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Case report

Vohwinkel Syndrome secondary to missense mutation D66H in GJB2 gene (connexin 26) can include epileptic manifestations

Pedro J. Serrano Castro *, Cristina Naranjo Fernandez, Pablo Quiroga Subirana, Manuel Payan Ortiz

Hospital Torrecardenas, Neurology and Neurophysiology Unit, Almeria, Spain

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ABSTRACT

Vohwinkel Syndrome (VS) is a type of diffuse hereditary palmoplantar keratodermas (DHPPK) accompanied by skeletal dimorphisms and sensorineural deafness. The most frequently reported genetic substrate in VS is a point mutation of GJB2 gene, responsible for encoding connexin 26, a gap-junction protein with a crucial role in neuronal migration in rats. We report the case of a 21-year-old male who is a second-generation member of a family with VS and developed cryptogenic focal epilepsy. Genetic study showed a nucleotide change (c.196G > C) in exon 1 of GJB2 gene, producing a missense mutation, D66H. It is plausible that a functional alteration of connexin 26, such as that resulting of the mutation of our case, can produce an alteration in cortical development with epileptogenic potential. The present case and experimental evidence that connexin 26 is related to animal epileptogenesis suggest that the phenotypic spectrum of VS could be expanded to include epileptic manifestations.

1. Introduction

Diffuse hereditary palmoplantar keratodermas (DHPPK) are a subgroup of genetically conditioned dermatological diseases with varied modes of inheritance. Their association with systemic clinical manifestations permits their classification as syndromes.[1] The genetic substrate is heterogeneous, but there have been several reports of a mutation in genes that encode connexins, transmembrane proteins with multiple biological functions.

Vohwinkel Syndrome is a DHPPK of dominant autosomal transmission with onset at an early age. It is usually accompanied by skeletal dimorphisms in the distal toe phalanxes and sensorineural deafness. The most frequently reported genetic substrate is a point mutation of GJB2 gene, responsible for encoding connexin 26 at locus 13q11–q12. There have also been reports of mutations of genes that encode connexin 26 in Bart-Pumphrey Syndrome and connexin 30 in Hydrotic Ectodermal Dysplasia.

Over the past few years, animal experiments have related alterations in the expression of certain connexin subtypes to epileptogenesis. Thus, functional alterations of connexins 26, 32, 36 and 43 are known to be implicated in the genesis and synchronization of cortical electrical activity in rats.[2] There is also evidence of the importance of connexins 26 and 43 for controlling the final stages of neuronal migration in rats.[3] Finally, a human study showed a significantly lower expression of connexins 32, 36, and 43 in the hippocampus of epileptic patients subjected to therapeutic amygdalohippocampectomy versus controls (autopsy samples from non-epileptic patients).[4]

Despite this accumulated knowledge of connexin proteomics, there is no consistent evidence in the literature of an association with epilepsy in DHPPK, only isolated cases. This may be explained by the extreme rarity of these diseases and the little information on their natural history.

We present a family affected by Vohwinkel disease type DHPPK in which at least one member of the family had cryptogenic partial epilepsy. The sequencing of GJB2 gene revealed a specific mutation. We discuss the possible biological meaning of this association.

2. Case report

We report the case of a 21-year-old male with mild psychomotor development retardation who is a second-generation member of a family with DHPPK. The mother and maternal grandfather show dermatological but not systemic involvement. The patient and his mother have clinically relevant sensorineural deafness, but it is not known whether this was also suffered by the maternal grandfather. There is no other history of interest.

From the age of 8 years, the patient suffered episodes that started with a cessation of activity, expression of fear, disconnection from the environment, and a subtle oral and swallowing automatism that lasted a few minutes. These episodes were considered compatible with complex partial seizures in the context of focal cryptogenic epilepsy. The only semiological data

* Corresponding author at: Unidad de Neurologia y Neurofisiología, Hospital Torrecárdenas, Paraje de Torrecárdenas, S/N, CP: 04009, Almeria, Spain.
Tel.: +34 671562365; fax: +34 950016963.
E-mail addresses: pedro.serrano.c@gmail.com, pedrojserrano.sspa@juntadeandalucia.es (P.J.S. Castro).

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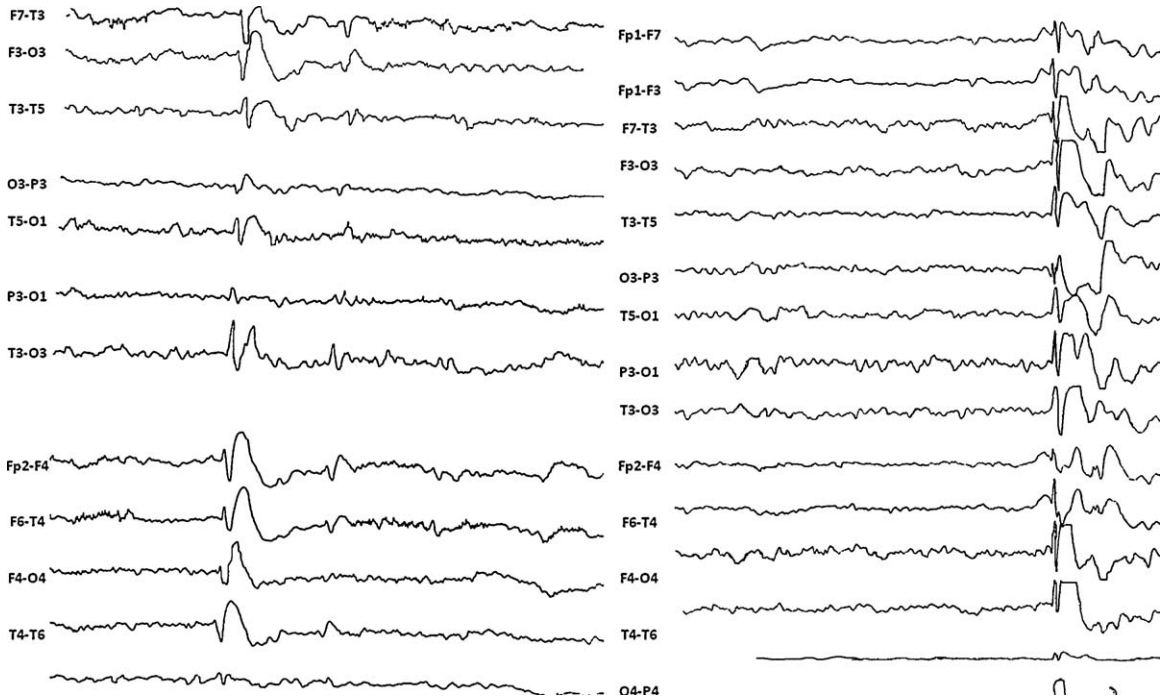

Fig. 1. EEG showing bifrontal epileptiform activity with left predominance.

with localization value was the expression of fear, which has been consistently related with temporal lobe origin. Nevertheless, interictal electroencephalograms showed bifrontal epileptiform activity with left predominance (Fig. 1), suggesting a possible frontal onset with rapid extension to fronto-temporal areas.

They occasionally culminated in generalized seizures. There is not a predominance of seizures during sleep and postictal period was always of short duration.

The frequency of seizures until 16 years old was about 1–2 seizures per week, but since this moment and coinciding with the start of the combination therapy with Carbamazepine plus Lamotrigine, the patient became free of seizures. Previously there had been several therapeutic trials in monotherapy or combination of AED including Phenobarbital, Fenitoine and Valproic Acid.

The basic neurological examination was normal. High-resolution encephalic MRI (1.5 T) with a specific epilepsy protocol found no relevant alterations.

Directed genetic study revealed a nucleotide change (c.196G > C) in exon 1 of GJB2 gene in heterozygosis, producing a missense mutation, D66H. This mutation involves the exchange of an aspartic aminoacid for a histidine codon in codon 66 and has been frequently reported in Vohwinkel Syndrome.[5] The same mutation was found in a sample from his mother, who has dermatological lesions but no reported epileptic seizures.

3. Discussion

Connexins are transmembrane proteins involved in intercellular communication processes.[6] In general, they permit cell metabolite exchange, second messengers, and electrical signals. There are 21 members of the connexin family in humans, with a widely heterogeneous distribution in different organs. There was initially believed to be a specific connexin for each cell type, but many tissues are now known to express two or more members of this family. Thus, keratocytes express connexins 26, 30, 30.3, 31, 31.1, and 43; cardiomyocytes, 40, 43, and 45; and hepatocytes, 26 and 32. Hence, a mutation in a specific connexin can produce alterations in various tissues.

Various authors recently suggested that the expression of certain subtypes of neuronal connexins may be altered in some types of epilepsy. Thus, Hempelmann et al. found evidence of an allelic and genotypic association between the connexin 36 gene and a subtype of patients with juvenile myoclonic epilepsy.[7] However, to our best knowledge, connexin 26 has yet to be related to any type of epilepsy.

Our patient presents an unusual phenotype, with pharmacosensitive cryptogenic partial epilepsy and palmoplantar keratoderma, with a mutation of exon 1 in the gene encoding connexin 26. This genetic substrate was described in a large British family with conventional Vohwinkel Syndrome, which had 10 members with this mutation, and it was subsequently detected in three non-related families of Spanish and Italian origin.[5] These patients suffered moderate-to-severe sensorineural hypoacusia but there were no reports of epileptic seizures. The authors suggested that this specific mutation of connexin 26 may affect epidermal differentiation and inner ear function. Other families have since been reported to have the same mutation and a classic phenotype of the Vohwinkel Syndrome.[8]

Connexin 26 has been experimentally demonstrated to participate in epidermal differentiation.[9] In 2007, it was reported to play a crucial role in neuronal migration in rats,[3] with the expression of connexins 26 and 43 in contact points between radial fibers and neurons during neuron migration, and a decrease in their expression was found to affect the cortical organization process. The authors also demonstrated that connexins guide neuronal migration in a novel manner, developing dynamic adhesive contacts that interact with the neuronal cytoskeleton and stabilize it along the radial fibers.

Based on the experimental evidence, it is plausible that a functional alteration of connexin 26, such as that resulting from D66H mutation of exon 1 in GJB2 gene, can produce an alteration in epidermal differentiation, responsible for keratoderma, and a simultaneous alteration in cortical development, with epileptogenic potential. This alteration would probably take place in the last stages of cortical development and may therefore not be detected in standard neuroimaging studies.

A review of the literature (MEDLINE 1967-to date), using the keywords "keratoderma" and "epilepsy", revealed a previous case of Vohwinkel Syndrome associated with a partial complex seizure, but the genetic substrate was not reported.[10]

In conclusion, D66H mutation of exon 1 in GJB2 gene may produce a multisystemic syndrome with palmoplantar keratoderma and sensorineural hypoacusia. The present findings and experimental evidence that connexin 26 is related to animal epileptogenesis and cortical organization suggest that this phenotypic spectrum can be expanded to include manifestations of cryptogenic focal epilepsy. Possible mutations of GJB2 gene should be investigated in patients with cryptogenic focal epilepsy with associated palmoplantar keratodermal lesions and/or familial sensorineural deafness.

Conflict of interest

None of the authors has any conflict of interest to disclose.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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