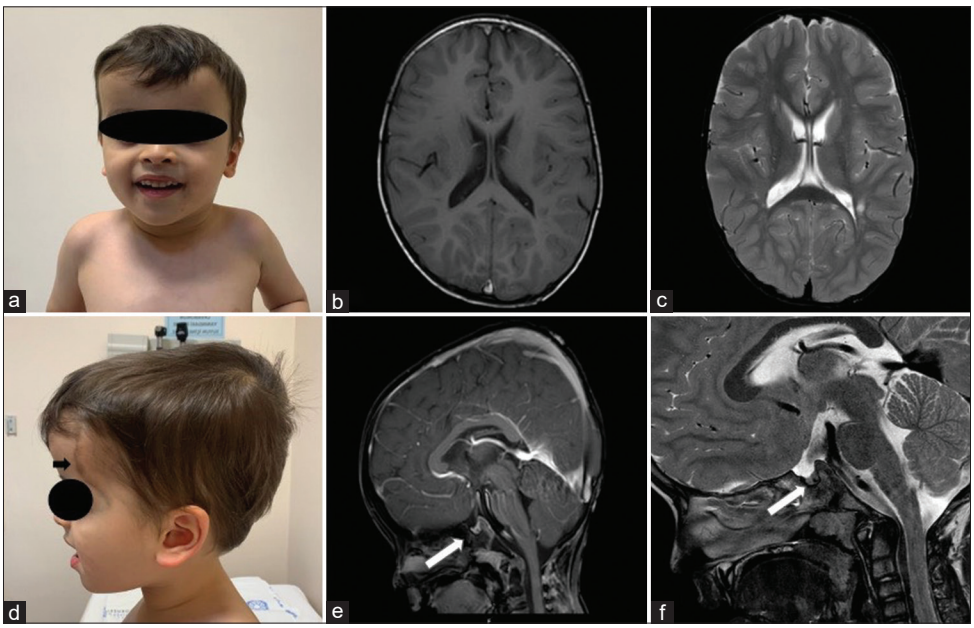

Figure 1: (a). Frontal aspect of the patient: Note to the prominent forehead. (b). Absence of hydrocephalus and polymicrogyria on T1-weighted axial image. (c). Absence of hydrocephalus and polymicrogyria on T2-weighted axial image. (d). Lateral aspect of the patient: Pay attention to the prominent forehead and easily visible venous lines (arrow). (e). Rathke cleft cyst of approximately 3 mm in size in the central part of the pituitary gland, at the pars intermedia level, with low signal on T1-weighted midline sagittal image. (f). Rathke cleft cyst with low signal on T2-weighted midline sagittal image

Table 1: Literature review of patients with non-syndromic megalencephaly due to *AKT3* mutation

	Case 1[10]	Case 2[9]	Case 3[9]	Case 4[9]	Case 5[9]	Index case
Gender	M	F	M	M	F	M
Ethnicity	Japanese	Hispanic	Caucasian	Caucasian	Hispanic	Turkish
Age last assessed	5y	8y	30m	6y10m	6y	4y
cDNA/amino acid change	c. 118G >A p.Glu40Lys	c. 159C >A p.Asn53Leu	c. 237G >T p.Trp79Cys	c. 1393C >T p.Arg465Trp	c. 1393C >T p.Arg465Trp	c. 237G >T p.Trp79Cys
Inheritance	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*	*De novo*
Zygosity	Heterozygous	NA	NA	NA	NA	Heterozygous
Consanguinity between parents	-	NA	NA	NA	NA	-
Birth OFHC–SD	+4.4	NA	+2.7	+2.7	NA	+2.79
Last OFHC–SD (Age)	+6.3 (57m)	+5 (8y)	+6.8 (29m)	+6 (NA)	+7–8 (6y)	+3.99 (4y)
Hypotonia	+	+	+	+	-	+
Motor developmental delay	+	+	+	+	+	+
Language developmental delay	NA	+	-	+	NA	+
Intellectual developmental delay	-	+	-	+	+	+
Autistic features	-	+	-	+	-	-
Hyperlaxity	+	-	-	-	-	+
Vascular malformation	-	-	+	+	-	+
Epilepsy	-	-	-	+	-	-
Dysmorphic findings	+	NA	-	NA	NA	+
Hypoglycemia	+	-	-	Unexplained episodes of hyper- and hypoglycemia	-	-
Other	Growth hormone deficiency	Feeding problems	-	Prenatal stroke, aplasia cutis congenita, severe vitamin A malabsorption	-	Bilateral SNHL, frequent infections, peripapillary hyperpigmentation
MRI findings						
Ventriculomegaly	Mild	-	Mild	Mild	-	-
Corpus callosum	Normal	Mildly thick	Normal	Dysplastic	Mildly thick	-
Other	-	-	Mild narrowing of the foramen magnum	Encephalomalacia and gliosis in right insular gyrus	-	Rathke's cleft cyst

M: male, F: female, y: year, m: month, NA: not available, OFHC: occipitofrontal head circumference, SNHL: sensorineural hearing loss, MRI: magnetic resonance imaging

was not elucidated precisely.[8] Besides, WES failed to detect any other genes responsible for SNHL in our patient. Based on these results, we concluded that the etiology of bilateral SNHL may be the *AKT3* mutation. The reason for the lack of speech can be this particular gene mutation, but bilateral SNHL may also be a justification. So far, five out of 21 megalencephalic patients due to *AKT3* mutation were described as non-syndromic megalencephaly.[1,2] Considering that there were only GDD and megalencephaly in our case, although the diagnosis shifted to non-syndromic megalencephaly, hyperlaxity and SNHL suggest a syndromic megalencephaly.

The c.237G>3 change in the *AKT3* gene was reported in only one patient with non-syndromic megalencephaly in whom OFHC was +2.7 and +6.8 SDs at birth and 29th month, respectively.[9] This steep increase was not observed in our patient in whom OFHC, which was +2.79 SDs at birth, increased to +3.99 at four years old. Hypotonia and GDD are similar features for both patients, but, despite the rapid increase in OFHC, compared to our patient, the neurodevelopment was reported to be better.[9] Social and language development were also reported to be normal unlike our patient. The fact that neurodevelopment is quite different even within the same variant highlights the phenotype diversity [Table 1].

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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