Athabaskan Brainstem Dysgenesis Syndrome:
A case of a rare HOXA1 mutation syndrome

Meghan Higley, Class of 2012

The University of Arizona College of Medicine Phoenix

ABSTRACT

The human HOXA1 mutation syndromes commonly present with abnormalities of the inner ear and internal carotid arteries. Previous cases describe varying degrees of hypoplasia or aplasia of the affected structures, often with asymmetrical involvement. We present imaging findings documenting complete absence of the internal carotid arteries bilaterally with bilateral complete labyrinthine aplasia of the inner ear, which had not been previously reported.

Based on the number of cases identified and birth rates within studied populations, we estimated the incidence of ABDS at 0.5-1:1000 live births on the White River Apache Reservation and 1:3000 live births in the Navajo population. If accurate, this suggests *a carrier frequency similar to that for cystic fibrosis in Caucasian populations*, raising questions of the possible benefit of genetic counseling for affected families.

However, cultural considerations bring into question the possible conflict between counseling based on gene theory and traditional beliefs.

INTRODUCTION

Two congenital syndromes with similar features, Bosley-Salih-Alorainy syndrome (BSAS) and Athabaskan brainstem dysgenesis syndrome (ABDS), are recessive disorders linked to loss of function mutations of the HOXA1 gene.

•BSAS has been documented in consanguineous marriages in Saudi Arabian and Turkish families [1-3].

• ABDS has been described in Native Americans of Athabaskan, primarily Navajo and Apache, descent [3-5]. (76C→T mutation: results in truncation of the normal 335 amino acid sequence to just 25 residues)

HOXA1 mutation syndromes are associated with a number of abnormalities which vary remarkably in penetrance and severity. The most common manifestations include:

•horizontal gaze abnormalities

•deafness

•internal carotid artery (ICA) malformations

•developmental delay

•congenital cardiac defects, central hypoventilation, facial paresis, swallowing dysfunction, and vocal cord paresis are variably seen [1-5]

CASE REPORT

A two-year-old female patient of Navajo descent was assessed for developmental delay. The child was unable to speak or walk, and had failed newborn hearing screens. Brainstem auditory evoked response testing confirmed bilateral sensorineural deafness. She also exhibited impairment of horizontal eye movements and facial diplegia with fasciculations.

MRI of the brain demonstrated absent ICA flow voids and complete absence of the bilateral inner ear structures and internal auditory canals. The 6th-8th cranial nerves could not be identified (Fig 1). MRA of the head confirmed bilateral absence of the ICA with markedly enlarged vertebral and basilar arteries supplying blood flow to the anterior and posterior circulations via an intact circle of Willis (Fig 2).

Based on findings of complete labyrinthine aplasia, ICA aplasia, horizontal gaze abnormalities and developmental delay in a Navajo child, the presumptive diagnosis of the HOXA1 mutation syndrome ABDS was made.

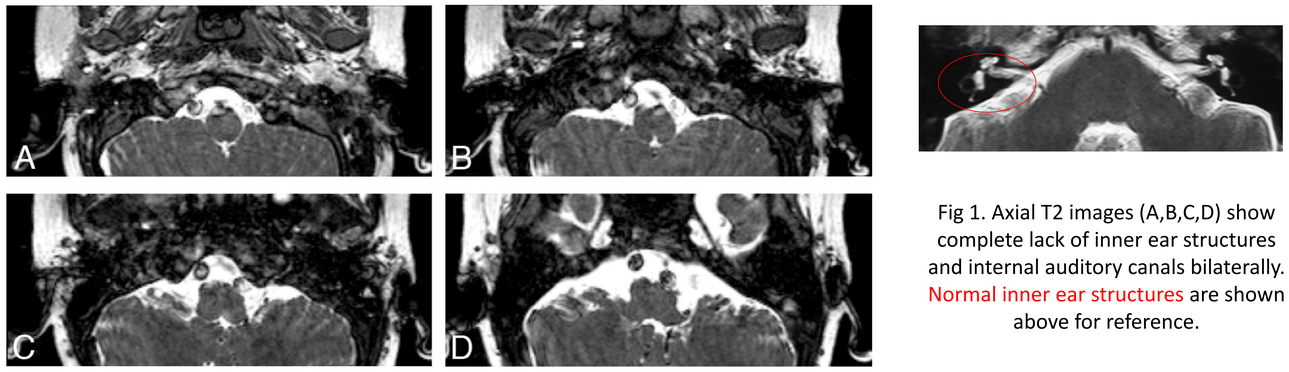

Fig 1. Axial T2 images (A,B,C,D) show complete lack of inner ear structures and internal auditory canals bilaterally. Normal inner ear structures are shown above for reference.

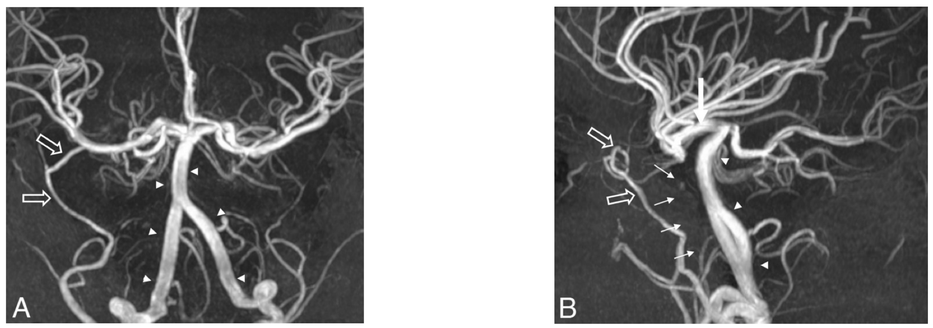

Fig 2. 3D time-of-flight maximum intensity projection images in anteroposterior and lateral projections demonstrate complete absence of the bilateral ICAs (small arrows). The vertebrobasilar system is enlarged (arrowheads) and supplies flow to the bilateral anterior cerebral arteries and middle cerebral arteries via enlarged posterior communicating arteries (large arrow). The right middle meningeal artery is enlarged (open arrows)

DISCUSSION

HOX (homeobox) genes:

HOX genes play an important role in determining cell identity along the anteroposterior axis of the embryo. The genes code for transcription factors that interact in a complex manner with a number of other signals to induce tissue differentiation. Different HOX genes are expressed in overlapping temporal patterns and spatial regions along the cranial-caudal axis. HOXA1 is the first of the HOX genes expressed in humans, and is found in the most cephalad distribution.

Two HOXA1-/- mouse models exhibit phenotypes similar to the human HOXA1 syndromes, with the exception that cerebrovascular malformations were not documented in mice [1].

Cultural Considerations:

The Navajo are one of several Native American tribes of Athabaskan descent. Recessive genetic disorders occur with increased frequency in Athabaskan tribes, likely due to genetic bottlenecks in the 1800's caused by conflicts with the US Army [5,6].

Genetic counseling may be helpful in preventing recurrence of recessive disorders, but traditional beliefs can include *a reluctance to name a disease or discuss the possibility of recurrence for fear of affecting the outcome*. Birth defects are more likely attributed to paternal behavior during pregnancy than genetic factors according to traditional beliefs.

CONCLUSION

There are only thirteen previously published cases of ABDS [3-5]. The present case exhibits the most extreme manifestations of ICA and inner ear abnormalities seen in ABDS with complete bilateral aplasia of both. However, unlike every previously reported case of ABDS, this patient has no documented central hypoventilation.

Considering the small number of patients previously studied, we suggest that *phenotypic variability is not yet fully appreciated* in ABDS.

The frequency of the disorder is also unclear, but preliminary estimates indicate that it *could be significantly underrecognized* among Athabaskan Native Americans.

Identification of any feature of the syndrome in a Native American child should prompt MR or CT evaluation for related abnormalities that would suggest the diagnosis of ABDS.

Further, *cultural sensitivity* should be considered when counseling affected families.

REFERENCES

1. Tischfield MA, Bosley TM, Salih MA, et al. Homozygous HOXA1 mutations disrupt human brainstem, inner ear, cardiovascular and cognitive development. *Nature Genet* 2005:37:1035-37.
2. Bosley TM, Salih MA, Alorainy IA, et al. Clinical characterization of the HOXA1 syndrome BSAS variant. *Neurology* 2007:69:1245-53.
3. Bosley TM, Alorainy IA, Salih MA, et al. The clinical spectum of homozygous HOXA1 mutations. *Am J Med Genet* 2008:146A:1235-40.
4. Friedman BD, Tarby TJ, Holve S, et al. Congenital horizontal gaze palsy, deafness, central hypoventilation, and developmental impairment: a brain stem syndrome prevalent in the Navajo population. (Abstract) *Am J Hum Genet* 1996: 59:A37.
5. Holve S, Friedman B, Hoyme HE, et al. Athatbascan brainstem dysgenesis syndrome. *Am J Med Genet* 2003:120A:169-73.
6. Erickson RP. Southwestern Athabaskan (Navajo and Apache) genetic diseases. *Genet Med* 1999:1:151-7.