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Characteristics of Hearing Loss in the Barakat Syndrome

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Abstract

Barakat syndrome, also known as HDR syndrome, is a clinically heterogeneous, rare genetic disorder characterized by the triad of hypoparathyroidism, sensorineural deafness, and renal disease. In most cases, the syndrome is caused by deletions or mutation in the zinc-finger transcription factor GATA3 on chromosome 10p14. Hearing loss is the most consistent feature of the syndrome, occurring in 96% of reported patients. Patients present with early onset, moderate to severe sensorineural hearing loss, usually bilateral and slightly worse at the higher end of the frequency spectrum. The outer hair cells play an important role in the etiology of the hearing loss. Using a next generation sequencing gene panels that included GATA3 in patients with apparently isolated deafness has allowed the early identification of GATA3 mutations in patients with previously unrecognized Barakat syndrome. Hearing treatment should be instituted as early as possible in children to help their speech, language, and social skills reach their full potential. We discuss here the characteristics and genetics of sensorineural hearing loss associated with the Barakat syndrome.

Keywords: Barakat syndrome; GATA3 mutations; HDR; Sensorineural hearing loss

Abbreviations

ABI: Auditory Brain Stem Implants; ABR: Auditory Brainstem Evoked Response; CKD: Chronic Kidney Disease; EHDI: Early Hearing Detection and Intervention; HCs: Hair Cells; HDR: Hypoparathyroidism, Deafness, Renal disease; NGS: Next Generation Sequencing; OAE: Otoacoustic Emission; SNHL: Sensorineural Hearing Loss

Introduction

Barakat syndrome, also known as HDR syndrome, is a clinically heterogeneous, rare genetic disorder characterized by the triad of Hypoparathyroidism (H), sensorineural Deafness (D), and Renal disease (R) [1]. The syndrome in most cases is caused by deletions or mutation in the zinc-finger transcription factor GATA3 on chromosome 10p14 [2]. In the past, patients have presented mainly with signs and symptoms of hypocalcemia secondary to hypoparathyroidism. Since the advent of routine newborn hearing screening and prenatal ultrasonography, hearing loss and renal disease have become the more common modes of presentation. Hearing loss is the most consistent feature of the syndrome, occurring in 96% of reported patients. The purpose of this paper is to discuss the characteristics, etiology, genetics, and treatment of hearing loss associated with the Barakat syndrome.

Barakat Syndrome

Barakat syndrome, also known as HDR syndrome was first described by Barakat et al. [3] in 1977. The syndrome is usually caused by deletions or mutation in the zinc-finger transcription factor GATA3 on chromosome 10p14 [1]. The syndrome may present with variable clinical features even in the same family. So far, all carriers of GATA3 mutations have been found to have at least one of the defects characterizing the syndrome [4]. To date, about 200 cases have been reported in the literature; however, most likely many cases have been missed or underreported. Reported pedigrees seem to follow an autosomal dominant pattern with variable expression and incomplete penetrance. The complete clinical triad (HDR) was found in 64% of reported patients [2]. Hearing loss is the most consistent feature of the syndrome, affecting 96% of reported patients, while hypoparathyroidism and renal disease affect 93% and 72% of patients, respectively. Patients with isolated Sensorineural Hearing Loss (SNHL) where other neurogenetic causes of deafness have been excluded should be suspected to have the syndrome, especially if there is history of hypoparathyroidism, deafness or renal disease in any member of the family. In these instances, GATA3 testing should be performed to confirm the diagnosis.

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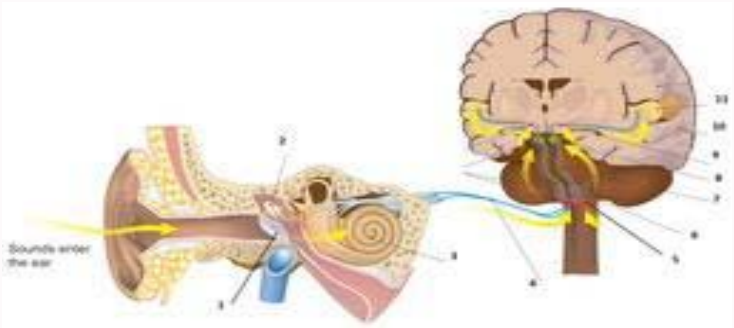

Figure 1: Auditory pathway of sound through the ear to the brain (yellow arrows). Tiny middle ear bones initially amplify the sound from the external auditory canal towards the cochlea, which sorts the sound by frequency. The vestibulocochlear nerve passes signal from cochlea to brainstem. Signal travels through the brain getting decoded along the way until the auditory cortex processes the sound.
Labels: 1: Tympanic membrane; 2: Ossicular bones; 3: Cochlea; 4: Vestibulocochlear nerve; 5: Cochlear nucleus; 6: Superior olivary nucleus; 7: Lateral lemniscus; 8: Inferior colliculus; 9: Medial geniculate body; 10: Temporal lobe; 11: Auditory receiving center
Figure modified from "© www.gograph.com/[PATTER]".

The presence of hypoparathyroidism should suggest the Barakat syndrome, and prompt audiometry and renal investigation, since it is caused only by few other disorders. Patients have historically presented with signs and symptoms of hypocalcemia (non-febrile seizures, tetany, myalgia, and irritability) and low serum Parathyroid Hormone (PTH). Since newborn hearing screening and prenatal ultrasonography have become the standard of care, it is more common now for the syndrome to present with deafness or renal disease. Renal disease associated with the syndrome is variable and consists of Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) in 40% of cases, hematuria, proteinuria, nephrotic syndrome renal tubular acidosis, CKD and others. Several additional features have been described in association with the syndrome, including congenital heart disease, facial abnormalities, cerebral infarctions, retinitis pigmentosa, basal ganglia calcifications, severe cognitive disability, and several others [2,5]. This clinical diversity underscores the phenotypic heterogeneity and variable penetrance of the syndrome [5].

Patients may exhibit the full phenotypic triad of HDR or only a subset of these. By age 50 years, nearly all patients will have the full spectrum of the syndrome, as the chances to develop any component of the syndrome increases with age [4]. In contrast, Barakat et al. [2] reported that the three components of HDR occurred in 64% of 180 reported cases. The authors did remark that it is possible that some clinical features might have been missed or may have appeared later in life in their study. Early diagnosis of Barakat syndrome provides an opportunity for early treatment and improved prognosis. Management should follow a comprehensive approach, which includes treatment of hypocalcemia and early identification and management of hearing loss. Since the prognosis usually depends on the severity of renal disease, early intervention is crucial in preventing or delaying CKD. Genetic counseling should be offered to identify affected family members and predict future risks.

Hearing Loss Overview

The World Health Organization defines hearing loss as the inability to hear a threshold of more than 25 dB in one or both ears. Hearing loss may be conductive, sensorineural, or mixed. Hearing impairment has a significant impact on spoken language, communication skills, visual reception, and development of fine motor skills [6]. The joint committee on infant hearing now promotes universal screening with state-run systems of Early Hearing Detection and Intervention (EHDI) [7]. The goal of the EHDI programs is to screen all infants prior to age 1 month. Infants who do not pass the initial screen would have a comprehensive audiologic evaluation by age 3 months, and if needed treatment implemented by age 6 months. Otoacoustic Emissions (OAEs) are used for newborn hearing screening. Incoming sounds and reflections occurring naturally within the cochlea are amplified by the outer hair cells and propagated out of the ear and detected by a microphone in the ear canal as an OAE [6]. OAE tests cochlear function only and do not detect pathology in the auditory nerve or auditory brainstem pathways. Auditory Brainstem Evoked Response (ABR) which detects hearing loss caused by outer hair cell dysfunction or problems in conveying the sound information to the brain provides another way to assess hearing in newborns. Passing the ABR test requires a normal middle ear, cochlea, auditory nerve, and auditory brainstem pathways (Figure 1) [6]. A newborn with auditory neuropathy, will pass OAE, but fail ABR testing.

Hearing Loss in Barakat Syndrome

Hearing loss affects 96% of patients affected with this syndrome. It is characterized by early onset, moderate to severe SNHL (56 dB to 70 dB) that is usually bilateral and slightly worse in the higher sound frequencies. This occurs when there is a problem translating the sound vibrations in the cochlear HCs into electrical signals, or in transmitting the information to the brain [8]. The higher frequency SNHL may progressively worsen with age [9]. The absence of Distortion Product Otoacoustic Emissions (DPOAEs) and presence of normal ABRs support a cochlear site for the lesion [10]. According to the authors, there is no evidence of vestibular dysfunction in these patients. A decrease in the age of onset of deafness and increased severity in subsequent generations may indicate the presence of genetic anticipation [11]. Deafness may be associated with many other hereditary kidney disorders; however, none of these is associated with hypoparathyroidism [1].

Genetics of Hearing Loss in Barakat Syndrome

Hearing loss is a common sensory disorder in children, affecting 1/1000 live births [10], with genetics responsible for about 50% to 60% of congenital hearing loss [12]. Over 6,000 variants within 150 genes have been identified in patients with congenital hearing loss, the majority of which are non-syndrome and genetically heterogenous [8,13]. Only 30% of inherited hearing loss is syndromic, which includes well known congenital disorders like Alport, Branchiotorenal, CHARGE, Jervell& Lange-Nielsen, Norrie,

Table 1: Genes, genomic location and inheritance in syndromic hearing loss (modified from: Hereditary Hearing Loss Homepage) [15].

Syndrome/Features	Type	Locus	Gene (OMIM)	Genomic Location	Inheritance
Alport Syndrome			COL4A3	2q36.3	AR
Nephritis, SNHL			COL4A4	2q36.3	AR
			COL4A5	Xq22.3	X-LR
Branchio-Oto-Renal Syndrome		BOR1	EYA1	8q13.3	AD
Branchial cleft cysts, renal abnormalities, structural ear defects		BOR2	SIX5	19q13.32	AD
			Unknown	1q31	AD
		BOR3	SIX1	14q23.1	AD
Charge Syndrome			SEMA3E	7q21.11	AD
Coloboma, heart anomaly, choanal, atresia, retardation, genital and ear anomalies			CHD7	8q12.2	AD
Jervell & Lange-Nielsen Syndrome		JLNS1	KNCQ1	11p15.5-15.4	AR
Prolonged QT interval, bilateral congenital, deafness		JLNS2	KCNE1	21q22.12	AR
Norrie Disease		NDP1	NDP	Xp11.3	X-LR
Progressive mental disorder, SNHL, blindness					
Pendred Syndrome			SLC26A4	7q22.3	AR
SNHL, goiter			FOXI1	5q35.1	AR
			KCNJ10	1q23.2	AR
Perrault Syndrome		PRLTS1	HSD17B4	5q23.1	AR
SNHL, ovarian dysfunction		PRLTS2	HARS2	5q31.3	AR
		PRLTS3/DFNB81	CLPP	19p13.3	AR
		PRLTS4	LARS2	3p21.31	AR
		PRLTS5	TWNK	10q24.21	AR
		PRLTS6	ERAL1	17q11.2	AR
Stickler Syndrome		STL1	COL2A1	12q13.11	AD
SNHL, myopia, retinopathy, epiphyseal dysplasia		STL2	COL11A1	1p21	AD
		STL3	COL11A2	6p21.32	AR/AD
		STL4	COL9A1	6q13	AR
		STL5	COL9A2	1p34.2	AR
Treacher Collins Syndrome		TCOF1	TCOF1	5q32-q33.1	AD
Craniofacial abnormalities, hearing loss		TCOF2	POLR1D	13q12.2	AD
		TCOF3	POLR1C	6p21.1	AR
Usher Syndrome[1]	Usher 1	USH1A	-	14q32	AR
SNHL, vestibular areflexia, retinitis pigmentosa		USH1B	MYO7A	11q13.5	AR
		USH1C	USH1C	11p15.1	AR
		USH1D	CDH23	10q22.1	AR
		USH1E	-	21q21	AR
		USH1F	PCDH15	10q21.1	AR
		USH1G	SANS/USH1G	17q25.1	AR
		USH1H	-	15q22-23	AR
		USH1J	?	15q25.1	AR
		USH1K	-	10p11.21-q21.1	AR
	Usher 2	USH2A	USH2A	1q41	AR
		USH2B	-	3p23-24.2	AR
		USH2C	ADGRV1/VLGR1/ GPR98?	5q14.3	AR
		USH2D	WHRN	9q32	AR
	Usher 3	USH3A	CLRN1	3q25.1	AR
		USH3B	HARS?	5q31.1	

Waardenburg Syndrome[2]	Type I	WS1	PAX3	2q36.1	AD
Pigmentary abnormalities, dystopia canthorum, SNHL	Type II	WS2A	MITF	3p13	AD
		WS2B	-	1p21-p13.3	AD
		WS2C	-	8p23	AD
		WS2D	SNAI2	8q11	AR
		WS2E	SOX10	22q13.1	AD
	Type III	WS3	PAX3	2q36.1	AD/AR
	Type IV	WS4A	EDNRB	13q22.3	AD/AR
		WS4B	EDN3	20q13.32	AD/AR
		WS4C	SOX10	22q13.1	AD
Barakat Syndrome			GATA3	10p14	AD
Hypoparathyroidism, SNHL, renal disease					

AR: Autosomal Recessive; AD: Autosomal Dominant; X-LR: X-Linked Recessive; ?: Questionable
1: Type I: Congenital, severe to profound Hearing Loss (HL), severe Vestibular Impairment (VI), Retinitis Pigmentosa (RP) onset 1st decade of life. Type II: Congenital, moderate to severe HL, no VI, RP onset 1st to 2nd decade of life. Type III: variable progressive HL, variable VI and RP.
2: Type I: Dystopia canthorum. Type II: no Dystopia canthorum. Type III: Type I and upper limb abnormalities. Type IV: Type II and Hirschsprung disease.

Pendred, Perrault, Stickler, Tracher-Collins, Usher, Waardenburg, and Barakat syndrome (Table 1) [2,14,15]. The establishment of high-resolution genetic and physical maps, genomic, and cDNA libraries made it easier to correlate the genes for hearing loss *via* cloning and knock-out methods, specifically the development of the human fetal cochlear cDNA library [16]. Barakat syndrome is primarily caused by mutations in GATA3 located on chromosome 10p (10p14) and is associated with a wide phenotypic spectrum [1,17,18]. GATA3 belongs to a family of dual zinc-finger transcription factors essential in the embryonic development of the parathyroid glands, auditory system, and kidneys, as well as the thymus and central nervous system [19,20]. Within the brain, GATA3 is expressed in spiral ganglion neurons, which play a key role in hearing by rapidly transmitting signals from the cochlea to the brain [21]. Deletion of GATA3 in knock-out mice was found to severely disrupt the hearing loss pattern by Appler et al. [21]. From this knock-out study, GATA3 was determined to be the first auditory-specific regulator in development of these neurons, providing a useful molecular entry point for efforts to engineer these neurons for the restoration of hearing [21]. Uncover an undiagnosed Barakat syndrome and allow earlier diagnosis and treatment of associated abnormalities. A similar genetic study by Van Wees et al. [22] found that ABR thresholds of alert heterozygous GATA3 knock-out mice analyzed from 1 to 19 months of age showed a hearing loss of 30 dB compared to wild-type littermates. The cochlea within the knockout mass developed significant progressive degeneration of the outer hair cells, which ultimate progressed to involve all cochlear hair cells within the entire cochlea. The brainstem, cerebral cortex, the outer and middle ear showed no physiological or morphological abnormalities. This development established GATA3 haploinsufficiency resulting in a peripheral nervous system origin rather than a central etiology of hearing loss. In addition, the defect is detectable in postnatal development and continues through adulthood [22]. In clinical studies, Lemos et al. [4] reported that 7.3% of all GATA3 mutations were discovered in patients with isolated deafness at the time of the genetic diagnosis [4]. The authors suggested that patients with isolated SNHL should be considered for GATA3 genetic testing when all other acquired or congenital causes have been excluded [4]. Belge et al. [23] reported eight patients with Barakat syndrome, one of whom had only hearing loss but had a new heterozygous substitution c.856A>G (p.N286D) involving a highly conserved amino acid within the zinc-finger transcription factor 1 motif (ZnF1). From this finding, it is possible that the other components of the syndrome may have been overlooked in this and some of the other reported patients affected with the syndrome.

Early identification of GATA3 mutations in patients with isolated deafness and previously unrecognized Barakat syndrome can be achieved by using Next Generation Sequencing (NGS) gene panels that include GATA3 [4,24]. This is very important due to the highly variable and heterogenous expression of hearing loss in individuals with Barakat syndrome to differentiate between non-syndromic and syndromic origin. Wang et al. [4,11] utilized this technique on their study identifying GATA3 mutations in isolated autosomal dominant hearing loss, which allowed them to uncover an undiagnosed Barakat syndrome and allow earlier diagnosis and treatment of associated abnormalities. With the right methodology, genetic identification of SNHL can be boosted to 50% to 60% diagnostic accuracy to reveal undiagnosed syndromes [24].

Treatment of Hearing Loss

Treatment of hearing loss in children should be instituted as early as possible to help their speech, language, and social skills reach their full potential. The fitting age of hearing aids is very critical in achieving these goals [25]. Since mild levels of hearing loss were shown to be associated with poor academic performance in primary school-aged children, children with mild hearing loss should be encouraged to wear their hearing aids [27]. The American Academy of Audiology recommends the Behind the Ear (BTE) hearing aids for pediatric patients because there is less of a swallowing risk compared to the In-the-Ear (ITE) hearing aids [28]. Children with bilateral hearing loss should use bilateral hearing aids as these have the advantage of enhancement of binaural hearing (brain making use of information from both ears), improved auditory localization, and speech understanding in noisy environments [28]. The standard treatment option for children with severe to profound SNHL is the use of the cochlear implant which directly stimulates the spiral ganglion cells which are the first order neurons of the auditory pathway [29]. This procedure was approved by the U.S. Food and Drug Administration (FDA) in 1990 for pediatric patients older than 24 months with profound SNHL who receive no auditory benefit from hearing aids. The FDA subsequently expanded the candidacy criteria of the cochlear implant to children under age 12 months because they have improved auditory and linguistic outcomes with minimal complications [30-

32]. The benefit of cochlear implantation in children with unilateral SNHL is still under clinical trial testing [33]. A systematic review of 296 articles on cochlear implantation in children with unilateral hearing loss was not able to draw firm conclusions on its effectiveness [34]. Unilateral cochlear implantation; however, has been approved for use in adults [35]. The Auditory Brain Stem Implant (ABI) is a neuroprosthetic device that provides hearing sensations to deaf patients who are ineligible for the cochlear implant due to anatomic constraints, such as cochlear deformity or absent cochlear nerve [36]. ABI bypasses the cochlear nerve to electrically stimulate second order neurons in the cochlear nucleus using a multichannel surface array in patients with cochlear and retro-cochlear pathologies [36]. Similar to cochlear implants, ABI consists of an external ear-level worn device and an internal receiver-stimulator implant. Both primary and revision ABI surgery in children are safe and effective [37]. While some patients achieve open-set speech perception, the majority experience limited environmental sound awareness and speech pattern recognition [30]. A key limitation of current ABIs is the highly variable and often unpredictable audiometric outcomes [30]. Recently, there has been significant progress in the development of gene therapy to treat SNHL in animal models *in vivo* [38]. However, the authors list some hurdles that need to be addressed before such technologies can be put into clinical use. These include the blood-labyrinth barrier, more specific and effective delivery vehicles, improving surgical access, and validating novel targets.

Conclusion

Hearing loss is the most consistent feature of Barakat syndrome. It affects 96% of reported patients, and presents with early onset, moderate to severe sensorineural hearing loss that is usually bilateral and slightly worse at the higher end of the frequency spectrum. Hearing loss following GATA3 haploinsufficiency is peripheral in origin, detectable from early postnatal development, and continues through adulthood. Using a Next Generation Sequencing (NGS). Gene panels that include GATA3 in patients with apparently isolated deafness allow early identification of GATA3 mutations in patients with previously unrecognized Barakat syndrome. Treatment of hearing loss in children should be instituted as early as possible to help their speech, language, and social skills reach their full potential.

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