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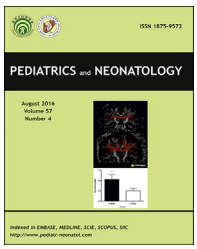

Letter to the Editor

Congenital hypothyroidism as the initial presentation of pendred syndrome associated with mutated IVS7-2A > G in *SLC26A4* gene in a Taiwanese neonate

Pendred syndrome (PS) is one of the common syndromic forms of hereditary sensorineural hearing loss. The *SLC26A4*/*PDS* gene, which encodes an anion transporter, known as pendrin, is the cause of PS.[1] The classical symptoms include sensorineural hearing impairment, associated with an enlarged vestibular aqueduct (EVA), and goiter due to an abnormal organification of iodide.[1] Thyroid function in PS is phenotypically variable, and not all affected individuals develop goiter. Here, we presented a case where neonatal screening revealed congenital hypothyroidism (CH), which later manifested language delay, while genetic investigation confirmed the diagnosis of PS.

A full-term female neonate was uneventfully born to Taiwanese parents who were not consanguineous. Her initial level of thyroid-stimulating hormone was up to 227 uU/ml (normal range: 0.25–4.00 uU/ml), T3 122.56 ng/dl (78–182 ng/dl), and T4 6.17 ug/dl (5–12 ug/dl), according to neonatal screening and confirmatory results. Physical examination did not reveal goiter, and a Tc-99 m pertechnetate thyroid scan showed a normal appearance of thyroid in paratracheal space (Supplemenatry Fig. 1). With a highly elevated TSH level suggesting a diagnosis of CH,[2] we expedited treatment with levothyroxine to maximize her potential for normal development according to the updated consensus guidelines.[3] Despite her growth curve and developmental milestones attained initially within a normal range during treatment with levothyroxine, she was found to be delayed in speech at the age of 18 months. Further auditory examination found bilateral sensorineural hearing impairment with a threshold around 100 db, although her neonatal hearing screening was unremarkable. Brain imaging showed bilateral EVAs (Supplementary Fig. 1). To identify the genetic cause of co-occurring CH and hearing impairment, genetic testing on *SLC26A4* gene revealed homozygous IVS7-2 (c.919-2A > G) mutations, which confirmed the diagnosis of PS. Social interaction and communication were significantly improved after rehabilitation. Throughout the clinical course, she remained euthyroid on levothyroxine supplement and absent of goiter or thyroid autoantibody as of now at age 9.

More than 200 pathogenic mutations in *SLC26A4* gene have been reported up to now, but the phenotype–genotype correlation remains inconclusive.[4] Certain genotypes have a distinctive population frequency across different ethnic groups, suggesting a genetic founder effect. Among all the pathogenic *SLC26A4* variants, IVS7-2A > G splice junction mutation has a disproportionately higher allele frequency in some East Asian populations, such as in Taiwan where it accounted for 84% of the mutated alleles in a small cohort of hearing-impaired patients and most patients carrying this mutation presented goiter from the second decade of life onward.[4,5] The single nucleotide variant located in the conserved splice site may cause the deletion of the entire exon 8, leading to a frameshift and premature termination of translation.[1] However, phenotypic presentations of this mutation are variable but rarely seen in screening-detected CH.

From a clinical perspective, CH patients can achieve milestones without delay if they are treated early and appropriately once upon diagnosis by neonatal screening. Genetic diagnosis for CH is not usually sought in practice. The diagnosis of PS can sometimes be delayed such as in our case who passed the initial neonatal hearing screening and manifested slow language development later in life. A perchlorate discharge test may be helpful to identify a defective organification of iodide but is infrequently used to differentiate the etiology of thyroid dyshormonogenesis, because it cannot suggest the specific underlying molecular

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mechanism.[6] Thus, a genetic study of *SLC26A4* gene may be indicated to confirm the diagnosis of PS in CH patients that are also hearing-impaired, because non-goitrous hypothyroidism can be a potential manifestation of PS.

As of yet, CH in PS has been sporadic, despite that nearly 50% of PS patients may have abnormal thyroid function, ranging from subclinical to overt hypothyroidism.[7] On the contrary, a survey of PS among a cohort of 197 Caucasians with hypothyroidism only found two patients to be compound heterozygotes for *SLC26A4* mutations and thus concluded that PS is rarely detected by neonatal screening for CH.[8] In another cohort of 192 Chinese CH patients, none was found to be compatible with PS, although eight cases were heterozygous for *SLC26A4* mutations.[9] Adding to current literature, our report highlights that vigilant monitoring of child development is warranted in CH patients, irrespective of their thyroid function status during treatment.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pedneo.2022.06.008.

References

1. Yang JJ, Tsai CC, Hsu HM, Shiao JY, Su CC, Li SY. Hearing loss associated with enlarged vestibular aqueduct and Mondini dysplasia is caused by splice-site mutation in the PDS gene. *Hear Res* 2005;**199**:22—30.
2. Saleh DS, Lawrence S, Geraghty MT, et al. Prediction of congenital hypothyroidism based on initial screening thyroid-stimulating-hormone. *BMC Pediatr* 2016;**16**:24.
3. van Trotsenburg P, Stoupa A, Léger J, Rohrer T, Peters C, Fugazzola L, et al. Congenital hypothyroidism: a 2020-2021 consensus guidelines update-an ENDO-European reference network initiative endorsed by the European society for pediatric endocrinology and the European society for endocrinology. *Thyroid* 2021;**31**:387—419.
4. Wu CC, Yeh TH, Chen PJ, Hsu CJ. Prevalent SLC26A4 mutations in patients with enlarged vestibular aqueduct and/or Mondini dysplasia: a unique spectrum of mutations in Taiwan, including a frequent founder mutation. *Laryngoscope* 2005;**115**:1060—4.
5. Lai CC, Chiu CY, Shiao AS, Tso YC, Wu YC, Tu TY, et al. Analysis of the SLC26A4 gene in patients with Pendred syndrome in Taiwan. *Metabolism* 2007;**56**:1279—84.
6. Kwak MJ. Clinical genetics of defects in thyroid hormone synthesis. *Ann Pediatr Endocrinol Metab* 2018;**23**:169—75.
7. Wémeau JL, Kopp P. Pendred syndrome. *Best Pract Res Clin Endocrinol Metabol* 2017;**31**:213—24.
8. Banghova K, Al Taji E, Cinek O, Novotna D, Pourova R, Zapletalova J, et al. Pendred syndrome among patients with congenital hypothyroidism detected by neonatal screening: identification of two novel PDS/SLC26A4 mutations. *Eur J Pediatr* 2008;**167**:777—83.
9. Fu C, Zheng H, Zhang S, Chen Y, Su J, Wang J, et al. Mutation screening of the SLC26A4 gene in a cohort of 192 Chinese patients with congenital hypothyroidism. *Arch Endocrinol Metab* 2016;**60**:323—7.

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