Familial Phenotype of Waardenburg Syndrome in One Family: A Case Series

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Abstract

Waardenburg syndromeis an accumulation of some genetic conditions which leads to sensorineural hearing loss (SNHL) and depigmentation of hair, skin, and eyes. The cause of sensorineural hearing loss in children can be congenital or hereditary, characterized by sensorineural deafness, associated with pigment disorders and tissue defects. Based on the accompanying symptoms, Waardenburg syndrome is divided into 4 types, where the most often ones are type 1 and 2. Clinical symptoms including dystopia canthorum, pigment disorders (white crest, abnormalities of eyebrow, eyelashes, body hair and iris heterochromia), sensorineural deafness, protruding nose and depigmentedhair at young age. Based on physical and additional examinations performed on five patients, all results showed mayor and minor symptoms of waardenberg syndrome accompanied by dystopia canthorum, therefore classified aswaardenburg type 1.

Conclusion: All patients are classified as type 1 Waandenberg syndrome which were inherited in the form of autosomal dominant.

Keywords: *SNHL, Waardenburg syndrome, dystopia canthorum, autosomal dominant.*

Introduction

Deafness is one of the problems in children that will affect speech, social, cognitive and academic development. Deafness can be caused by congenital or acquired abnormalities.(1) In developed countries, the rate of congenital deafness ranges from 0.1 to 0.3% of live births, whereas the number in Indonesia is about 0.1% based on a survey conducted by the health department in 7 provinces from 1994 to 1996. Congenital deafness in Indonesia is estimated to be around 214,100, considering the number of total population is 214,100,000 million. This number will increase every year with an increase in population due to the high birth rate, 0.22% from the previous one.(2) Congenital deafness occurs in a baby due to factors that affect pregnancy and delivery processes. Congenital deafness can be genetic (hereditary) and non genetic. Non genetic congenital deafness is determined by the mother's condition during pregnancy and delivery processes.(3)

Waardenburg syndrome is one of congenital hereditary deafness, firstly discovered by an ophthalmologist from the Netherlands named Petrus Johannes Waardenburg in 1947. He initially found some symptoms of canthorum dystopia, different eye pigment colors (heterochromia) and deafness.(1,4) In 1951, after identifying other patients with the same symptoms, Waardenburg classified patients with these symptoms into Waardenburg type I syndrome. In 1971, Arias further defined Waardenburg type II syndrome.(5) Then in 1981, Shah and other researchers discovered infants with Hirschprung's disease and white forelock which is classified as Waardenburg type IV syndrome. Then in 1983, Klein discovered patients with type I symptoms accompanied by abnormalities of arm hypoplasia and arthrogyposis on the hands and wrists, which were then classified as Waardenburg type III syndrome.(6)

Waardenburg syndrome is an accumulation of some genetic conditions which leads to sensorineural hearing

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loss (SNHL) and depigmentation of hair, skin, and eyes. Although most people with Waardenburg syndrome have normal hearing, waardenburg syndrome can also cause moderate to very severe hearing loss which can occur in one or both ears and can occur from birth. Someone with this condition often has very pale blue eyes or even different eye color one to another,in some cases one eye is blue while the opposite eye is brown. Sometimes one eye even has two different colors. Typical hair coloring such as white hair or hair that turns into premature gray is another common sign of waardenburg syndrome.[7,8]

The most common characteristic of waardenburg syndrome is iris color differentiation between the two eyes: one eye usually has brown iris and the opposite eye is blue. Sometimes color differences are found in one eye, or in some cases both eyes are bright blue. Since deafness often arises as a symptom of this syndrome, hearing examination and treatment, such as the use of hearing aids and the selection of schools suitable for child development, should be a concern.[7,8]

Case Report: An examination was conducted on a family with some family members who had a lineage of waardenburg syndrome where the phenotype of waardenburg syndrome was present in the last 3 generation.There were no recorded inbreeding in the family and there were no marriages of family members with other people known to suffer from waardenburg syndrome.

Case 1: A 16-year-old girl (Ms.F) is suspected of having hearing loss since she was a baby,for she did not respond when called and could not speak at all. Her eyes are blue since birth, and there were family members having the same abnormalities which were her sister and aparents. No abnormalities were found in the prenatal, perinatal and postnatal history. Motor developments were good according to her age.

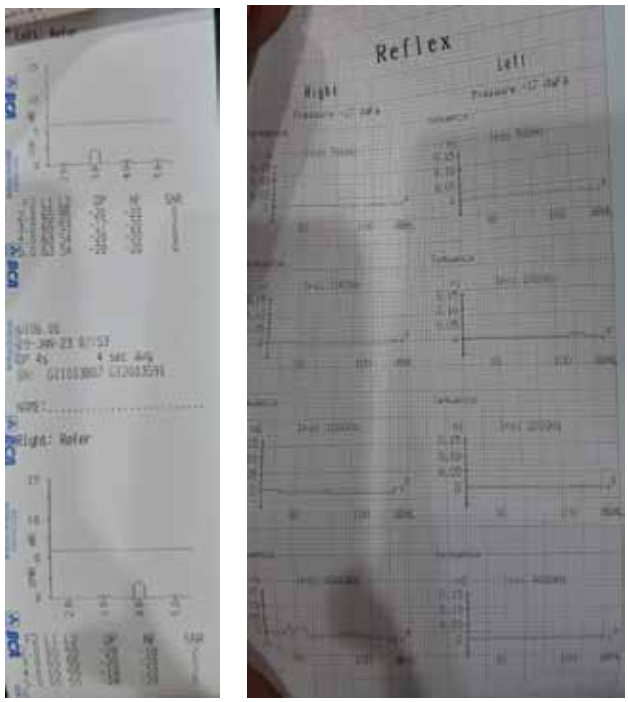
Physical examination of the ear, nose, oropharynx and neck revealed no abnormalities, while the examination on maxillofacial region showed abnormalities of iris pigments in the form of complete iris heterochromia, canthorumdystopia, and alanasi hypoplasia. Musculoskeletal and gastrointestinal were normal.

Audiological examination revealed total deaf audiogram, with type A/type Atympanogram, and no acoustic reflexes in both ears. OAE examination referred to both ears, concluded as abnormality in left/right outer cochlear hair cells.

Case 2: A 38-year-old woman (Mrs. H) was suspected of having hearing loss since she was a baby, for she did not respond when called and could not speak at all. Her eyes are blue since birth, and there was a history of hair pigment changes (whitening) before the age of 30, along with familial history of the same abnormality. Her son also has blue eyesyet without any hearing loss.

Examination of the ear, nose, oropharynx and neck showed no abnormalities, whereas examination of the maxillofacial region showed irregular pigment abnormalities in the form of complete heterocromia of the iris, canthorumdystopia (W index>1.95), premature gray hair and broad nasal root. Musculoskeletal and gastrointestinal tract are within normal limits.

The result of the audiology examination showed total deafness,with type A/type A tympanogram, and no acoustic reflexes in both ears. OAE examination showed refer to both ears, concluded as abnormality in left/right outer cochlear hair cells.



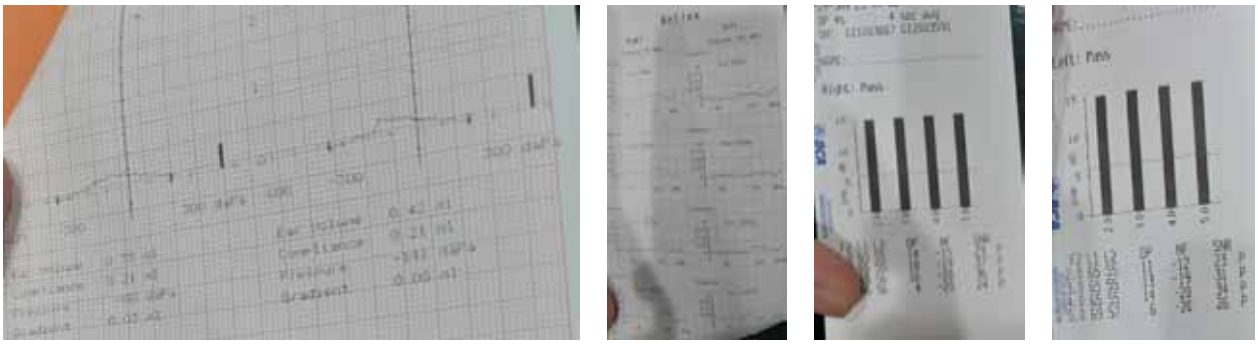
Picture 1. The result of OAE and reflexes examination in Mrs.H

Case 3: A boy (M) aged 1 year 10 months has unilateral blue eye from birth, with no abnormalities in the prenatal, perinatal and postnatal periods. His mother does not have a history of serious illness during

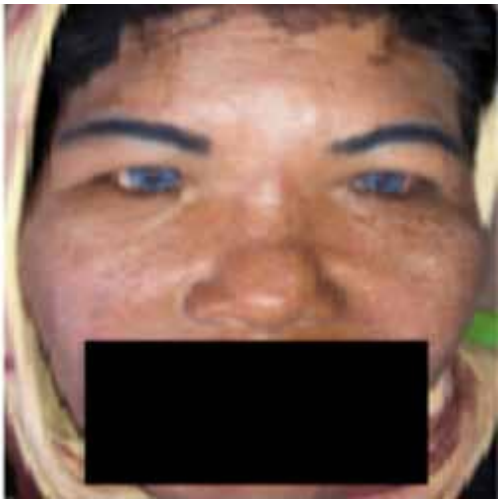
pregnancy. The patient is a child of a mother suffering from type 1 waardenberg syndrome and a father who is deaf. There is no history of seizures.

Physical examination of the ear, nose, oropharynx and neck did not show any abnormalities, while examination of the maxillofacial region showed pigment abnormalities in the form of partial heterochromia, dystopia canthorum, synophyrys and alanasihypoplasia. Musculoskeletal and gastrointestinal tract are within normal limits.

The result of the tympanometry examination are type A/type Atympanogram, and the acoustic reflexes in both ears are within normal limits. OAE examination revealed a pass in both ears, so it was concluded that there was no disruption of the right/left outer cochlear hair cells.



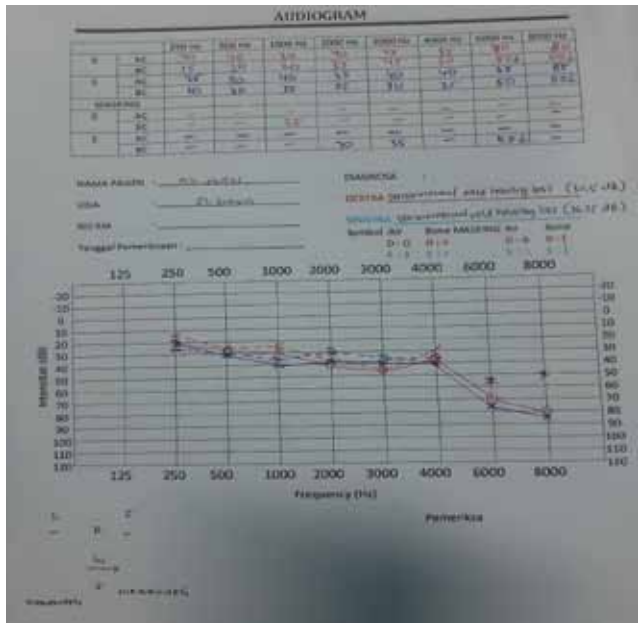
Picture 2. The result of tympanometry and OAE in boy M



Picture 3. Heterochromia in Mrs.M

Case 4: A 52-year-old woman (Mrs. M) has blue eyes since birth, and there is a history of changes in hair pigment (whitening) before the age of 30. There is a family history of the same abnormality. The patient has a boy who has blue eyes yet without hearing loss.

Examination of the ear, nose, oropharynx and neck showed no abnormalities, whereas examination of the maxillofacial region showed pigment abnormalities in the form of complete heterocromia of the iris, canthorumdystopia (W index>1.95), premature gray hair and broad nasal root. Musculoskeletal and gastrointestinal tract are within normal limits. Audiometry examination showed mild sensorineural hearing loss.



Picture 4. The result of audiometry in Mrs. M

Case 5: A 45-year-old woman (Mrs. R) has a history of changes in hair pigment (turning white) before the age of 30, without blue eyes. There is a family history of the same disorder. The patient had a boy who had blue eyes

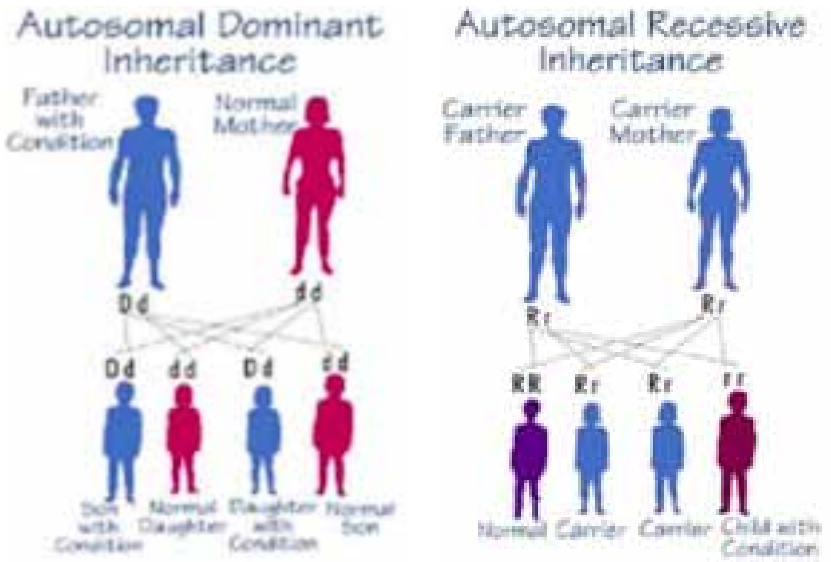
without hearing loss, and one girl who had blue eyes accompanied by severe sensorineural hearing loss from birth.

Picture 5. Heterochromia in Mrs.F

Examination of the ear, nose, oropharynx and neck showed no abnormalities, whereas examination of the maxillofacial region showed pigment abnormalities in the form of complete heterocromia of the iris, canthorumdystopia (W index>1.95), premature gray hair and broad nasal root. Musculoskeletal and gastrointestinal tract are within normal limits. Audiometry examination showed moderate sensorineural hearing loss.

Waardenburg syndrome is an autosomal dominant inherited disorder with the most frequent manifestations of congenital sensorineural deafness and disorders of hair and skin pigmentation.[1,2]

Waardenburg syndrome types 1, 2 and 3 are inherited autosomal dominant, whereas type 4 is inherited autosomal recessive.[8]



Picture 6. The flow of inherited dominant and recessive autosomal[13]

Waadenburg type 1 is characterized by the presence of non-progressive congenital sensorineural deafness, dystopia canthorum, white forelock, and several minor abnormalities such as congenital leukoderma. Waardenburg type 2 and type 3 are characterized by the presence of dystopia canthorum and musculoskeletal abnormalities in the upper extremities (aplasia of the ribs, carpal bone abnormalities, cystic formation of sacrum bones, amyoplasia, joint stiffness and bilateral syndactyly). Furthermore, Waardenburg type 4 syndrome is characterized by iris heterochromia, sensorineural hearing loss and is accompanied by Hirschprung's disease.[3,4]

Table 1. Classification of clinical manifestation in Waardenburg syndrome[13]

Type	Clinical manifestation
I	Dystopia canthorum W > 1.95
II	No dystopia
III (Klein waardenburg)	Hypoplasia of extremity muscles such as elbow and fingers
IV (Shah- waadenburg)	Hirschsprung's disease

Waardenburg syndrome is an auditory-pigmentary disorder with a basic cause of hearing loss is the need for melanocytes in the cystic vascular cyst of the unexplained, for example in the case of albinism where hearing remains normal, but there is no melanocytes that cause the vascular stria to become thin, there is no growth of endocochlear, and the development of Reissner membrane is collapsed which leads to the damage of the organ of Corti. All melanocytes, except for the retina, originate from embryonic neural crest. The absence of melanocytes can be caused by failure of differentiation in the neural crest, failure of melanoblast to migrate, or failure of late differentiation or persist in the end place of melanoblast which can be caused by mutations in the genes that regulate it (PAX3, MITF, SOX10, and EDNRB).[11]

The Waardenburg Consortium in 1992 established diagnostic criteria for Waardenburg type 1 syndrome, where patients must have at least 2 major symptoms or 1 major symptom with 2 minor symptoms. Major symptoms include congenital sensorineural hearing loss; iris pigment disorders that can be in the form of complete heterochromic iris (both eyes are of different color), partial or segmental heterochromia (there are pigmented blue or brown segments in one eye or both eyes), hypoplastic blue eyes (bright blue eyes in both eyes), hair hypopigmentation in the form of white forelock, dystopia canthorum (w index> 1.95), with abnormalities also found in siblings. Furthermore, minor symptoms include congenital leukoderma (hypopigmentation areas can be found in several places), synophyrys (thick eyebrows that meet medially); wide or high nasal base; hypoplasia of alanasi, premature graying hair (especially scalp hair, before the age of 30 years). On the other hand, symptoms for type 2 Waardenburg syndrome by Lui et al include the presence of 2 major symptoms, with the exception of dystopia canthorum and including premature graying.[1,2,4]

Table 2. Diagnostic criteria of Waardenberg syndrome[12]

Major criteria	Minor criteria
• Congenital sensorineural hearing loss • White forelock, hair hypopigmentation • Pigmentation abnormality of the iris – Complete heterochromiairidum (irides of different color) – Partial/segmental heterochromia (two different colors in same iris, typically brown and blue) – Hypoplastic blue irides, or brilliant blue irides • Dystopia canthorum, W index >1.95 • Affected first-degree relative	• Skin hypopigmentation (congenital leukoderma) • Synophyrys/medial eyebrow flare • Broad/high nasal root, prominent columella • Hypoplasticalaenasi • Premature gray hair (before age 30 years)

Clinical abnormalities in Waardenburg type 1 can vary even if found in one family. The most common abnormality is sensorineural deafness which is congenital, unilateral or bilateral, and not progressive, with a very severe degree (>100 dB). In the eyes can also be found differences in color, generally one eye is blue and one eye is brown.[12,13]

Dystopia canthorum is determined from the W Index calculated based on the distance between the medial canthus (a), lateral canthus (c), and the distance between pupils (b) in millimeters, with the following formula. The diagnosis is established if the W index is more than 1.95.[3]

Congenital sensorineural deafness is a manifestation that often accompanies Waardenburg syndrome. Therefore, audiology examination has a very important role. Audiology screening can be performed on infants and children whose parents or families have a history of Waardenburg syndrome, although there are no clinical manifestations.

Congenital deafness causes problems with individual and social development of individuals. The use of hearing aids is one of the options that can be used as early as possible, to prevent the development of speech, language, mental, and intellectual development, so that patients are expected to live a normal life.

There are 2 method recommended for use in the examination of hearing loss in newborns, namely Otoacoustic Emission (OAE) and Auditory Brainstem Responses (ABR)/Brainstem Evoked Response Audiometry (BERA), which is usually done in a hospital in a state of calm sleep babies. Both are fast and easy to do, not invasive, inexpensive, and quite sensitive in detecting hearing loss.[10]

In the first case, the patient was diagnosed as type 1 waardenburg syndrome because of the bluish iris color and very severe neural sensory deafness, accompanied by dystopia canthorum. Furthermore, patient in the second case was also diagnosed as waardenburg type 1 syndrome due to bluish iris color and severe sensorineural deafness, and accompanied by dystopia canthorum. For the third case, the patient was diagnosed as waardenberg type 1 syndrome because of a unilateral grayish iris color without hearing loss, accompanied by dystopia canthorum.

In the fourth case, the patient was diagnosed as waardenburg type 1 syndrome due to a bluish iris color and moderate degree of sensorineural deafness, accompanied by dystopia canthorum. Subsequently, the fifth case was diagnosed as waardenberg type 1 syndrome due to unilateral gray iris color without hearing loss, accompanied by dystopia canthorum. All patients examined did not show any musculoskeletal and gastrointestinal abnormalities.

Management in patients with Waardenburg syndrome should be done as early as possible by using hearing aids (ABD) and auditory verbal therapy (AVT). In reported cases, treatment is aimed at deafness and correcting anatomical abnormalities through surgical procedures.

Deafness must be detected immediately and get treatment as early as possible. Genetic counseling can be done and attention is directed towards providing information about clinical manifestations that will emerge and the likelihood that a child will suffer from this syndrome from parents who have suffered from Waardenburg syndrome, so that disorders that must be treated immediately can be of concern to parents and family.[7,9]

Consultation with a geneticist is important, because people with type 1 and 2 Waanderburg generally have a 50% risk to inherit the syndrome to their baby during pregnancy. Consultation and examination by an ophthalmologist is needed to evaluate the visual and visual field and other abnormalities in the eye field. In general, people with Waardenburg syndrome have vision within normal limits. A dermatologist's consultation is done if there are abnormalities in the skin to rule out other diseases or malignancies. Evaluations by pediatricians are carried out for growth and development examinations, while surgeon evaluations are performed if there are abnormalities in other organs such as hirschprung's disease.[1,5]

Congenital deafness causes problems of individual and social development. Early detection and treatment offers hope in individual development. The use of hearing aids is one of the options that needs to be given as early as possible to prevent impaired speech, language, mental and intellectual development so that patients are expected to be able to live a normal life.[10]

In the field of otorhinolaryngology, the management of Waardenburg syndrome is aimed at hearing screening, evaluation of sensorineural deafness for hearing instrumentation, and when possible using cochlear implants. Other treatment is speech therapy so that people with Waardenburg syndrome can communicate.[15]

Early diagnosis and improvement of hearing defects are important for the psychological development of children with this congenital abnormality and also to help reduce feelings of isolation.[2] Management of hearing loss depends on the severity of the hearing loss. Cochlear implants are still the main choice for rehabilitation of hearing function in children with severe to severe sensorineural hearing loss. In patients with Waardenburg syndrome, the normal level of intelligence is normal and the hearing loss that occurs is sensoryneural, so that the use of cochlear implants can provide good results if accompanied by an intensive rehabilitation program.[14] The process of hearing rehabilitation in sensoryneural hearing loss provides a good prognosis, so that the implant kolkea is recommended for people with Waardenburg syndrome if there are no anatomical abnormalities in the inner ear, including cochlear hypoplasia, internal acoustic canal, absence of posterior semicircular canals and malformations in the other two semicircular canals.[14] Cochlear implants provide direct stimulation to the cochlear nerve fibers. Cochlear implants are indicated in both adults and children with very severe hearing loss who do not benefit from the use of conventional hearing aids. Prognosis of hearing, language development and sociability in young

children (deafness) is not only dependent on the optimal amplification of hearing aids or cochlear implants, but also depends on the type of rehabilitation education that the patient receives. There are various types of education that can be used as a rehabilitation process for patients with hearing loss. In education based on auditory-verbal communication, patients learn to use sound instructions optimally by practicing understanding languages and pronouncing language correctly. In oral communication, patients learn to hear and speak with the help of lip readings. In the type of total communication rehabilitation, a combination of oral language and sign language is taught to maximize communication skills.[14]

Management of hearing loss includes prevention, education, and psychological assessment. Prevention is done by avoiding predisposing factors such as marriage between sufferers of congenital deafness and marriage between families. Screening should start as early as possible, ideally all children aged 6-9 months have a definite hearing function, and then immediately after entering school at the age of 5-6 years. Very important at the educational stage is the rehabilitation of early training in deaf children, namely by using hearing aids (ABD) to utilize the remaining hearing function. Installation of ABD devices in children with severe or very severe deafness must begin as early as possible. This is done so that the development of speech and education is not too late. Cochlear implant considerations as indicated. In addition, speech therapy is also needed to correct speech disorders caused by congenital deafness. Home training includes early training that depends on the sufferer's parents. If it can be detected and treated early and well, then people with Waardenburg can live normally in the community.[15]

Family counseling is a very important component, because in case 2 it can be seen that the sufferer is married to a fellow deaf, and there is a family history of Waardenburg syndrome. If the patient is still planning to have a child, then an explanation is given that there is a tendency for his child to suffer from Waardenburg syndrome. After the child is born, hearing screening must be done as a first step. In the third case, the sufferer lives with his mother and father who are also deaf and speech impaired, so that both of them need counseling that their children need word learning by involving other family members who are not hearing impaired and talk impaired, or can also with the help of informatics media.[15]

Conclusion

Waardenburg syndrome is an autosomal dominant inherited disorder, with the most frequent manifestations of congenital sensorineural deafness and disorders of hair and skin pigmentation. Waardenburg syndrome is classified into 4 types, namely Waardenburg syndrome type 1, type 2, Klein-Waardenburg or type 3, and Waardenburg-Shah or type 4. Genetic mutations are suspected as a cause of Waardenburg syndrome. Interactions between the PAX3, MITF, SNAIL2 and SOX10 genes cause manifestations of deafness and pigmentation disorders. The five patients who were reported as belonging to type 1 waardenburg syndrome, based on the phenotype of each patient who was inherited autosomal dominant. Treatment is aimed at deafness and repairing anatomic abnormalities through surgery. Deafness must be detected immediately and get treatment as early as possible. Genetic counseling can be done, and attention is paid to providing information about clinical manifestations that will emerge and the possibility of a child suffering from this syndrome from parents who have suffered from Waardenburg syndrome, so that disorders that must be treated immediately can be of concern to parents and family.

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