Neuroradiology (2019) 61:949–952
https://doi.org/10.1007/s00234-019-02230-z

SHORT REPORT

Hypothalamic malformations in patients with X-linked deafness and incomplete partition type 3

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Received: 25 February 2019 / Accepted: 20 May 2019 / Published online: 8 June 2019

Abstract

Patients with X-linked deafness carry mutations in the POU3F4 gene and have pathognomonic inner ear malformations characterised by symmetrical incomplete partition type 3 (absent modiolus and lamina spiralis but preserved interscalar septum in a normal-sized cochlea) and large internal auditory meatus (IAM) with an increased risk of gusher during stapes surgery. We describe a range of fairly characteristic malformations in the hypothalamus of some patients with this rare condition, ranging from subtle asymmetric appearance and thickening of the tuber cinereum to more marked hypothalamic enlargement. We discuss the role of POU3F4 in the normal development of both the inner ear and hypothalamus and the proposed pathophysiology of incomplete partition type 3.

Keywords X-linked deafness · Hypothalamic hamartoma · Magnetic resonance imaging · Gusher · Incomplete partition

Introduction

X-linked deafness (OMIM entry: #304400), also known as DFNX2 and conductive deafness with stapes fixation, is a genetic disease with X-linked mode of inheritance due to a mutation in POU3F4 gene, located on chromosome Xq21 [1]. This is characterised by bilateral profound sensorineural hearing loss with a possible association with a conductive component and high risk of perilymphatic gusher at stapes surgery. Diagnosis of POU3F4 can be achieved by imaging due to the pathognomonic appearance of the otic capsule. In fact, the cochlea in these subjects has a normal external dimension with preserved interscalar septum but with absent modiolus, lamina spiralis and bony partition between the cochlear basal turn and the fundus of the internal auditory meatus (IAM) [2]. Cochleovestibular and facial nerves are present in these patients and no associated brain abnormalities have been reported to date.

In this paper, we describe a series of 15 patients from six institutions with this rare genetic anomaly in association with peculiar malformations in the hypothalamus ranging from thickened and moderately dysmorphic appearance to hamartoma-like enlargement. Only three patients had normal hypothalamic morphology. All the patients had a

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00234-019-02230-z) contains supplementary material, which is available to authorized users.

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pathognomonic malformation of the cochlea in keeping with incomplete partition type 3. POU3F4 has a critical role in the development of both the hypothalamus and inner ear and we discuss current knowledge regarding this gene and related domains [3].

Cases description

Using Electronic Documents Manage (EDM) system and personal archives, a total of 17 patients with X-linked deafness, confirmed POU3F4 mutation and typical inner ear findings were found retrospectively. Cases were from two university hospitals and four tertiary paediatric hospitals. Two subjects were excluded because only computed tomography images were available. All subjects included in the study were male (age range 6 months to 19 years) including two sets of brothers. MRI of these 15 patients included high-resolution T2 weighted images (WI) of the inner ears and standard sequences of the brain that were analysed in consensus by the first and last authors. All of them had typical incomplete partition type 3 as described in the literature with a normally sized cochlea, preserved interscalar septum and absent modiolus and lamina spiralis with large IAM [2, 4] (Fig. 1a, e, i). Furthermore, 9/15 patients had mild but characteristic dysmorphism of the hypothalamus, which appeared thickened and irregular on axial, bulky on coronal and with a "bumpy" profile of the tuber cinereum on sagittal images (Fig. 1b, c, d). Three patients demonstrated more marked hamartoma-like hypothalamic enlargement [5] (Figs. 1h, l and 2a, b). Such abnormalities were isointense to grey matter on T1-WI, iso- or slightly hyperintense on T2-WI and showed no contrast enhancement (when post-contrast images were available). Only 3 patients had a normal looking hypothalamus. None of the patients had seizures or endocrinological imbalance. In 11 patients, there was a subtle inferior bulging of the tuber cinereum, visible on sagittal, without any radiological sign of obstructive hydrocephalus (Fig. 1d, h, l). In four subjects, on axial, the dysmorphic hypothalamus showed a very peculiar "double S" shape (Figs. 1f and 2c). No other brain abnormalities were found.

Discussion

X-linked deafness is due to mutation of POU3F4 (which is a gene on chromosome Xq21) or to abnormalities in the regulatory region of this gene [6]. The existence of a syndrome characterised by mixed, bilateral, progressive

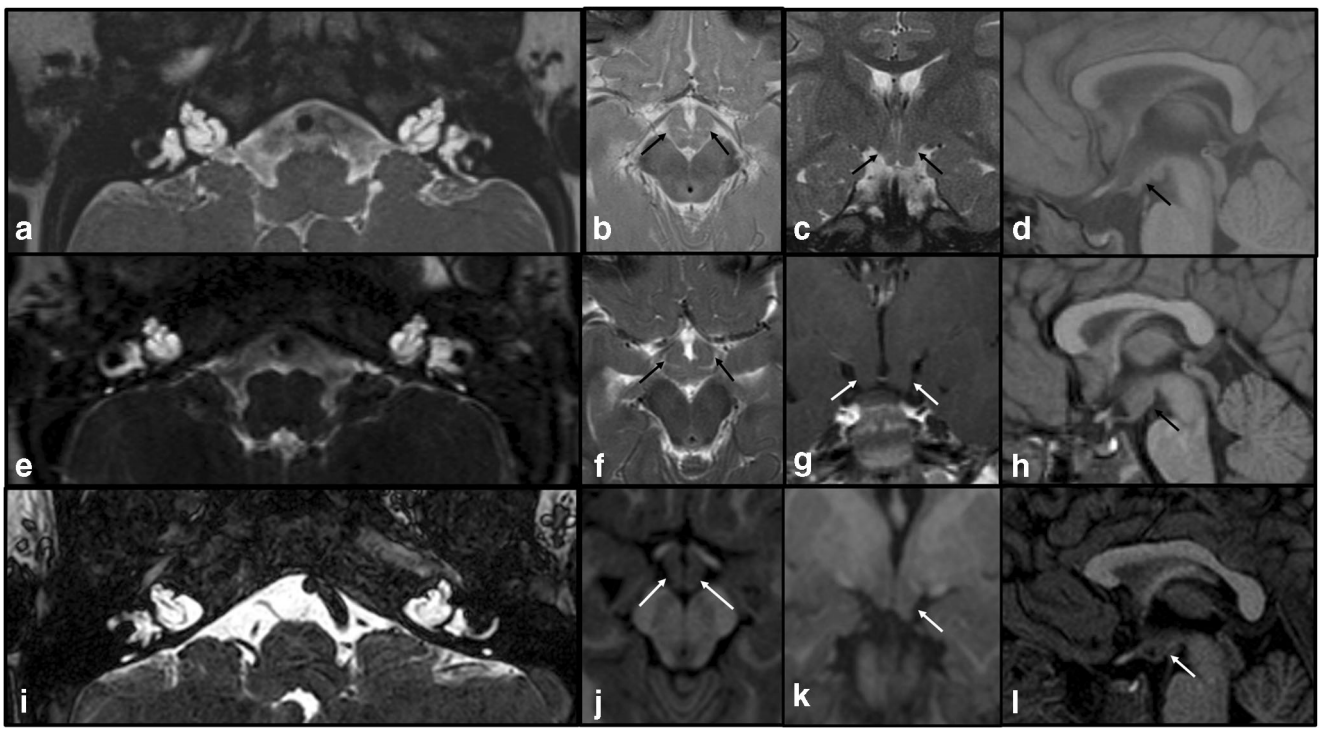

Fig. 1 **a**, **e**, **i** Axial high-resolution WI at the level of the inner ears in three different patients with confirmed diagnosis of X-linked deafness showing bilateral and symmetrical malformations of the cochlea and IAM in keeping with incomplete partition type 3. **b**, **f** Axial T2 WI and **j** 3D T1 WI show a bulky and wrinkly appearance of the hypothalamus (arrows), **c**, **g**, **k** which is also thickened in the coronal plane with some asymmetry noted in few patients (arrow in **k**). In the sagittal plane, the appearance varies from an **d** irregular bumpy profile to **h**, **l** frank hamartoma-like lesion; there is a caudal displacement of the tuber cinereum noted in all patients in the sagittal midline

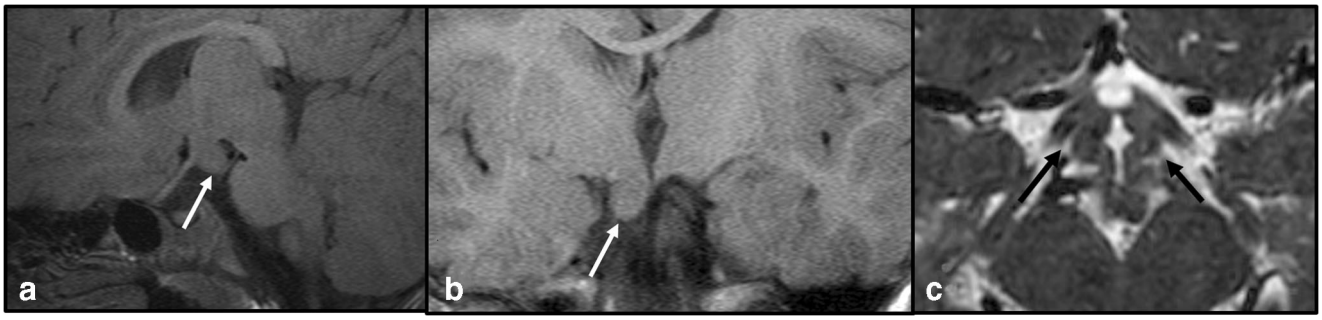

Fig. 2 **a** Sagittal and **b** coronal T1WI in a patient showing a pedunculated lesion resembling a hypothalamic hamartoma (arrows). Axial 3D T2 WI in another patient shows characteristic "double-S" shaped hypothalamus that was found in 4/15 patients (arrows in **c**).

sensorineural hearing loss in males with fixed stapes and high risk of stapes gusher was proposed for the first time in 1968 [7]. Subsequently, several authors described a specific, symmetrical inner ear malformation in affected subjects characterised by large and bulbous IAM, absent modiolus and lamina spiralis (i.e. absent internal cochlear structure) with maintained external dimension of the cochlea and preservation of the interscalar septum [2, 8]. Cochleovestibular and facial nerves are present and the vestibule and semicircular canals are generally less affected with possible abnormalities in the endolymphatic sac; furthermore, the otic capsule is thinner than normal. In terms of possible etiopathogenesis, it has been speculated that, instead of the usual three layers, the otic capsule in these individuals may only have the endosteal layer [4], explaining why the labyrinthine portion of the facial nerve is in an abnormal position above the cochlea. Proposed pathophysiology is an impairment of vascular supply from middle ear mucosa during normal foetal life and consequent abnormal development of the otic capsule and modiolus [4].

In this case series, we describe a high prevalence of malformation of the hypothalamus in patients with POU3F4 mutation which are usually very subtle but may be also more pronounced. POU3F4 (also known as Brn-4) encodes a DNA transcription factor involved in the development of the nervous system, hypothalamus, pituitary gland, and inner ears [3]. Particularly, there is a possible role of this gene in the formation of the hypothalamic nuclei as well as regulation of the proglucagon promoter [3]. This genetic link may explain the coexistence of hypothalamic and inner ear malformations.

The pituitary gland was anatomically normal in all our patients and the clinical relevance of this malformation is unknown since the subjects seem to not have hypothalamic symptoms. An asymptomatic hypothalamic abnormality called "interhypothalamic adhesion" has been described recently, its clinical significance is unclear and is characterised by a band of tissue connecting the medial hypothalamic across the III ventricle. Despite some similarities, the appearances are different from our cases [9]. Furthermore, asymptomatic hypothalamic hamartomas have been described in Pallister-Hall syndrome, which interestingly can also present with cochlear hypoplasia [10].

Conclusion

We report for the first time an association between incomplete partition type 3 and a variable degree of hypothalamic malformations in patients with X-linked deafness and discuss genotype-phenotype correlation in patients with the mutation of the POU3F4 gene.

Funding No funding was received for this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional research committee (Clinical Research Adoption Committee) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study or legal authorized representatives (LAR).

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