Incidence and Prevalence of Erythropoietic Protoporphyria in Colombia Between 2014 and 2018☆

Incidencia y prevalencia de la protoporfiria eritropoyética en Colombia, 2014-2018

To the Editor:

Erythropoietic protoporphyria (EPP, OMIM: 177000) is an innate error of the metabolism caused by autosomal recessive hereditary mutations in the gene FECH (Gene ID: 2235), which cause a ferrochelatase enzyme deficiency (EC 4.99.1.1) (<30% of normal). Ninety-six percent of affected individuals have composite heterozygotic mutations: from one parent, they inherit an allele with a loss of function that leads to almost no ferrochelatase activity and from the other parent, they inherit an allele with low expression, which produces ferrochelatase activity that is less than 50% of normal (c.315-48T > C; also known as IVS3-48T > C). Four percent of cases inherit 2 FECH alleles with complete loss of function. Some rarer erythropoietic porphyrias are caused by hereditary mutations linked to the X chromosome (OMIM: 300752) or by mutations in the gene CLPX (OMIM: 618015), which explain less than 10% of cases. These diseases are characterized by acute, painful, and burning nonampullary lesions that appear within less than 30 minutes of exposure to light. The lesions are caused by the accumulation of protoporphyria IX in the endothelium of the blood vessels close to the surface of the skin, which absorbs light in the Soret band and passes into an excited state that generates free radicals, which, in turn, damage the surrounding cutaneous tissue.[1] To prevent these lesions, patients develop an aversion to light and a preference for enclosed spaces, which significantly affects their style and quality of life.[2] Most available treatments (e.g., beta-carotene, N-acetyl-L-cysteine, and vitamin C) have shown no clear benefit supported by clinical trials.[3] Afamelanotide (Scenesse, Clinuvel Pharmaceuticals) is a potent analogue of α-melanotide stimulating hormone, which has been shown to reduce the incidence and severity of phototoxic reactions and to improve quality of life in the long term.[4,5] This drug, however, is not yet available in many countries.

The prevalence and incidence of EPP have not been estimated in Colombia or in many other Latin-American countries (Fig. 1). This information is important for evaluating the burden of this disease on the population and the associated health care service requirements. This information is also essential for introducing new therapies into the national health service and coverage by the insurance companies. Finally, the lack of information available on EPP is one of the biggest concerns for patients and their family members.[2] We therefore performed a study based on prospective information from the Colombian Comprehensive Social Protection Information System database for the period between 2014 and 2018. We identified patients suffering from EPP by means of the international classification of diseases code E80.1 and only included those with a confirmed new diagnosis. The reference population was obtained from the database of the Colombian National Statistics Administrative Department. The annual incidence was calculated as the number of new cases in a year over the total population for that year. Prevalence was estimated from the incidence, assuming a mean duration of EPP of 77 years (prevalence = incidence $\times$ mean duration of EPP).[6] All of this assumes that, during the study period, the population of the country remained relatively stable and the annual incidence was constant.

Table 1 Annual Incidence, Estimated Prevalence, and Sociodemographic Characteristics of Erythropoietic Protoporphyria in Colombia, 2014-2018.

	EPP[a]
Patients	40
Sex, female; n, %	23, 57.5
Mean (SD) age	32.4 (23.1)
Mean annual incidence (95% CI)[b]	0.2 (0.1-0.4)
Prevalence (95% CI)[b]	15.4 (14.3-16.5)

Abbreviations: SD indicates standard deviation; 95% CI, 95% confidence interval.
[a] Includes X-linked and congenital protoporphyria.
[b] Reference population: 45,000,000 inhabitants, estimated per million inhabitants.

Table 2 Prevalence and Incidence of Erythropoietic Protoporphyria in Colombia Compared to Other Countries.

Country	Prevalence	Incidence
Colombia	15.4	0.2
Norway[6]	27.7	0.36
Switzerland[6]	27.0	0.35
United Kingdom[6]	25.4	0.33
Netherlands[6]	13.9	0.18
Sweden[6]	13.9	0.18
Ireland[6]	6.2	0.08
Italy[6]	5.4	0.07
France[6]	4.6	0.06
Poland[6]	1.5	0.03
Spain[6]	2.3	0.03

Reference population: 45,000,000 inhabitants, estimated per million inhabitants.

The study showed that the annual incidence (0.2 new cases per million inhabitants) and the estimated prevalence (15.4 cases per million inhabitants) of EPP in Colombia are similar to those reported for the Netherlands and Sweden but differ from those of many other countries[6] (Tables 1 and 2). Considerable variability has previously been reported in the epidemiology of EPP between countries in comparison with acute hepatic porphyria. The prevalence of EPP may vary depending on the frequency of the low expression allele (c.315-48T>C) in the population, which may range from 1% in Africans to 43% in Japanese.[1] The frequency of this allele in Colombians in unknown. Moreover, expression of the disease may change in relation to the degree of skin pigmentation, such that greater melanin deposits lead to

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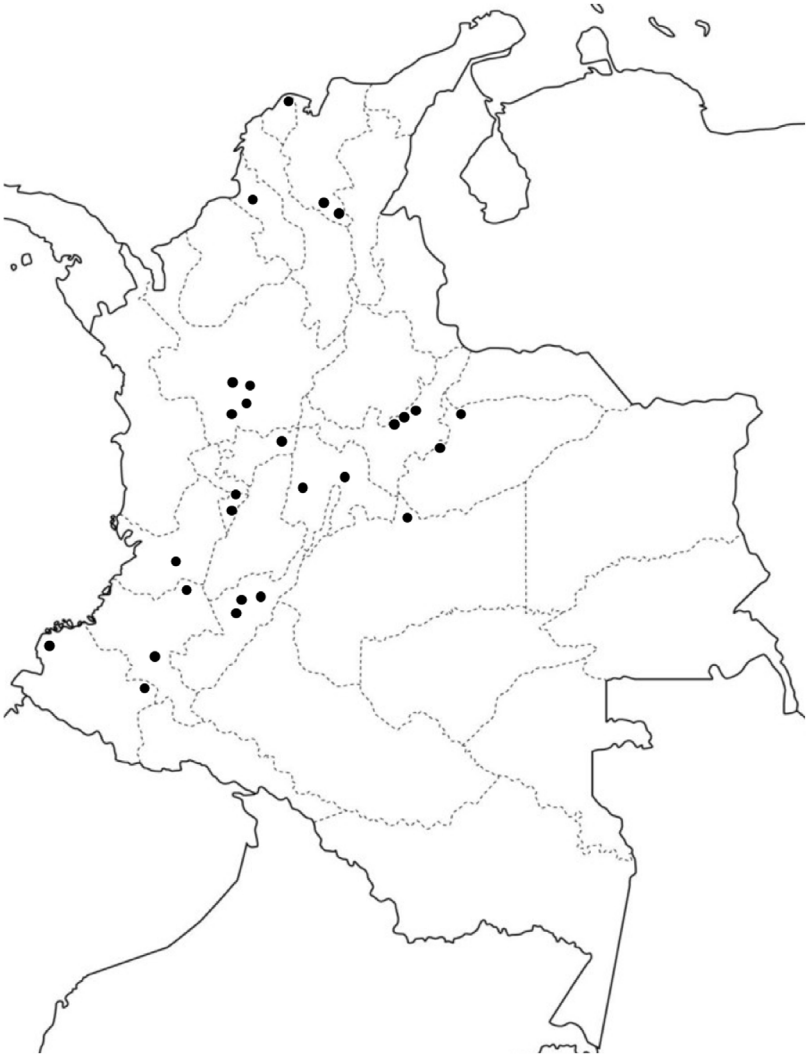

Figure 1 Geographic distribution of erythropoietic protoporphyria (EPP) in Colombia.

less pronounced symptoms.[6] EPP affects men and women relatively equally in Colombia, which agrees with observations in other populations. The symptoms of EPP usually start in childhood and advanced age at the time of diagnosis may therefore indicate a long delay in diagnosis. This is in the context of the fact that most patients in developed countries with ample experience in treating this disease report delays in diagnosis of up to 18 years.[2,7] Deficiencies have been shown in the diagnosis of porphyria in Colombia and a greater delay in diagnosis is therefore to be expected.[8] Furthermore, it is likely that the predominance of mixed-race people in Colombia is linked to a higher proportion of mild cases. One limitation of this study is that, although the database queried made it possible to identify cases with a confirmed diagnosis of EPP, it is not possible to verify the methods used to confirm the diagnosis. Situations such as coding errors and limits to the number of diagnostic codes available may affect the accuracy of epidemiologic estimates based on administrative sources. An overestimation of the incidence and prevalence of EPP cannot therefore be ruled out in this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Double Nail of the Fifth Toe☆

Doble uña del quinto dedo del pie

To the Editor:

A 44-year-old man visited our department with prominences on both sides of the fifth toe, which had appeared following a walk, on which he had worn tight footwear. The patient complained of discomfort only when pressure was applied to this area. Physical examination revealed external rotation of the fifth toe and increased width of the nail plate on both small toes. Each of these nails was also covered by cuticle, divided by a longitudinal cleft, and the nail plate showed lateral thickening (Fig. 1A and Fig. 2A). Dermatoscopy confirmed that the nail consisted of 2 clearly demarcated parts (Fig. 1, Fig. 2, and Fig. 2B). The patient was not aware of this abnormality in any family member. A simple anteroposterior and lateral x-ray of both feet was requested and ruled out the presence of accessory phalanges or other bone abnormalities (Fig. 3). No treatment was indicated, other than reduction of the direct trauma.

The double nail of the fifth toe (DNFT) or accessory nail of the fifth toe was described in 1969 by Huindeker and is an apparently common entity, although few published cases exist.[1–4]

The most common clinical presentation is the appearance of a wider-than-normal nail divided by a longitudinal cleft, fold, or depression, and the part corresponding to the accessory nail is smaller. A cuticle covers both nail plates in the proximal area of the nail. DNFT may be unilateral or bilateral, and when both toes are affected there tends to exist considerable symmetry.[3,4] Clinical or aesthetic problems due to the size of the nail occur only occasionally.[3,4]

It is rare to find abnormalities in the x-ray of the fifth toe. Of 10 x-rays performed in 1 series, only 3 patients presented a lazy Y on the tip of the distal phalanx, and another patient presented a thorn-like bony excrescence.[4] A Y-shaped tip of the terminal phalangeal bone was identified during surgery in 2 patients.[4] DNFT was initially thought to be a hereditary process limited to the Han ethnic group, the largest ethnic group in China.[3] Haneke, however, found that the entity showed no racial or ethnic predilection.[4] Autosomal dominant heredity with variable expression has been proposed.[4] Familial cases show no clear predisposition by sex, although women consult more for this abnormality.[5,6] DNFT may represent an initial form of hexadactyly, which would give rise to a rudimentary nail.[4] Acute trauma may act on vestigial bone, inducing the appearance of a nail or on the onychodermis which, as specialized nail mesenchyma, would lead to nail formation and growth. The onychodermis is made up of onychofibroblasts and takes part in nail formation and growth.[7]

The histology of excised accessory nails varies from a depression like a sack of skin with hyperkeratosis like a nail plate, to a small nail with a matrix, proximal fold, nail bed, and hyponychium.[5,6]

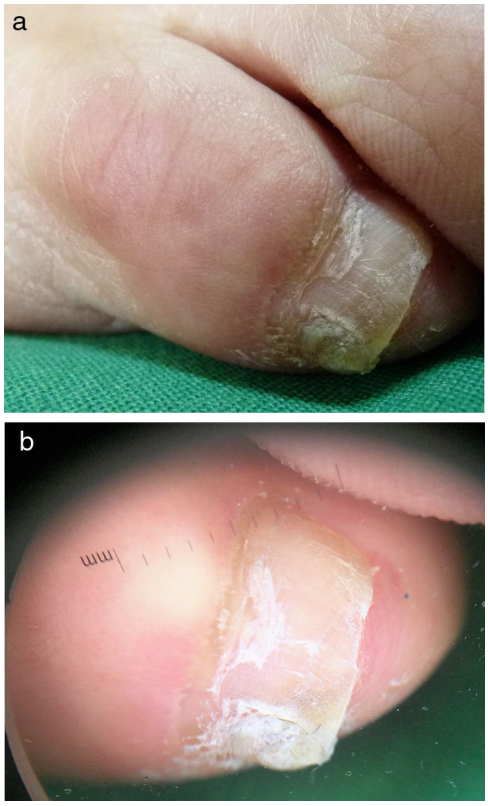

Fig. 1 Clinical image of the fifth toe. A, right toe. B, left toe presenting external rotation and increased nail size, with a longitudinal fissure dividing the nail plate.

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