Identification of Waardenburg Syndrome and the Management of Hearing Loss and Associated Sequelae: A Review for the Pediatric Nurse Practitioner

Jonathan Ringer, MS, CPNP-PC

Waardenburg syndrome (WS) is a rare genetic disorder that is further divided into four subtypes with distinguishing clinical manifestations, categorized by phenotypic variations based on activation or deactivation of six specific gene types. The criteria for clinical diagnosis are established based on these phenotypic variants. While key clinical features may cause suspicion of WS, genetic testing confirms the diagnosis. Pigmentary defects are one of the hallmark features of WS while some individuals may exhibit sensorineural hearing loss, which can be progressive. Audiological treatment is essential to mitigate hearing loss and to minimize speech and language deficits as well as behavior and socioemotional development. Associated complications include musculoskeletal abnormalities and Hirschsprung disease. This article aims to discuss the role of the pediatric nurse practitioner in the early identification, diagnosis, treatment, and long-term management of affected children in the primary care setting. J Pediatr Health Care. (2019) *33*, 694–701

Jonathan Ringer, Certified Pediatric Nurse Practitioner, Doctorate of Nursing Practice Candidate, Columbia University School of Nursing, New York, NY.

Conflicts of interest: None to report.

Correspondence: Jonathan Ringer, MS, CPNP-PC, Columbia University School of Nursing, 560 West 168th Street, New York, NY 10032; e-mail: jr3561@cumc.columbia.edu

J Pediatr Health Care. (2019) *33*, 694-701

0891-5245/$36.00

Published online July 31, 2019.

https://doi.org/10.1016/j.pedhc.2019.06.001

KEY WORDS

Waardenburg syndrome, sensorineural hearing loss, pigmentary defects, autosomal dominant, genetic mutation

INTRODUCTION

Waardenburg syndrome (WS) is a rare autosomal dominant disorder with four diverse subtypes. The four subtypes of WS are generally characterized by a wide range of key clinical features including pigmentation defects and craniofacial dysmorphic features (Pardono et al., 2003). Congenital sensorineural hearing loss (SNHL) is largely associated with WS and severity varies among individuals and within families (Pingault et al., 2010). The current literature explains the more common clinical manifestations of the disorder. However, there is a need for discussion surrounding the potential sequelae of untreated complications and effective primary care management. This article will review the four variants of WS, pathophysiology, and subsequent management in the pediatric primary care setting. It will also discuss the role of the pediatric nurse practitioner (PNP) in long-term management including follow-up, education, and resources that will enable families to manage care of the child affected with WS.

BACKGROUND

History

In 1951, Dutch ophthalmologist and geneticist Petrus J. Waardenburg presented a "deaf-mute" patient in a paper published in the *American Journal of Human Genetics* defining

WS I syndrome. It was not until almost 20 years later that WS was further subdivided into types I and II based on the presence or absence of dystopia canthorum (Read & Newton, 1997). David Klein, a colleague of Waardenburg, later presented a similar WS I patient with severe musculoskeletal dysfunction (WS III). In 1981, Shah et al. described 12 infants with typical WS presentation with a clear association to Hirschsprung disease (HD; WS IV; Read & Newton, 1997; Shah et al., 1981).

Prevalence

WS I–IV affects approximately one in 40,000 individuals and accounts for approximately 2% of congenital sensorineural deafness (Gad, Laurino, Maravilla, Matsushita, & Raskind, 2008; Wildhardt et al., 2013).

Etiology

There are six genes involved, including *PAX3*, *MITF*, *EDNRB*, *EDN3*, *SNAI2*, and *SOX10*. Phenotypic variation will depend on the presence or absence of one or more of these specific gene mutations, thereby differentiating the varying subtypes of the disorder (Pingault et al., 2010). The *PAX3* gene mutation is associated with both WS subtypes I and III. *MITF* and *SNAI2* mutations are associated with WS II. *SOX10, EDNRB*, and *EDN3* are involved in WS subtype IV (or Shah-Waardenburg; Genetics Home Reference, 2019). Heterozygous mutation of *SOX10* has been largely identified in both familial and isolated patients with WS IV. Carriers of the *SOX10* mutation may present with central nervous system symptoms including, but not limited to, ataxia and seizures (Amiel & Lyonnet, 2001). While WS is autosomal dominant, some inheritance patterns have been noted as autosomal recessive, in which case the carrier possesses a single copy of the mutated gene without phenotypic expression (Genetics Home Reference, 2019). Spontaneous or de novo mutations can also occur within families with no prior history of gene mutation (Milunsky, 2017).

Pathology

Defects in pluripotent neural crest cells migrate throughout the neural tube during embryological development and give rise to the clinical presentation seen in WS (Bondurand et al., 2007). These migratory cells are found throughout the peripheral nervous system, craniofacial skeletal tissue, and melanocytes of the skin, hair, eyes, and inner ear. Otopathology demonstrates the abnormal migratory pattern of cells from the neural crest, which leads to the absence of melanocytes and the stria vascularis of the cochlear duct, missing hair cells, and defective tectorial membrane (Wong, 2012). This causes abnormal development of the inner ear structures, which leads to SNHL, as well as the severe musculoskeletal features (i.e., limb hypoplasia) seen in WS III. HD associated with WS IV is a direct consequence of the untimely arrest of vagal neural crest cell migration in the hindgut. This movement craniocaudally continues to form the enteric nervous system between 5 and 12 weeks of gestation (Amiel & Lyonnet, 2001).

CLINICAL PRESENTATION

The varied phenotypic presentations of WS I–IV reflect the specific gene mutations in individuals and families. WS is primarily an auditory-pigmentary disease and the most common features include hypopigmentation in the irises, hair, and skin (Chatzinasiou, Stratigos, & Rigopoulos, 2015). Iris heterochromia (eye hypopigmentation) may be complete (i.e., a distinct color in each eye) or partial (i.e., two distinct colors in a single eye). If heterochromia is partial, it can present unilaterally or bilaterally. If bilateral, heterochromia can present symmetrically or asymmetrically (Read & Newton, 1997). The white forelock (in some cases documented as red or black) is a hallmark sign typically found midline of the scalp but may be seen in other areas of the scalp. Additionally, the white forelock may disappear and reappear in the adolescent period. Hypopigmentation of the hair in adolescence is considered premature graying (Read & Newton, 1997). Furthermore, skin hypopigmentation or leucoderma may be seen on the face, trunk, or limbs (Chatzinasiou et al., 2015). Figure demonstrates an example of a WS IV child but with classic WS presentation that can be seen in any of the four subtypes.

Another major manifestation of WS is SNHL, which can be unilateral or bilateral (Read & Newton, 1997). Hearing loss and deafness occur in approximately 50% of patients with WS II and in 25% with WS I (Wong, 2012). Furthermore, nearly all WS I affected individuals will exhibit dystopia canthorum (also called telecanthus), which is lateral displacement of the inner canthus of the eye. This displacement gives the impression of a widened nasal bridge. Dystopia canthorum presents in 95% to 99% of WS I and is virtually undetectable in WS II (Pardono et al., 2003). WS III presents like WS I with additional dysmorphic features including hypoplasia of the upper limb muscles and contracture of the elbows and fingers (Read & Newton, 1997). WS IV is characterized by the comorbid presence of HD, a congenital malformation causing intestinal blockage and severe constipation (Chatzinasiou et al., 2015). Usually diagnosed in the newborn period, WS IV features abdominal distention, vomiting, and failure to pass meconium within 24 hr after birth. More severely, WS IV may present with neonatal enterocolitis. Symptoms in older children are more chronic and include failure to thrive (Amiel & Lyonnet, 2001). For a summary of clinical manifestations and corresponding gene involvement in WS I–IV, refer to Table 1.

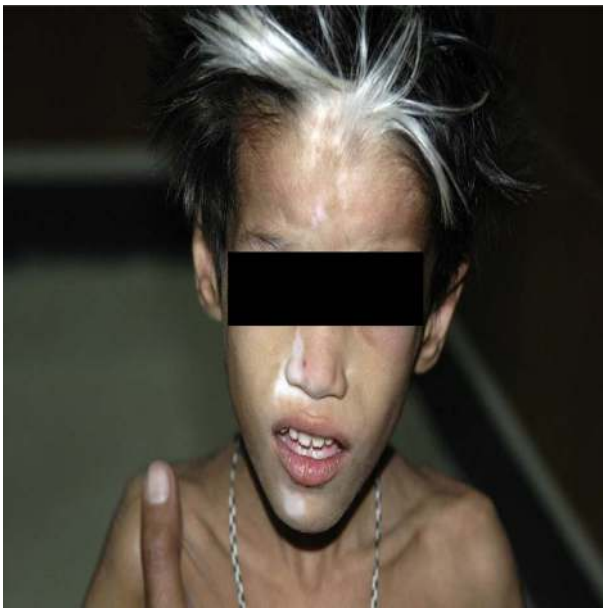
CLINICAL DIAGNOSIS

Clinical diagnosis is based on the aforementioned key features of WS discovered during physical examination as well as a complete medical and family history. If suspicious of WS, diagnosis is confirmed by genetic testing.

Physical Examination

Physical examination findings for WS include craniofacial dimorphisms as well as neurological, musculoskeletal, or gastrointestinal features, all of which could potentially point to one of the rarer variants of WS subtypes III and IV. Further assessment and screenings may be necessary based on

FIGURE. Child with WS type 4 with heterochromia, a white forelock, and leukoderma (hypopigmented skin) as seen also in WS 1 and 2. Reprinted with permissions from Jan, Stroedter, Haq, & Din, 2008.



(This figure appears in color online at www.jpedhc.org.)

examination findings. On head and neck examination, clinical features may include ocular, skin, and hair hypopigmentation. If WS is suspected in a child, one way for the examiner to distinguish between subtypes I and II is to use the W index for dystopia canthorum. The W index is based on three measurements: (1) inner canthi distance; (2) interpupillary distance; and (3) outer canthi distance. If strabismus is discovered on examination, interpupillary distance cannot be included as an accurate measurement (Milunsky, 2017; Read & Newton, 1997). An index of greater than 1.95 will support the diagnosis of WS I; however, providers should keep in mind that this is not an absolute measurement, as there can be observed overlap between WS I and II (Read & Newton, 1997).

In rare cases, children may present with signs and symptoms of HD, so the examiner will perform a digital rectal examination. If there is sudden evacuation of the stool, further work-up is indicated to confirm the diagnosis of HD. Deformities of the upper limbs seen in WS III may be more obvious but full examination will help to rule out other musculoskeletal-related disorders.

Diagnostic Criteria

The Waardenburg Syndrome Consortium established the diagnostic criteria for WS in 1992 (Wong, 2012). There are major criteria and minor criteria to clinically diagnose WS I–IV. One must have two major criteria to diagnose WS I and WS II (which may or may not include dystopia canthorum) or one major with two minor criteria. See Table 2 for diagnostic criteria for WS I–IV. Dystopia canthorum in WS is not an absolute finding. Pardono et al. (2003) presented cases in which WS individuals did not exhibit dystopia canthorum; however, these patients had at least one WS I affected family member (Read & Newton, 1997). To clinically diagnose WS III and IV, respectively, the patient must meet the criteria for WS I along with either musculoskeletal abnormalities (WS III) or the presence of HD (WS IV).

INDICATIONS FOR FURTHER DIAGNOSTICS

Audiological Screening

To assess hearing loss not picked up in the newborn period, there are several objective methods providers may use in primary care; furthermore, practitioners should be equipped with screening tools that are age specific, developmentally appropriate, and administered in quiet areas with minimal distractions to improve detection of hearing loss (Cunningham & Cox, 2003). Because of the strong association of SNHL in WS children, it would be beneficial for the examiner to use screening tools to identify SNHL versus bone conduction loss. An otoscopic examination can be utilized routinely in primary care settings to rule out certain conductive losses because of impacted cerumen or the presence of

TABLE 1. Clinical manifestations in WSI–IV and associated gene mutations

Type	Clinical features	Gene mutated (chromosome)
I (WS1)	Dystopia canthorum, broad nasal root	*PAX3* (2q35)
II (WS2)	No dystopia canthorum	*MITF* (3p14.2-p14.1) *SNAI2* (*SLUG*; 8q11)
III (WS3) (Klein-Waardenburg)	Hypoplasia of limb muscles, contractures of elbows, fingers	*PAX3* (2q35)
IV (WS4) (Shah-Waardenburg)	Hirschsprung disease	*EDN3* (20q13.2-q13.3) *EDNRB* (13q22) *SOX10* (22q13.1)

Note. *Adapted from Chatzinasiou, Stratigos, & Rigopoulos, 2015, Permission granted (2019) from above cited journal and Creative Commons Attribution 4.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. WS, Waardenburg syndrome*

TABLE 2. Diagnostic criteria for WSI–IV

Major criteria (at least two out of five)	Minor criteria (4)
Congenital sensorineural hearing loss	Congenital leucoderma (hypopigmented skin)
Complete or partial heterochromia orhypoplastic blue eyes	Synophyrys (unibrow)
White forelock	Broad high nasal root
Dystopia canthorum[a]	Hypoplasia of ala nasi
Positive first degree relative	Premature graying of hair or white hair predominance (in individuals <30 years of age)

Note. *For diagnosis of WS, one must have at least two major criteria (including dystopia canthorum) OR one major and two minor criteria. For diagnosis of WS II, one must meet diagnostic criteria of WS (not including dystopia canthorum). For diagnosis of WS III (Klein-WS), one must meet the diagnostic criteria of WS and have associated musculoskeletal abnormalities and contractures of the upper limbs. For diagnosis of WS IV (Shah-WS), one must have associated Hirschsprung disease. Table created from Read & Newton, 1997. WS, Waardenburg syndrome*

[a]*W index is based on a formula that measures both inner and outer canthal distance and interpupillary distance, which is measured in mm. W index >1.95 is abnormal and therefore signifies dystopia canthorum.*

a foreign body but cannot identify SNHL (Gregg, Wiorek, & Arvedson, 2004).

Providers use universally mandated otoacoustic emissions for screening neonates in the nursery and infants in primary care settings; however, this is not a true test of hearing, as it is limited to detecting the structural integrity of the ear (Sirimanna, 2001). While otoacoustic emissions are not helpful in determining the degree of cochlear (inner ear) malfunction seen in SNHL, tympanometry excludes conductive losses (e.g., otitis media effusion; Sirimanna, 2001). These examinations are likely to help rule out bone conduction loss in WS children but are not able to definitively determine the degree of hearing loss. More reliable subjective behavioral audiograms must be obtained to confirm hearing deficits warranting referral to audiology for evaluation and interpretation.

Renal Assessment

Currently, there is no indication to assess renal function, as there is virtually no current data showing renal anomaly associations with WS. However, Ekinci, Ciftci, Senocak, & Büyükpamukçu (2005) discuss three cases of renal anomalies discovered in one WS newborn and two WS infants; some even exhibited frequent urinary infections. Although there is no substantial evidence that these renal and urinary complications were directly associated with WS, it may be beneficial for the practitioner to ask for a complete health and family history before considering further evaluation of renal function or referral to nephrology, if necessary.

Genetics Testing

WS is not part of the universal newborn screening for infants, but diagnostic testing can be used to identify WS and to rule out other specific genetic or chromosomal disorders (Genetics Home Reference, 2019). Sequence analysis and copy number analysis of *PAX3* and *MITF* genes are deletion and duplication screening methods that have been found successful as molecular diagnostic strategies in WS patients (Wildhardt et al., 2013). Direct Sanger sequencing is a form of DNA sequencing that has also been used to confirm a diagnosis of WS (Kim et al., 2015).

Genetic screening is also thought to be useful in the identification of newborns with hearing loss that may be too mild to detect using current screening programs (Linden Phillips et al., 2013). A molecular diagnosis along with supportive clinical diagnostic criteria will confirm WS. Defining the specific genes involved will lead to better diagnosis, more accurate counseling, and advanced treatment (Read, 2000). It is important to refer to genetics if suspicious of WS.

DIFFERENTIAL DIAGNOSES

There are a variety of disorders with similar auditory-pigmentary characteristics and gene involvement that can be mistaken for WS. The more common differentials discussed in the literature include piebaldism, Cross–McKusick–Breen syndrome (CMBS), and Tietz syndrome (TS). For a summary of common differential diagnoses, see Table 3.

Piebaldism

A rare autosomal dominant disorder, piebaldism is characterized by patches of depigmented hair and skin because of the congenital absence of melanocytes. Both males and females are affected equally with no race spared (Chatzinasiou et al., 2015). These depigmented lesions are present at birth and typically remain static around the entire trunk, midupper arm to wrist, and midthigh to midcalf, continuing distally to the shin (Chatzinasiou et al., 2015). A distinguishing feature of piebaldism is hyperpigmented macules within areas of hypopigmentation or normal pigmentation of the skin (Chatzinasiou et al., 2015). The disorder's phenotypic severity is strongly related to a site of mutation within the *KIT* gene. Approximately 80% to 90% of patients present with a white forelock; however, these patients do not experience hearing loss (Wong, 2012).

Cross–McKusick–Breen Syndrome

CMBS or oculocerebral-hypopigmentation syndrome is an autosomal recessive disorder that has familial

TABLE 3. List of common differential diagnoses

Diagnoses	Common clinical features
Piebaldism	Patchy depigmented hair (white forelock, 80% to 90%) Hyperpigmented macules within hypopigmented lesions No hearing loss
Cross–McKussick–Breen syndrome	Generalized hypopigmentation of skin, hair, eyes (albinism) Microcephaly Growth retardation Cognitive delay Wide-spaced teeth No hearing loss
Tietz syndrome	Severe, variable hearing loss Frank albinism Hearing loss

Note. *Adapted from Chatzinasiou, Stratigos, & Rigopoulos, 2015. Permission granted (2019) from above cited journal and Creative Commons Attribution 4.0 License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.*

transmission. Its clinical features include generalized hypopigmentation (i.e., albinism) of the skin and hair with noted ocular involvement (Chatzinasiou et al., 2015). Associated features and complications include microcephaly, intellectual disability, hypogonadism, growth retardation, widely spaced teeth, and gingival fibromatosis (Chatzinasiou et al., 2015). CMBS has a variety of sequelae not commonly seen in WS, so complete family history and thorough physical examination will aid in excluding this diagnosis.

Tietz Syndrome

TS and WS share the *MITF* mutation but the mutation occurs at a different region of the gene (Grill et al., 2013). TS is an autosomal dominant disease characterized by depigmentation and deafness, while both features are more severe and less variable in TS (Read, 2000). For example, TS patients have frank albinism, which contrasts the patchy hypopigmented appearance observed in WS (Wildhardt et al., 2013).

MANAGEMENT

Treatment for WS is individualized based on the presenting symptoms and management ultimately depends on the subtype and severity (Chatzinasiou et al., 2015). Interventions and individualized care for those suspected of WS subtypes I–IV should be based on thorough clinical evaluation at any point throughout the lifespan of the child. The use of standardized screening tools and diagnostic tests will confirm deficits. WS treatment will include interventions for managing hypopigmentary defects and the rarer complications seen in WS III and IV. Most providers managing WS will explore the treatment of SNHL as well as issues associated with speech and language development. Indication for referrals, when necessary, will be also be discussed later in this section.

Hypopigmentary Defects

The dysfunction of melanocyte migration and further absence of melanin in the skin (hypopigmentation) have a relatively benign course and there is no indication for treatment. There is some evidence that suggests an increased risk of skin cancers and sunburn in an individual with hypopigmentation because of lack of melanin. Therefore, it may be beneficial to avoid prolonged sun exposure and to use sunscreen with high sun protection factor (National Organization of Rare Disorders [NORD], 2019). Long-sleeved clothing may also be suggested to protect the skin; tinted glasses or contact lenses may reduce sensitivity to light (NORD, 2019).

Klein (III) and Shah (IV) WS

Management of musculoskeletal deformities or contractures in WS III patients is not routine in primary care. However, occupational therapy or physical therapy may provide preventive and supportive measures to maintain activities of daily living by improving the child's range of motion and fine motor functioning (Skalsky & McDonald, 2012). In severe circumstances, orthopedics may be consulted for a surgical consultation (NORD, 2019). For the child suspected to have WS IV, referral to gastroenterology is necessary for further evaluation. The work-up for HD may include abdominal X-ray, barium enema, and full-thickness rectal biopsy. It is not uncommon to see a distended small bowel and proximal colon with an empty rectum on X-ray or a classic image of aganglionic stenosis of the distal gut. However, full-thickness rectal biopsy may rule out meconium ileus in newborns or other intestinal malformations or obstructions in older children (Amiel & Lyonnet, 2001). Treatment will depend on the severity of the disease and may include both removal of the aganglionic region of the gastrointestinal tract and resection of the healthy tissues of the intestines. A temporary colostomy may be necessary before surgical correction to maintain colonic outlet (NORD, 2019).

Hearing Loss Treatment

After referral is made, the audiologist will confirm the type and severity of hearing loss. Individualized treatment depends on the degree of loss measured. Interventions may include amplification devices (hearing aids), frequency modulated systems (FM), or cochlear implantation (CI) to optimize cognitive development in children with prelingual deafness, thereby improving the ability to hear language and acquire speech (Gifford, Holmes, & Bernstein, 2009; Gregg et al., 2004; Shearer, Hildebrand, & Smith, 2016). A sensorineural deficit threshold greater than 25 dB for at least two frequencies between 250 and 4,000 Hz without evidence of middle ear effusion or other factors will fit the major criteria

for hearing loss in WS (Chatzinasiou et al., 2015). For severe-to-profound SNHL, implantable devices seem to be most appropriate and effective assistive technology allowing stimulation of the auditory nerve to send impulses to the brain (Gifford et al., 2009; NORD, 2019).

Amplification and frequency modulated systems

Use of hearing aids or amplification is one form of assistive technology widely accepted in treating mild-to-moderate hearing loss in children (Gregg et al., 2004). There are various types and styles of hearing aids and children must be refitted as they grow older; children must also be medically cleared before installation. Conventional and programmable analog types are appropriate for most children; however, fully digital aids are more complex and help facilitate manipulation and increase signal processing (Gregg et al., 2004). Many can be installed behind the ear, are durable with long battery life, and are compatible with assistive listening devices (Gregg et al., 2004). For most school age hearing-impaired children, FM systems are commonly used in the classroom or in group environments to assist the child in discriminating sounds and to reduce noisy environments (Gregg et al., 2004).

Cochlear implantation

For SNHL in children, CI is an approved strategy for enhancing auditory impairment and has been successfully utilized in individuals with WS (Chatzinasiou et al., 2015). For severe-to-profound hearing loss, CI is considered in children older than 1 year, particularly between 18 months and 2 years of age (Sirimanna, 2001; Shearer et al., 2016). CI relies on electrical as opposed to acoustic stimulation of the auditory nerve, which is more commonly used in mild-to-moderate hearing loss. CI is a great option for prelingual and postlingual deaf children and candidacy is evaluated on a case-by-case basis by a multidisciplinary professional team (Gregg et al., 2004).

One challenge with CI is that certain children may show more benefits than others depending on cognitive, developmental, or physical comorbid factors. In particular, there have been studies measuring auditory and speech outcomes of WS children with CI. Amirsalari et al. (2011) published a prospective study on the outcome of CI in children with WS by comparing the effects on children with SNHL alone. Three hundred thirty-six cochlear implanted WS and non-WS children were monitored for 3 years (2008−2010). The study concluded that CI was effective in all participants but WS children had lower speech intelligibility ratings than those with only SNHL. While this small disparity is unclear, CI is still proven effective and beneficial in WS children for both speech intelligibility and auditory perception.

Auditory Malfunction and Its Effects on Speech and Language

SNHL is one of the more profound and severe manifestations of WS. It is important to screen for, identify, and manage hearing loss early. The American Academy of Pediatrics recommends early detection of congenital hearing loss at 4 weeks, definitive diagnosis by 3 months, and intervention by 6 months (Erenberg, Lemons, Sia, Trunkel, & Ziring, 1999; Gifford et al., 2009). Evidence from the Joint Committee on Infant Hearing (American Speech-Language Hearing Association, 2000) suggests that early identification of hearing loss, especially within the first 6 months of life, will prevent speech deficits and promote language acquisition. However, congenital hearing loss may not present until later in childhood (Cunningham & Cox, 2003). It is the recommendation of the American Academy of Pediatrics that all objective screening should begin in the newborn period and continue periodically throughout childhood and adolescence (Cunningham & Cox, 2003). Universal newborn hearing screening programs allow for early hearing detection and intervention (Gifford et al., 2009).

The consequences of failure to detect congenital hearing loss include poor academic performance, emotional and behavioral issues, and personal-social maladjustments (Cunningham & Cox, 2003). It has been demonstrated that children who participate in early hearing detection and intervention programs exhibit higher performance than their later-detected peers in vocabulary skills and intellectual development—at almost 100% auditory capacity of their unimpaired peers (Gifford et al., 2009). Auditory screening is important to assess in suspected WS children. If there is a failed screening, children should be referred to audiology for further testing to confirm the degree of hearing loss and subsequent treatment and management.

Speech and language intervention

A child who does not form two-word sentences or has a vocabulary of less than 50 words by the second year of life is considered to have speech development delay (Bright Futures, 2019). These children are often called "late talkers" and have age-appropriate language but no active vocabulary or sentence structure. Speech development disorder is considered in individuals who beyond the age of 36 months display speech development delay by two standard deviations from the mean age or cognitive development delay by one standard deviation from the mean age (Lang-Roth, 2014). Children who receive immediate speech and language intervention along with corrected audio impairment are able to catch up by age three (i.e., late bloomers). Any child with impairment beyond age three will require continued therapeutic intervention (Lang-Roth, 2014).

PROGNOSIS

There is little supportive documentation discussing the prognosis of WS. With the rarer and more severe subtypes such as WS IV, there is a high incidence of colonic aganglionosis with or without small bowel involvement seen in HD. If not properly treated, this pathology may lead to further complications and mortality in the newborn and early infant (Mahmoudi et al., 2013). Therefore, early identification of symptoms and appropriate subsequent management along

TABLE 4. Resources for families of the hearing impaired

Organization	Web site	Mission
Hearing First	https://hearingfirst.org/	Helping deaf or hard of hearing children to achieve learning and literacy.
American Society for Deaf Children	http://deafchildren.org/	Empowering families with deaf children by providing access to language-rich environments.
NOAH	http://www.albinism.org	Providing updated information about all aspects of albinism and a place for people to gain resources including support and fellowship.
GARD Information Center	https://rarediseases.info.nih.gov/GARD	Providing the public access to information related to rare or genetic diseases for patients, family members, friends, and health professionals.
CID	https://cid.edu/	Maximizing learning with the provision of audiology, speech-language pathology, occupational therapy, and school counseling.

Note. *Created by Author. CID, Central Institute for the Deaf; GARD, genetic and rare diseases; NOAH, National Organization for Albinism and Hypopigmentation*

with routine follow-up will enhance the quality of health for individuals with WS.

ROLE OF THE PNP

Clinical

The PNP should carefully evaluate suspected children with WS, help manage symptoms, make appropriate referrals, and monitor these patients long-term. Audiological screening and referral for treatment will help to prevent further progression of hearing loss. The results of hearing screening should be explained carefully to parents and clearly documented in the child's medical record, and developmental surveillance of skills and school performance should continue at each well-child visit (Harlor & Bower, 2009). Genetic counseling should be offered to families, as some members may be unknown carriers of WS-associated genes (e.g., *PAX3*). This may increase understanding of the genetic pattern of the disease and aid in future family planning. The PNP should coordinate care among the multidisciplinary team to ensure proper management of presenting symptoms and consistent follow-up for children with WS for individualized management.

Education of the PNP

It is essential that the PNP remain cognizant that children learn most of their speech and language skills from 0 to 3 years of age. The more time within this critical period that elapses without proper management, the poorer the prognosis (Gregg et al., 2004). Practitioners should be familiar with community resources, support groups, and organizations available for hearing-impaired children and their families. For a list of resources, see Table 4. The PNP should also coordinate care among members of the multidisciplinary team: specifically, otolaryngologists, audiologists, and speech-language pathologists who possess special training and experience in the pediatric population (Bush, 2003; Cunningham & Cox, 2003). It is imperative for PNPs to stay abreast of emerging literature on the sequelae of WS as well as relevant guidelines in pediatric primary care so that they may provide the most appropriate care for patients.

Further Research

Further research is needed to understand the importance of treatment and management of hypopigmentation of the eyes and skin as well as potential comorbid associations seen in patients with WS III and IV. Although the association of WS and renal anomaly is extremely rare and only reported in a few cases, more studies should investigate the potential association or causative nature of renal disease with WS patients. Further investigation can therefore support early testing, diagnosis, and management of both common and rare sequelae of WS.

CONCLUSION

WS is an autosomal dominant auditory-pigmentary disease. It is caused by the mutation of certain genes leading to abnormal melanocyte migration from the neural crest throughout the body, including skin, hair, eyes, and areas of the inner ear. This pathology results in hypopigmentation and SNHL. Resulting clinical manifestations may vary among children depending on specific gene mutations. Clinical diagnosis and molecular genetic testing will definitively determine the WS subtype. Early detection of SNHL has been shown to provide better outcomes for younger children by preventing further deterioration of hearing and thereby improving speech and language development. Severe complications seen in WS III and IV may require additional support and management. Continued support and follow-up among the multidisciplinary medical team will ultimately improve the quality of life for the child affected with WS. Finally, additional resources such as genetic counseling, education, and support groups for the hearing impaired should be suggested to families based on their specific needs.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.pedhc.2019.06.001.

REFERENCES

American Speech-Language Hearing Association (ASHA). (2000). *Year 2000 position statement: Principles and guidelines for early hearing detection and intervention*. Retrieved from http://lobby.la.psu.edu/003_Hearing_Screenings/Organizational%20Statements/ASHA/ASHA_Joint_Committee_on_Infant_Hearing_Statement.htm

Amiel, J., & Lyonnet, S. (2001). Hirschsprung disease, associated syndromes, and genetics: A review. *Journal of Medical Genetics, 38*(11), 729–739.

Amirsalari, S., Ajallouyean, M., Saburi, A., Haddadi Fard, A., Abed, M., & Ghazavi, Y. (2011). Cochlear implantation outcomes in children with Waardenburg syndrome. *European Archives of Oto-Rhino-Laryngology, 269*(10), 2179–2183.

Bondurand, N., Dastot-Le Moal, F., Stanchina, L., Collot, N., Baral, V., Marlin, S., … Pingault, V. (2007). Deletions at the *SOX10* gene locus cause Waardenburg syndrome types 2 and 4. *American Journal of Human Genetics, 81*(6), 1169–1185.

Bright Futures. (2019). *Early childhood: 1–4 years*. Retrieved from https://www.brightfutures.org/bf2/pdf/pdf/EC.pdf

Bush, J. S. (2003). AAP issues screening recommendations to identify hearing loss in children. *American Family Physician, 67*(11), 2409–2413.

Chatzinasiou, F., Stratigos, A., & Rigopoulos, D. (2015). Pigment genodermatoses affecting melanocyte development and migration from the neural crest: Piebaldism, Waardenburg syndrome and Cross–McKusick–Breen syndrome. *Journal of Pigmentary Disorders, 2*(3), 1–6.

Cunningham, M., Cox, E. O., & Committee on Practice and Ambulatory Medicine and the Section on Otolaryngology and Bronchoesophagology. (2003). Hearing assessment in infants and children: Recommendations beyond neonatal screening. *Pediatrics, 111*(2), 436–440.

Ekinci, S., Ciftci, A. O., Senocak, M. E., & Büyükpamukçu, N. (2005). Waardenburg syndrome associated with bilateral renal anomaly. *Journal of Pediatric Surgery, 40*(5), 879–881.

Erenberg, A., Lemons, J., Sia, C., Trunkel, D., & Ziring, P. (1999). Newborn and infant hearing loss: Detection and intervention. American Academy of Pediatrics. Task Force on Newborn and Infant Hearing, 1998- 1999. *Pediatrics, 103*(2), 527–530.

Gad, A., Laurino, M., Maravilla, K. R., Matsushita, M., & Raskind, W. H. (2008). Sensorineural deafness, distinctive facial features, and abnormal cranial bones: A new variant of Waardenburg syndrome? *American Journal of Medical Genetics Part A, 146A*(14), 1880–1885.

Genetics Home Reference. (2019). *Waardenburg syndrome*. Retrieved from https://ghr.nlm.nih.gov/condition/waardenburg-syndrome#diagnosis

Gifford, K. A., Holmes, M. G., & Bernstein, H. H. (2009). Hearing loss in children. *Pediatrics in Review, 30*(6), 207–215.

Gregg, R. B., Wiorek, L. S., & Arvedson, J. C. (2004). Pediatric audiology: A review. *Pediatrics in Review, 25*(7), 224–234.

Grill, C., Bergsteinsdóttir, K., Ogmundsdóttir, M. H., Pogenberg, V., Schepsky, A., Wilmanns, M., … Steingrímsson, E. (2013). MITF mutations associated with pigment deficiency syndromes and melanoma have different effects on protein function. *Human Molecular Genetics, 22*(21), 4357–4367.

Harlor, A. D., Bower, C., & Committee on Practice and Ambulatory Medicine, & Section on Otolaryngology—Head and Neck Surgery. (2009). Hearing assessment in infants and children: Recommendations beyond neonatal screening. *Pediatrics, 124*(4), 1252–1263.

Jan, I. A., Stroedter, L., Haq, A. U., & Din, Z. U. (2008). Association of Shah-Waardenburgh syndrome: A review of 6 cases. *Journal of Pediatric Surgery, 43*(4), 744–747.

Kim, S. H., Kim, A. R., Choi, H. S., Kim, M. Y., Chun, E. H., Oh, S. H., & Choi, B. Y. (2015). Molecular etiology of hereditary single-side deafness: Its association with pigmentary disorders and Waardenburg syndrome. *Medicine, 94*(43), e1817.

Lang-Roth, R. (2014). Hearing impairment and language delay in infants: Diagnostics and genetics. *GMS Current Topics in Otorhinolaryngology—Head and Neck Surgery, 13:Doc05.*

Linden Phillips, L., Bitner-Glindzicz, M., Lench, N., Steel, K. P., Langford, C., Dawson, S. J., … Packer, C. (2013). The future role of genetic screening to detect newborns at risk of childhood-onset hearing loss. *International Journal of Audiology, 52*(2), 124–133.

Mahmoudi, A., Rami, M., Khattala, K., Elmadi, A., Afifi, M. A., & Youssef, B. (2013). Shah–Waardenburg syndrome. *Pan African Medical Journal, 14*, 60.

Milunsky, J. (2017). Waardenburg syndrome type I. In M. P. Adam, H. H. Ardinger, R. A. Pagon, et. al. (Eds.), *GeneReviews*. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1531/

National Organization for Rare Disorders (NORD). (2019). *Waardenburg syndrome*. Retrieved from http://rarediseases.org/rare-diseases/waardenburg-syndrome/

Pardono, E., van Bever, Y., van den Ende, J., Havrenne, P. C., Iughetti, P., Maestrelli, S. R. P., … Otto, P. A. (2003). Waardenburg syndrome: Clinical differentiation between types I and II. *American Journal of Medical Genetics Part A, 117A*(3), 223–235.

Pingault, V., Ente, D., Dastot-Le Moal, F., Goossens, M., Marlin, S., & Bondurand, N. (2010). Review and update of mutations causing Waardenburg syndrome. *Human Mutation, 31*(4), 391–406.

Read, A. P. (2000). Hereditary deafness: Lessons for developmental studies and genetic diagnosis. *European Journal of Pediatrics, 159*(S3), S232–S235.

Read, A. P., & Newton, V. E. (1997). Waardenburg syndrome. *Journal of Medical Genetics, 34*(8), 656–665.

Shah, K. N., Dalal, S. J., Desai, M. P., Sheth, P. N., Joshi, N. C., & Ambani, L. M. (1981). White forelock, pigmentary disorder of irides, and long segment Hirschsprung disease: Possible variant of Waardenburg syndrome. *Journal of Pediatrics, 99*(3), 432–435.

Sirimanna, K. S. (2001). Management of the hearing impaired infant. *Seminars in Neonatology, 6*(6), 511–519.

Skalsky, A. J., & McDonald, C. M. (2012). Prevention and management of limb contractures in neuromuscular diseases. *Physical Medicine and Rehabilitation Clinics of North America, 23*(3), 675–687.

Shearer, A. E., Hildebrand, M. S., & Smith, R. J. H. (2016). Deafness and hereditary hearing loss overview. In M. P. Adam, H. H. Ardinger, R. A. Pagon, et. al. (Eds.), *GeneReviews [Internet]*. Seattle (WA): University of Washington, Seattle. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1434/

Wildhardt, G., Zirn, B., Graul-Neumann, L. M., Wechtenbruch, J., Suckfüll, M., Buske, A., … Steinberger, D. (2013). Spectrum of novel mutations found in Waardenburg syndrome types 1 and 2: Implications for molecular genetic diagnostics. *BMJ Open, 3*,(3) e001917.

Wong, J. (2012). A male infant who has a white hair tuft and hypopigmented macules. *Pediatrics in Review, 33*(3), e18–e21.