

Auditory Interhemispheric Transfer Deficits, Hearing Difficulties, and Brain Magnetic Resonance Imaging Abnormalities in Children With Congenital Aniridia Due to *PAX6* Mutations

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Objective: To assess auditory processing, hearing difficulties, and brain magnetic resonance (MR) imaging abnormalities in children with panocular developmental aniridia due to *PAX6* mutations.

Design: Case-control study.

Setting: Great Ormond Street Hospital and Institute of Child Health.

Participants: Eleven case subjects with *PAX6* mutations and 11 age-matched and sex-matched healthy control subjects.

Interventions: All subjects completed a structured hearing questionnaire, baseline audiometry, and central auditory tests (dichotic speech tests, frequency and duration pattern tests, and gaps-in-noise test). Case subjects underwent brain MR imaging with volumetry, and the results were compared with those of age-matched and sex-matched healthy control subjects randomly selected from the Radiology and Physics Unit database.

Main Outcome Measures: Brain MR imaging, central auditory test results, and questionnaire scores.

Results: The corpus callosum area was significantly smaller on brain volumetry in the cases compared with the controls. The anterior commissure was small in 7 cases and was normal in 3 cases on visual inspection of brain MR images (conducted in 10 of 11 cases). Audiograms showed no abnormalities in any of the children. Central auditory test results were normal in all the controls and were abnormal in all the cases except for 1 case with a pattern of abnormalities consistent with reduced auditory interhemispheric transfer. The cases had greater difficulty localizing sound and understanding speech in noise than the controls.

Conclusions: Despite normal audiograms, children with *PAX6* mutations may experience auditory interhemispheric transfer deficits and have difficulty localizing sound and understanding speech in noise. In view of their additional visual difficulties, thorough audiological evaluation of these children is indicated to initiate appropriate management.

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HEARING IS A CORNERSTONE of communication in humans. Impaired brain structure or function may cause an auditory processing disorder with little effect on hearing thresholds but with deficits in other aspects of the hearing process.¹ This disorder may affect as many as 7% of children.² Auditory processing deficits may be associated with communication, learning, and other difficulties¹; therefore, early identification and appropriate management of these disorders in children is crucial.

Findings from recent studies^{3,4} suggest the presence of auditory processing deficits in the form of impaired auditory interhemispheric transfer in adults with struc-

tural brain abnormalities due to *PAX6* mutations. The *PAX6* gene encodes a transcriptional regulator.⁵ Heterozygous *PAX6* mutations are characterized by panocular features of developmental aniridia,⁵ while adult human heterozygotes show structural brain abnormalities. The anterior commissure is often absent or hypoplastic, and the corpus callosum is present but reduced in size on brain magnetic resonance (MR) imaging in adults with *PAX6* mutations.⁶ Both of these structures contain auditory interhemispheric fibers.⁷

The objectives of this study were to demonstrate whether auditory interhemispheric transfer is impaired in children with *PAX6* mutations (similar to adults) and whether this is associated with abnormali-

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Table 1. Questionnaire Results in the Cases and Controls*

Question†	Group	Answer			
		No Difficulties Almost Always	Some Difficulties		
			Frequently	Occasionally	Almost Never
Understand speech in quiet	Case	6	3	0	0
	Control	9	0	0	0
Understand speech in noise	Case	3	3	2	1
	Control	8	1	0	0
Understand feeling by tone of voice	Case	5	2	2	0
	Control	8	1	0	0
Understand intonation and voice inflection	Case	4	3	2	0
	Control	8	1	0	0
"Get a joke" as well as his or her peers	Case	4	4	1	0
	Control	8	1	0	0
Tell where a sound is coming from	Case	3	0	6	0
	Control	7	2	0	0

*The sample size was 9 each for cases and controls.

†The children's parents were the respondents.

ties on MR imaging of the brain and with parent-reported hearing difficulties in these children. Defects of interhemispheric auditory transfer might have implications for management in children bearing *PAX6* mutations, as they already have visual disability.

METHODS

This case-control study was conducted at Great Ormond Street Hospital and the Institute of Child Health from May 1, 2004, to May 31, 2006. It was approved by their joint ethics committee.

SUBJECTS

We recruited 11 case subjects (4 boys and 7 girls) who attended the ophthalmology clinic at Great Ormond Street Hospital for their visual difficulties. All children were in mainstream educational settings. Inclusion criteria for the case subjects were (1) aniridia diagnosed by 1 of us (A.T.M.), (2) a family history of congenital aniridia with a pattern indicating autosomal dominant inheritance or known *PAX6* mutation in the family, and (3) an age of 7 years or older.

We recruited an equal number of healthy control subjects by sending an e-mail invitation to all hospital staff. Children of all grade levels of hospital staff were recruited and were matched to the subjects for age (± 6 months), sex, handedness, and mean hearing thresholds (at 500, 1000, 2000, and 4000 Hz) in each ear. Informed consent was obtained from each tested child and from 1 of his or her parents.

TEST PROTOCOL

All subjects (cases and controls) completed standard baseline audiometric tests, behavioral central auditory tests, and a short structured hearing questionnaire. Audiological assessment took place at the Academic Unit of Audiological Medicine, Institute of Child Health. Genetic testing had been previously performed in the cases for identification of the mutation. In addition, the cases underwent brain MR imaging with volumetry at the Radiology and Physics Unit, Institute of Child Health. Comparable MR images from an equal number of age-matched and sex-matched healthy controls randomly selected from the unit's database were used for comparison as control images.

PROCEDURES

Brain MR Imaging

Magnetic resonance imaging acquisition techniques included conventional T1-weighted and T2-weighted multisection images and T1-weighted 3-dimensional fast low-angle shot images for volumetric and morphometric analyses. Imaging was performed on a 1.5-T MR imaging system (Magnetom Vision; Siemens, Erlangen, Germany).

One of us (S.L.F.) who was blinded to the subject's status (case or control) measured the corpus callosum area. Quantitative analysis was performed on the 3-dimensional T1-weighted images in 9 cases and in 9 corresponding controls.^{8,9}

Standard Baseline Audiometric Tests

Pure-tone audiometry was carried out bilaterally using an audiometer (GSI 61; VIASYS Healthcare Inc, Conshohocken, Pa) with earphones (TDH-49; Northeastern Technologies, Glen Cove, NY) in a sound-treated room.¹⁰ Audiograms were considered normal if thresholds were better than 20-dB hearing level in each frequency tested across 500 Hz to 8 kHz.

Tympanometry was obtained bilaterally with a continuous probe signal tone of 226 Hz at 85-dB sound pressure level using a middle ear analyzer (GSI 33; Lucas-Grason-Stadler Inc, Littleton, Mass). Tympanogram findings were considered normal if middle ear pressure was greater than -150 mm H₂O and compliance was greater than 0.3 cm³.

Transient-evoked otoacoustic emission measurements were carried out bilaterally using an analyzer with a standard default setup (ILO88/92; Otodynamics, Hatfield, Hertfordshire, England).¹¹ The presence of normal transient-evoked otoacoustic emissions (across 500-4000 Hz) was determined by an overall response amplitude signal-noise ratio of at least 6 dB and a waveform reproducibility of greater than 70% in at least 3 adjacent octave bands.¹²

Behavioral Central Auditory Tests

We conducted the following 3 tests: (1) dichotic speech tests, including digits,¹³ consonant vowel (CV) dichotic nonsense syllable test,¹⁴ and fused rhymed words,¹⁵ in which a different speech item is presented to each ear, and the listener has to repeat what he or she hears; (2) pattern tests (frequency¹⁶ and duration¹⁷),

Table 2. Summary of Mutation, Brain Magnetic Resonance (MR) Imaging, and Main Central Auditory Test Findings in the Cases and Their Affected Parent

Individual/ Sex/Age, y	Family	Mutation	Brain MR Imaging Findings	Central Auditory Test Results			
				Dichotic Digit Test	Frequency Pattern Test	Duration Pattern Test	Gaps-in- Noise Test
I/F/35*	Mother of I:1 and I:2	Haploinsufficiency R240X	Small AC, normal CC	Abnormal	Normal	Normal	Normal
I:1/M/12	Son of I	Haploinsufficiency	Normal	Abnormal	Abnormal	Abnormal	Normal
I:2/F/7	Daughter of I	Haploinsufficiency	Small splenium	Abnormal	Abnormal	Abnormal	Normal
II/F/44*	Mother of II:1	C-terminal extension X432L	Normal	Normal	Abnormal	Abnormal	Normal
II:1/F/16	Daughter of II	C-terminal extension	Small AC	Normal	Abnormal	Abnormal	Normal
III/M/50*	Father of III:1 and III:2	Missense K55R	Cyst beneath striatum	Abnormal	Normal	Normal	Normal
III:1/F/14	Daughter of III	Missense	Cyst in splenium	Abnormal	Normal	Abnormal	Normal
III:2/M/17	Son of III	Missense	Small AC, small posterior CC	Normal	Normal	Normal	Normal
IV/M/33*	Father of IV:1	Inframe deletion, splicing mutation	Normal	Normal	Normal	Normal	Normal
IV:1/F/10	Daughter of IV	Inframe deletion, splicing mutation	Small AC, small posterior CC	Abnormal	Abnormal	Abnormal	Normal
V/F/29*	Mother of V:1	Haploinsufficiency, frameshift C478insCC	Absent AC	Not tested	Not tested	Not tested	Not tested
V:1/M/10	Son of V	Haploinsufficiency, frameshift C478insCC	Small AC, small splenium	Abnormal	Abnormal	Abnormal	Normal
VI/F/54*	Mother of VI:1	Missense G36R	Not tested	Abnormal	Abnormal	Abnormal	Abnormal
VI:1/F/16	Daughter of VI	Missense	Small AC	Normal	Abnormal	Abnormal	Normal
VII:1/F/14	Sister of VII:2	Haploinsufficiency, antistart missense	Small AC	Abnormal	Abnormal	Abnormal	Normal
VII:2/F/11	Sister of VII:1	Haploinsufficiency, antistart missense	Small AC	Abnormal	Abnormal	Abnormal	Abnormal
VIII/M/13	...	Haploinsufficiency, inversion of chromosome 11	Not tested	Normal	Normal	Abnormal	Normal

Abbreviations: AC, anterior commissure, CC, corpus callosum; ellipses, not applicable.

*Parents of children recruited to this study: I and II were described by Bamiou et al⁴; III, IV, and VI are described herein; and V was described by Sisodiya et al.⁶

in which a sequence of sounds that differ in frequency or duration is presented monaurally and the listener has to label the sequence (eg, high, high, low); and (3) a temporal resolution test (gaps in noise¹⁸), in which the listener has to count the gaps embedded in a white noise segment.

All tests were available on CD and were administered using a CD player (Sony Corporation, Thatcham, Berkshire, England) and routed through the speech circuitry of the GSI 61 audiometer. All central auditory test material was presented at a 50-dB sensation level, with the sensation level referenced to the pure-tone audiogram mean (at 0.5, 1, 2, and 4 kHz) after a brief practice session. The percentage of correct responses was calculated for each ear for all tests (as well as a threshold value for the gaps-in-noise test). Normative values were available for the dichotic digit, frequency pattern, duration pattern, and gaps-in-noise tests.

Questionnaire

A structured hearing questionnaire was given to the parents to complete during the time their child was being tested (**Table 1**). The questions were selected on the basis of previously reported auditory difficulties experienced by patients with abnormalities of the interhemispheric pathway. The parent was asked to pick 1 of the following answers for each question: “almost never” (0 points), “occasionally” (1 point), “frequently” (2 points), or “almost always” (3 points).

OUTCOME MEASURES

Outcomes of brain MR imaging included the volumetric results and the findings on visual inspection of the images. Other

outcomes measures in the study were the questionnaire scores and the central auditory test results.

STATISTICAL ANALYSIS

The results were analyzed using SPSS software version 12.0 (SPSS Inc, Chicago, Ill). We used Mann-Whitney nonparametric tests to examine differences between the cases and the controls in questionnaire scores, corpus callosum cross-sectional area, and test scores for the tests without normative data (ie, the dichotic CV and dichotic rhyme tests). Linear regression analysis was performed to assess the relationship between questionnaire scores and test scores in the entire group.

RESULTS

GENETIC TESTING

Genetic mutation testing was performed by 1 of us (V.V.). The following are 5 major known subgroups of pathological alterations of PAX6^{19,20}: (1) haploinsufficiency, an intragenic mutation leading to a truncated or absent PAX6 protein, identified in 6 children (cases I:1, I:2, V:1, VII:1, VII:2, and VIII) in our study (**Table 2**); (2) inframe deletion due to a splicing error, identified in case IV:1; (3) mutation causing a predicted C-terminal protein extension, identified in case II:1; (4) missense mutation, identified in 3 chil-

Table 3. Dichotic Consonant Vowel (CV) and Dichotic Rhyme Test Results in the Cases and Controls

Variable	Mean Rank		U Value	P Value
	Cases	Controls		
Dichotic CV test				
Right ear	9.33	8.63	33.000	.82
Left ear	7.89	10.25	26.000	.37
Dichotic rhyme test				
Right ear	12.20	9.91	43.000	.43
Left ear	8.10	13.64	26.000	.04

dren (cases III:1, III:2, and VI:1); and (5) deletion of the entire gene, which was not found in any of the children in this cohort.

BRAIN MR IMAGING FINDINGS

Structural brain MR imaging was conducted in 10 of 11 cases, and the images were inspected and reported on by 1 of us (W.K.C.). Compared with the controls, the anterior commissure was small in 7 cases and was normal in 3 cases. The corpus callosum was small in 4 cases and was normal in 5 cases, with a cyst in the splenium of the corpus callosum in case III:1 (Table 2). Overall, the brain MR images were completely normal only in case I:1.

Brain volumetry to measure the corpus callosum area was performed in 9 cases. The data were compared with the corpus callosum area of 9 randomly chosen age-matched healthy controls. The corpus callosum area was significantly smaller in the cases ($P = .02$, Mann-Whitney test).

STANDARD BASELINE AUDIOMETRIC TESTS

All the cases and controls had normal tympanograms and pure-tone audiograms. They also had normal results on transient-evoked otoacoustic emission measurements.

CENTRAL AUDITORY TESTS

Central auditory test results were normal in all of the controls. The results in the cases are summarized in Table 2; only case III:2 had entirely normal results on all of the central auditory tests.

Dichotic Speech Tests

On the dichotic digit test, all of the cases had normal results in the right ear, and 7 cases had abnormal results in the left ear. On the dichotic CV test, there was no significant difference in the right ear and left ear scores between the cases and the controls; these results are summarized in **Table 3**. On the dichotic rhyme test, there was no significant difference in the right ear scores between the cases and the controls, but the left ear scores were lower among the cases.

Frequency and Duration Pattern Tests and Gaps-in-Noise Test

Eight of 11 cases had abnormal results on the frequency pattern test. Ten of 11 cases had abnormal results on the duration pattern test. All of the cases except case VII:2 had normal results on the gaps-in-noise test.

QUESTIONNAIRE FINDINGS

Questionnaire results were obtained from parents of 9 cases and from 9 controls. The results are summarized in Table 1. The cases had significantly lower scores (denoting greater difficulty) for localizing sound and for understanding speech in noise ($P = .03$ for both).

COMMENT

To our knowledge, this is the first report of auditory processing test deficits, associated hearing difficulties (despite normal audiograms), and structural abnormalities of the auditory interhemispheric pathway on brain MR imaging in children with *PAX6* mutations. In view of the additional visual disability associated with *PAX6* mutations, our findings have implications for the management of these children, particularly in the classroom setting.

In adult humans, *PAX6* mutations are associated with structural abnormalities of the interhemispheric pathway, with an absent or hypoplastic anterior commissure, and with a present (but in some cases smaller) corpus callosum.⁶ Both of these structures contain auditory interhemispheric fibers.⁷ In this pediatric study of *PAX6* mutations, the main structural findings on brain MR imaging were a smaller anterior commissure and corpus callosum cross-sectional area in the cases than in the healthy controls. The corpus callosum findings are similar to the brain MR imaging abnormalities reported in adults with *PAX6* mutations.^{6,8,21} However, there are some differences between the brain MR images in adult vs pediatric cases. In our pediatric sample, the anterior commissure was present in 10 of 10 imaged cases but was smaller than normal in 7 cases. In the series by Sisodiya et al,⁶ the anterior commissure was present in only 4 of 14 adult cases with *PAX6* mutations. Free et al,⁸ reporting on the original 14 cases⁶ and an additional 10 cases, found the anterior commissure to be present in only 9 of 24 imaged adults with *PAX6* mutations. In view of the small sample sizes in these studies, it is difficult to interpret the significance of the differences between the pediatric and adult findings. The differential effect of various mutations on the presence or absence of the anterior commissure needs to be considered. So far, no obvious genotype-phenotype correlations have been noted. It has been proposed that *PAX6* may have a maintenance function in the adult eye.⁵ Therefore, the effect of age and the possibility of age-related degeneration of the interhemispheric structures should also be considered in a larger prospective pedigree study.

The functional role of the corpus callosum and the anterior commissure in audition has been examined in patients who have had these pathways sectioned. These subjects typically have normal results on monaural speech tests,

with severely decreased left ear performance on dichotic digit and CV tests²² and with increased right ear performance on dichotic rhyme tests.²³ The dichotic speech test findings have been explained based on the following 3 assumptions: (1) language perception takes place in the left hemisphere; (2) in the monaural situation, the ipsilateral and contralateral pathways are functional for sound transmission; and (3) in the dichotic situation, the contralateral pathway becomes dominant in auditory speech signal transmission. Therefore, in dichotic speech tests, speech stimuli from the left ear will be transmitted to the right (nonlanguage) hemisphere and will require transfer via the interhemispheric commissures to the left hemisphere for linguistic processing.^{24,25} For the frequency and duration pattern tests, it has been proposed that for a sequence of sounds the right hemisphere determines the pattern of the sequence as a gestalt, but the labeling of the sequence occurs in the left (language) hemisphere.²⁶ Therefore, tasks that require labeling of sound sequences depend on transfer of information from the right hemisphere to the left hemisphere via interhemispheric commissures.²⁶ In contrast, the gaps-in-noise test does not depend on callosal transfer. In our study, the constellation of auditory test abnormalities in 11 cases (ie, reduced left ear scores in the dichotic digit test, bilaterally reduced scores in the frequency and duration pattern tests, and normal results on the gaps-in-noise test) is consistent with findings in adults with *PAX6* mutations.^{3,4} Our results are also similar to the test findings in patients with section of the posterior part of the corpus callosum albeit less severe.^{22,27} There are some subtle differences between test findings in children vs adults with *PAX6* mutations. For example, children had a reduced left ear score in the dichotic rhyme test with no significant differences between the right ear and left ear scores on the dichotic CV test in our study, while adults had a significantly reduced left ear score on the dichotic CV test but no significant differences between the right ear and left ear scores on the dichotic rhyme test.⁴ It is not clear whether these differences are due to sample size, variation in brain MR imaging, or age-related or developmental changes of the auditory interhemispheric pathway.

There were some limitations in this study. We did not conduct any formal psychometric measures; therefore, the effect of IQ on the test results remains unknown. However, there were no concerns regarding low IQ for any of the children expressed by the parents or noted in their educational environments, and all of the children were in mainstream educational settings. Moreover, a study²⁸ among adults with *PAX6* mutations did not find any cognitive deficits compared with healthy controls. We did not examine the effect of any top-down processes (such as attention) on the test results. Furthermore, the number of cases was too small to make inferences about genotype-phenotype associations or structural brain abnormalities and test findings. Notwithstanding these limitations, the auditory processing deficits found in children with *PAX6* mutations as a group are broadly similar to what has previously been reported in adults^{3,4} and are indicative of reduced auditory interhemispheric transfer.

It is interesting to compare our results with findings among subjects with congenital aplasia of the auditory

interhemispheric pathway. Subjects with callosal agenesis, with or without an anterior commissure, may experience a range of central auditory deficits that include deficient phonological processing as shown on rhyming tasks,²⁹ impaired sound localization,³⁰ and dichotic speech test abnormalities with small but reliable ear asymmetries.³¹⁻³³ These auditory deficits are associated with educational difficulties^{29,34} in the absence of a close correlation between the auditory deficits and the subjects' IQ.³⁵ Congenital aplasia or early life damage of the corpus callosum causes mild impairment of auditory interhemispheric transfer, which is probably related to development of alternative pathways resulting from brain plasticity.^{31,32} These reports are broadly consistent with our findings.

The finding of deficient auditory interhemispheric transfer in children may explain their parent-reported difficulties with localizing sound.³² Subjects with callosal agenesis are less accurate than control subjects in localizing fixed³⁶ and moving³² sounds, as the auditory interhemispheric pathway may facilitate integration of binaural inputs in the 2 hemispheres. The deficient auditory interhemispheric transfer may similarly underline the parent-reported difficulties with understanding speech in noise. Processing of speech in background noise seems to activate both hemispheres.³⁷ Oral language comprehension requires integration of semantic and syntactic information (processed in the left hemisphere) with prosodic information (processed in the right hemisphere), subserved by the corpus callosum.³⁸ Presentation of oral language in noise may increase the complexity of this task. Interhemispheric interaction may, in this case, help increase the brain's processing capacity by dividing the processing demands of the complex auditory task between the 2 hemispheres, making maximum use of hemispheric specialization,³⁹ and by recruiting other top-down executive functions (ie, attention).⁴⁰ As observed in our study, the left ear deficit on the dichotic digit test may be an indirect measure of speech competition difficulties.

More than half of the children in our study with *PAX6* mutations were also reported to have problems understanding prosody, although the difference between the cases and the controls was not significant. Patients with agenesis of the corpus callosum are reported to have difficulties with the pragmatic aspects of language in that they may interpret speech very literally or may misinterpret the meaning of nonliteral expressions such as idioms.⁴¹⁻⁴³

In conclusion, we demonstrated the presence of auditory processing deficits indicative of reduced auditory interhemispheric transfer and reported difficulties with localizing sound and understanding speech in noise among children with congenital aniridia due to *PAX6* mutations, in the presence of normal audiograms and of MR imaging–documented abnormalities of the auditory interhemispheric pathway in the brain. The combined effect of auditory and visual difficulties may result in a significant handicap, particularly in the classroom setting. Thorough audiological evaluation of these children is indicated to initiate appropriate management in the form of auditory training and environmental modifications.⁴⁴ Further research is needed to assess how the au-

ditory deficits affect academic performance in children with PAX6 mutations and what is the best management to improve academic performance and communication in these children.

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Announcement

Submissions. The Editors welcome contributions to Picture of the Month. Submissions should describe common problems presenting uncommonly, rather than total zebras. Cases should be of interest to practicing pediatricians, highlighting problems that they are likely to at least occasionally encounter in the office or hospital setting. High-quality clinical images (in either 35-mm slide or electronic format) along with parent or patient permission to use these images must accompany the submission. The entire discussion should comprise no more than 750 words. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations. For details regarding electronic submission, please see: <http://archpedi.ama-assn.org>.