UNDERSTANDING GENODERMATOSES – INSIGHTS FROM EPIDEMIOLOGICAL ANALYSIS ON A SELECTED CASE COHORT

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Summary

Genodermatoses are diseases with significant psychosocial impact despite being relatively rare conditions, with a reported incidence that varies between 1:6000 and 1:500,000 [1] and is continually increasing, most likely due to the development of more effective diagnostic methods.

Severity of the clinical expression of the genetic defects responsible for the occurrence of genodermatoses varies widely, with some cases taking the form of serious diseases that cause significant alteration of patients' quality of life, as well as that of their families, and also reduce the patients' life expectancy. Given the fact that genodermatoses are chronic, incurable diseases that are frequently associated with incapacitating disabilities and even with malignant degeneration potential, their management requires collaboration among members of a multidisciplinary team and a complex therapeutic regimen, which also demands considerable resources. Therefore, taking into account all these considerations, genodermatoses represent important public health issues.

In the current paper we present the results of a prospective and retrospective study conducted between 2013 and 2023 on a number of 253 newly diagnosed patients with various clinical forms of genodermatoses, admitted to Dermatology departments in Bucharest.

Keywords: *genodermatoses, ichthyosis, keratodermas, Darier's disease, neurofibromatosis, epidermolysis, porphyrias.*

Received: 27.02.2024 *Accepted: 23.03.2024*

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Introduction and Objectives

In the category of genodermatoses, there are over 1000 cutaneous conditions with genetic determinism, including chromosomal abnormalities and mono- or plurigenic defects with a polymorphic clinical expression that may not manifest at birth and often associate multiorgan and multisystemic manifestations [2,3,4,5], as well as a complex oncological pathology, thus impairing quality of life and increasing morbidity and mortality rates among patients [6].

Molecular diagnosis of genodermatoses has seen significant progress since 1987, following the discovery of steroid sulfatase deletions that cause ichthyosis, and also due to the "Human Genome Project" launched in 1990 and completed in 2003 [7].

The present study aims to examine the various clinical manifestations of genodermatoses and their correlations with information from the specialized literature, as well as the impact of genodermatoses on patients' quality of life, with the objective of making progress in recognizing and managing these rare and redoubtable conditions.

Considering the rarity of these diseases and the fact that they present extremely complex and varied clinical forms, with multiple implications in other medical specialties, it is crucial to have a collaborative multidisciplinary effort to clarify the complex aspects raised by genodermatoses, so that patients and their families can benefit from genetic counseling, effective prenatal diagnosis methods and early instituted correct treatment to improve patients' prognosis and quality of life.

Material and Method

In the current study, we conducted a prospective and retrospective open clinical-epidemiological study on a total of 253 newly diagnosed patients with various clinical forms of genodermatoses admitted to Dermatology departments in Bucharest during 2013–2023.

Considering the rarity of these conditions and the fact that some genodermatoses present serious comorbidities that do not require admission to the dermatology department and necessitate referral to other medical services, it was necessary to choose a longer time interval for conducting this study in order to identify as many varieties of cutaneous conditions with genetic determinism as possible.

From the examined observation records, there were extracted information related to identification, age, gender, environment of origin, personal pathological and heredocolateral antecedents, familial investigation, disease history and clinical evolution, comorbidities, paraclinical explorations, particularly histopathological examination, discharge diagnosis (clinical form of the disease and etiopathogenic classification of the condition), available therapeutic options and treatment received by patients, length of hospitalization, inheritance type, genetic counseling and screening methods.

Results

Between 2013 and 2023, a total of 36,899 patients diagnosed with dermatovenerological conditions were registered in Dermatology departments in Bucharest, of which 253 patients (0.68%) were diagnosed with various etiopathogenic and clinical forms of genodermatoses and were included in the study presented in this paper (figure 1).

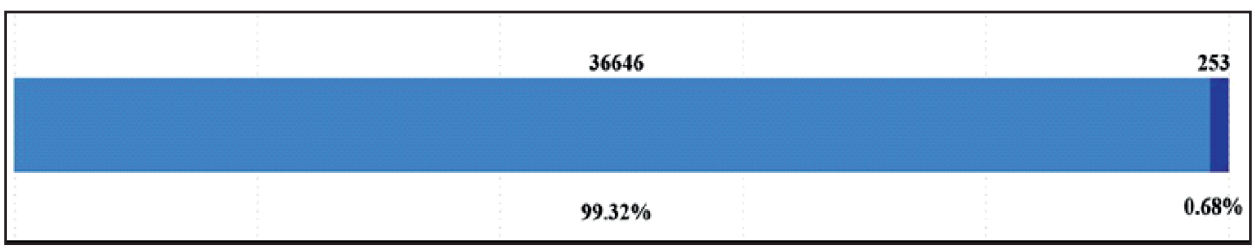

Figure 1. The numerical relationship between the total number of patients diagnosed with dermatological conditions and the number of patients diagnosed with genodermatoses during the period 2013–2023

Table 1. Distribution of genodermatoses according to the clinical-etiopathogenic form of the disease

Index	NAME OF THE DISEASE	Total	
		Number	Percentage
1	Ichthyosis vulgaris	13	5.14%
2	Congenital bullous ichthyosiform erythroderma	1	0.40%
3	Congenital ichthyosis	4	1.58%
4	Other forms of ichthyosis	25	9.88%
5	Palmoplantar keratodermas	46	18.18%
6	Darier's disease	23	9.09%
7	Acrokeratosis verruciformis of Hopf	1	0.40%
8	Epidermolysis bullosa simplex	3	1.19%
9	Dystrophic epidermolysis bullosa	2	0.79%
10	Other bullous epidermolyses	14	5.53%
11	Hailey-Hailey disease	6	2.37%
12	Porphyria cutanea tarda	29	11.46%
13	Hereditary erythropoietic porphyria	6	2.37%
14	Other porphyrias	7	2.77%
15	Neurofibromatoses	63	24.90%
16	Tuberous sclerosis	7	2.77%
17	Fox-Fordyce disease	2	0.79%
18	Peutz-Jeghers syndrome	1	0.40%
	Total	**253**	**100%**

These data correspond to those found in specialized literature, as genodermatoses represent rare conditions with a low incidence in the general population.

The distribution according to the etiopathogenic and clinical category of disease of the genodermatoses cases studied is presented in Table 1 and illustrated in Figure 2.

The presented study indicates that the most frequent genodermatoses encountered between 2013 and 2023 in dermatology departments in Bucharest are represented by neurofibromatosis, palmoplantar keratodermas, ichthyoses and porphyrias (Table 2).

From the distribution according to gender of the genodermatoses cases studied, presented in Table 3 and illustrated in Figure 3, a slight predominance of the female sex is observed.

The data presented in Table 3 correspond to those reported in specialized literature, with a few exceptions. Thus, in the case of ichthyosis vulgaris, tuberous sclerosis and Hailey-Hailey disease, a predominance of the female sex is noted, while in the specialized literature a relatively equal distribution between sexes is described, so it can be speculated that in the case of mild forms of disease it is possible that the addressability of female patients to specialized services may be higher due to aesthetic criteria.

From the analysis of data related to the distribution of patients according to the environment of origin, presented in Table 4 and illustrated in Figure 4, a predominance of patients from urban areas is observed. This may be due to patients' lack of medical information and their tendency to avoid or delay seeking

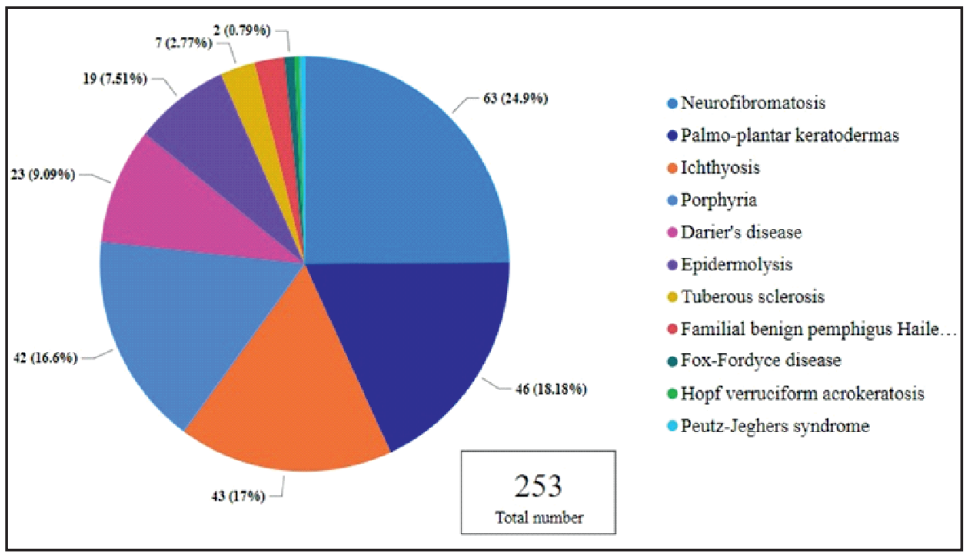

Figure 2. Distribution of genodermatoses according to the clinical-etiopathogenic form of the disease

Table 2. Distribution of genodermatoses according to the incidence of etiopathogenic categories

Index	NAME OF THE DISEASE	Total	
		Number	Percentage
1	Neurofibromatosis	63	24.90%
2	Palmoplantar keratodermas	46	18.18%
3	Ichthyoses	43	16.99%
4	Porphyrias	42	16.60%
5	Darier's disease	23	9.09%
6	Bullous epidermolysis	19	7.50%
7	Tuberous sclerosis	7	2.77%
8	Hailey-Hailey disease	6	2.37%
9	Fox-Fordyce disease	2	0.79%
10	Acrokeratosis verruciformis of Hopf	1	0.40%
11	Peutz-Jeghers syndrome	1	0.40%
	Total	**253**	**100%**

specialized medical services until advanced stages of disease. Exceptions are neuro-fibromatoses and more severe forms of porphyrias, bullous epidermolyses and ichthyoses, where a relatively equal distribution of patients was noted concerning the environment of origin, most likely due to the severity of clinical manifestations.

The distribution according to age categories is presented in Table 5 and Figure 5, where it is observed to vary between ages under 1 year and over 85 years, with the most frequent age categories being 45-54 years and 55-64 years old. In most cases, the age of diagnosis coincided with the onset of the disease, especially in cases with moderate-severe clinical manifestations

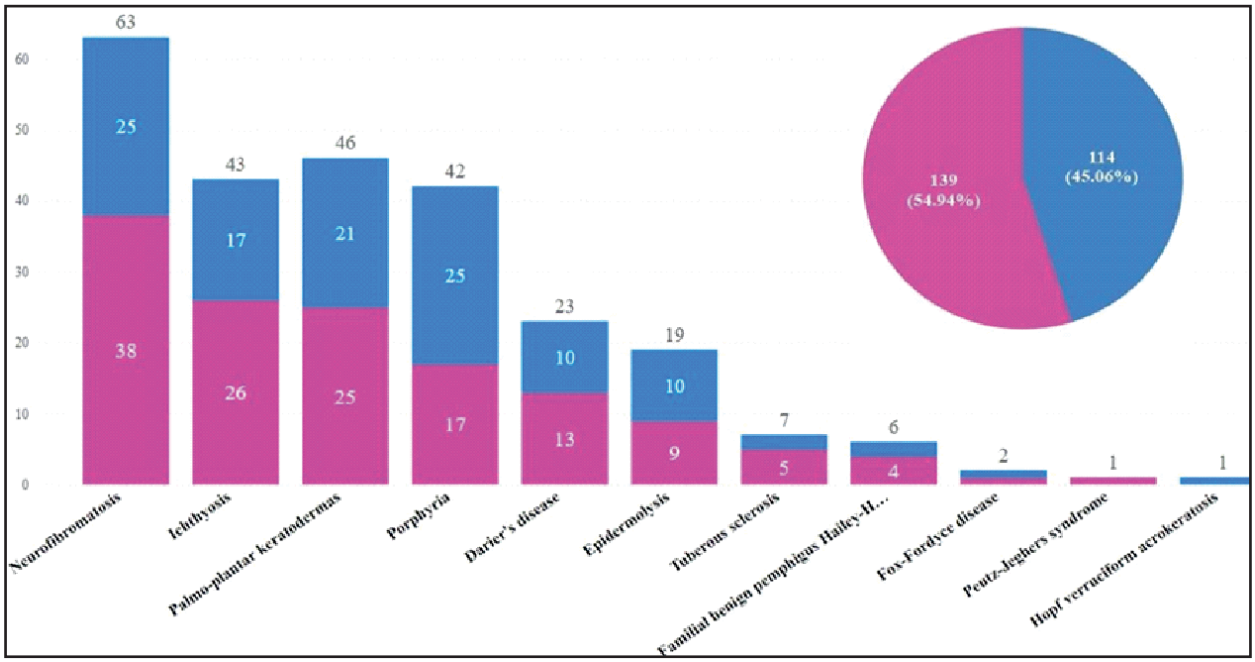

Figure 3. Distribution of genodermatoses according to the patient's gender.

Table 3. Distribution of various clinical-etiopathogenic forms of genodermatoses according to the patient's gender

Index	NAME OF THE DISEASE	Distribution by sex		Total
		Men	Women	
1	Ichthyosis vulgaris	2	11	13
2	Congenital bullous ichthyosiform erythroderma	1	0	1
3	Congenital ichthyoses	2	2	4
4	Other forms of ichthyoses	12	13	25
5	Palmoplantar keratodermas	21	25	46
6	Darier's disease	10	13	23
7	Acrokeratosis verruciformis of Hopf	1	0	1
8	Epidermolysis bullosa simplex	1	2	3
9	Dystrophic epidermolysis bullosa	2	0	2
10	Other bullous epidermolyses	7	7	14
11	Hailey-Hailey disease	2	4	6
12	Porphyria cutanea tarda	20	9	29
13	Hereditary erythropoietic porphyria	3	3	6

Table 3. (continued)

Index	NAME OF THE DISEASE	Distribution by sex		Total
		Men	Women	
14	Other porphyrias	2	5	7
15	Neurofibromatoses	25	38	63
16	Tuberous sclerosis	2	5	7
17	Fox-Fordyce disease	1	1	2
18	Peutz-Jeghers syndrome	0	1	1
	Total	**114**	**139**	**253**

Table 4. Distribution of the various etiopathogenic clinical forms of genodermatoses depending on the environment of origin

Index	NAME OF THE DISEASE	The environment of origin		Total
		Rural	Urban	
1	Ichthyosis vulgaris	3	10	13
2	Congenital bullous ichthyosiform erythroderma	1	0	1
3	Congenital ichthyoses	2	2	4
4	Other forms of ichthyoses	12	13	25
5	Palmoplantar keratodermas	15	31	46
6	Darier's disease	5	18	23
7	Acrokeratosis verruciformis of Hopf	0	1	1
8	Epidermolysis bullosa simplex	1	2	3
9	Dystrophic epidermolysis bullosa	2	0	2
10	Other bullous epidermolyses	8	6	14
11	Hailey-Hailey disease	1	5	6
12	Porphyria cutanea tarda	11	18	29
13	Hereditary erythropoietic porphyria	2	4	6
14	Other porphyrias	3	4	7
15	Neurofibromatoses	32	31	63
16	Tuberous sclerosis	3	4	7
17	Fox-Fordyce disease	0	2	2
18	Peutz-Jeghers syndrome	1	0	1
	Total	**102**	**151**	**253**

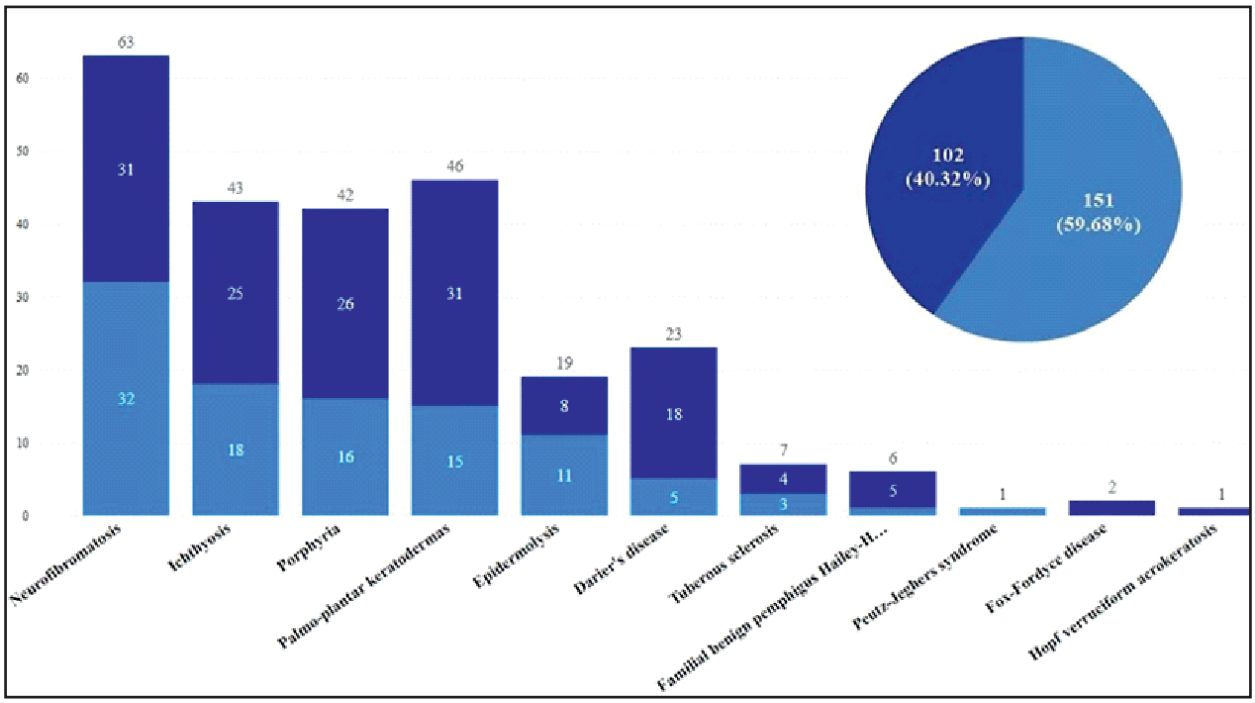

Figure 4. Distribution of various clinical-etiopathogenic forms of genodermatoses according to the environment of origin

(ichthyoses, epidermolysis bullosa, neurofibromatoses, tuberous sclerosis). In cases of ichthyoses, keratodermas and Darier's disease with mild manifestations, discrepancies between the age of onset and diagnosis are observed, possibly due to the tendency to neglect the disease.

The distribution of the various clinical-etiopathogenic forms of genodermatoses in

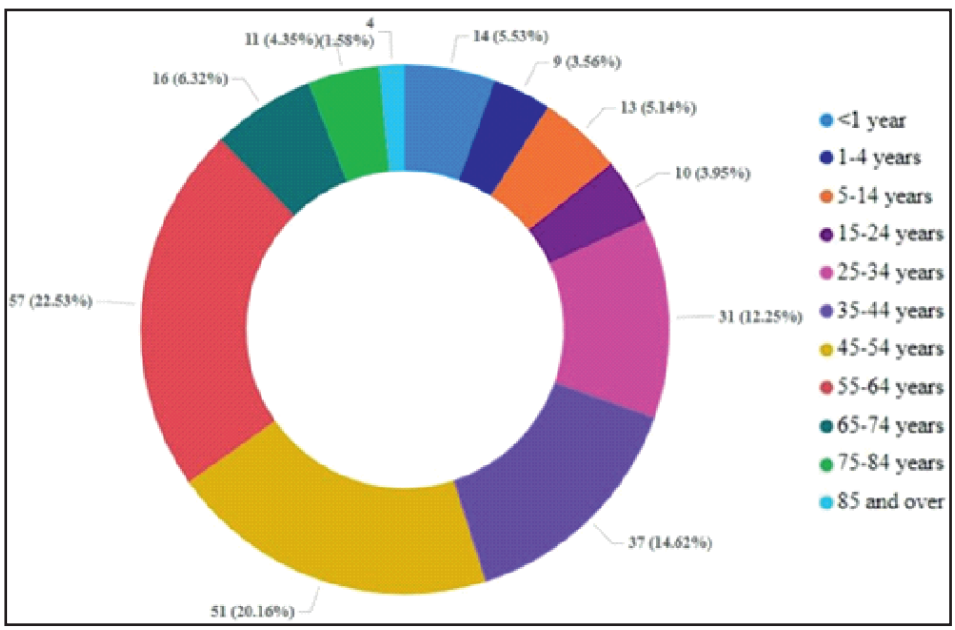

Figure 5. Distribution of the studied genodermatoses according to the age of the patients

relation to the most affected age category is highlighted in orange in Table 5, and the data largely correspond to those found in specialized literature. Although cutaneous lesions in neurofibromatoses appear in childhood, the most frequent age category is 25-34 years, possibly due to neglect of mild forms of disease or seeking specialized services when complications arise or

Table 5. Distribution of various clinical-etiopathogenic forms of genodermatoses according to age categories

INDEX	NAME OF THE DISEASE	Distribution of discharged patients by age group (years)											Total
		< 1	1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	> 85	
1	Ichthyosis vulgaris	0	1	4	0	0	0	2	2	1	1	2	**13**
2	Congenital bullous ichthyosiform erythroderma	0	1	0	0	0	0	0	0	0	0	0	**1**
3	Congenital ichthyoses	0	0	2	1	0	0	1	0	0	0	0	**4**
4	Other forms of ichthyoses	0	0	0	0	0	3	9	7	6	0	0	**25**
5	Palmoplantar keratodermas	0	1	1	0	2	11	6	17	3	4	1	**46**
6	Darier's disease	0	0	0	1	1	4	5	7	4	1	0	**23**
7	Acrokeratosis verruciformis of Hopf	0	0	0	0	0	0	0	1	0	0	0	**1**
8	Epidermolysis bullosa simplex	0	0	0	0	2	0	0	1	0	0	0	**3**
9	Dystrophic epidermolysis bullosa	0	0	0	0	0	0	2	0	0	0	0	**2**
10	Other bullous epidermolysis	10	0	0	0	0	2	1	1	0	0	0	**14**
11	Hailey-Hailey disease	0	0	0	0	1	1	2	1	0	1	0	**6**
12	Porphyria cutanea tarda	0	0	0	0	3	4	6	14	1	1	0	**29**
13	Hereditary erythropoietic porphyria	0	0	0	1	0	0	2	2	0	1	0	**6**
14	Other porphyrias	0	0	0	0	1	1	4	0	0	0	1	**7**
15	Neurofibromatoses	4	5	6	4	20	9	9	4	1	1	0	**63**
16	Tuberous sclerosis	0	1	0	3	1	0	1	0	0	1	0	**7**
17	Fox-Fordyce disease	0	0	0	0	0	2	0	0	0	0	0	**2**
18	Peutz-Jeghers syndrome	0	0	0	0	0	0	1	0	0	0	0	**1**
	Total	**14**	**9**	**13**	**10**	**31**	**37**	**51**	**57**	**16**	**11**	**4**	**253**

for various comorbidities. For other forms of ichthyoses, dystrophic epidermolysis bullosa, benign familial pemphigus Hailey-Hailey, hereditary erythropoietic porphyria, other forms of porphyria, and Peutz-Jeghers syndrome, the most common age range is 45-54 years, probably due to mild forms of disease and clinical improvement with age in some forms of ichthyoses, respectively due to the possibility of onset in adulthood in some forms of porphyria and lastly, due to referral to specialized services when complications arise (malignancy of digestive polyps) in the case of Peutz-Jeghers syndrome. For keratodermas, Darier's disease, acrokeratosis verruciformis of Hopf, epidermolysis bullosa simplex, porphyria cutanea tarda, and hereditary erythropoietic porphyria, the most frequent age category is 55-64 years, probably due to evolutionary mechanisms of keratinization in palmoplantar keratodermas, mild clinical manifestations of Darier's disease and acrokeratosis verruciformis of Hopf, improvement of clinical manifestations with age in the case of epidermolysis bullosa simplex, and respectively, due to onset in adulthood and intermittent evolution of variable severity in the case of cutaneous porphyrias.

The distribution according to the number of hospitalization days of the studied genodermatoses cases is presented in Table 6 and illustrated in Figure 6. The highest number of hospitalization days was recorded for ichthyoses, cutaneous porphyrias, neurofibromatoses and keratodermas, probably due to the severity of clinical manifestations and the increased number of cases compared to the total number of diagnosed genodermatoses. Fewer hospitalization days were recorded for epidermolysis bullosa, familial benign pemphigus, Fox-Fordyce disease and tuberous sclerosis, possibly due to smaller number of patients and because pediatric cases were referred to specialized services. The lowest number of hospitalization days was recorded for Darier's disease and acrokeratosis verruciformis, probably due to milder clinical manifestations. The increased number of hospitalization days for the single patient diagnosed with Peutz-Jeghers syndrome was due to the thorough clinical and paraclinical investigation and the surgical intervention for diagnostic-curative purposes for the suspected malignancy of the colonic polyps.

Table 6. Distribution of various forms of genodermatoses according to the number of hospitalization days for the total number of discharged patients.

Index	NAME OF THE DISEASE	Patients	Hospitalization days	Percentage
1	Ichthyoses	43	405	28.36%
2	Porphyrias	42	380	26.61%
3	Neurofibromatoses	63	261	18.27%
4	Palmoplantar keratodermas	46	184	12.88%
5	Bullous epidermolysis	19	86	6.02%
6	Hailey-Hailey disease	6	38	2.66%
7	Fox-Fordyce disease	2	23	1.61%
8	Tuberous sclerosis	7	21	1.47%
9	Peutz-Jeghers syndrome	1	14	0.98%
10	Darier's disease	23	14	0.98%
11	Acrokeratosis verruciformis of Hopf	1	2	0.14%
	Total	**253**	**1428**	**100%**

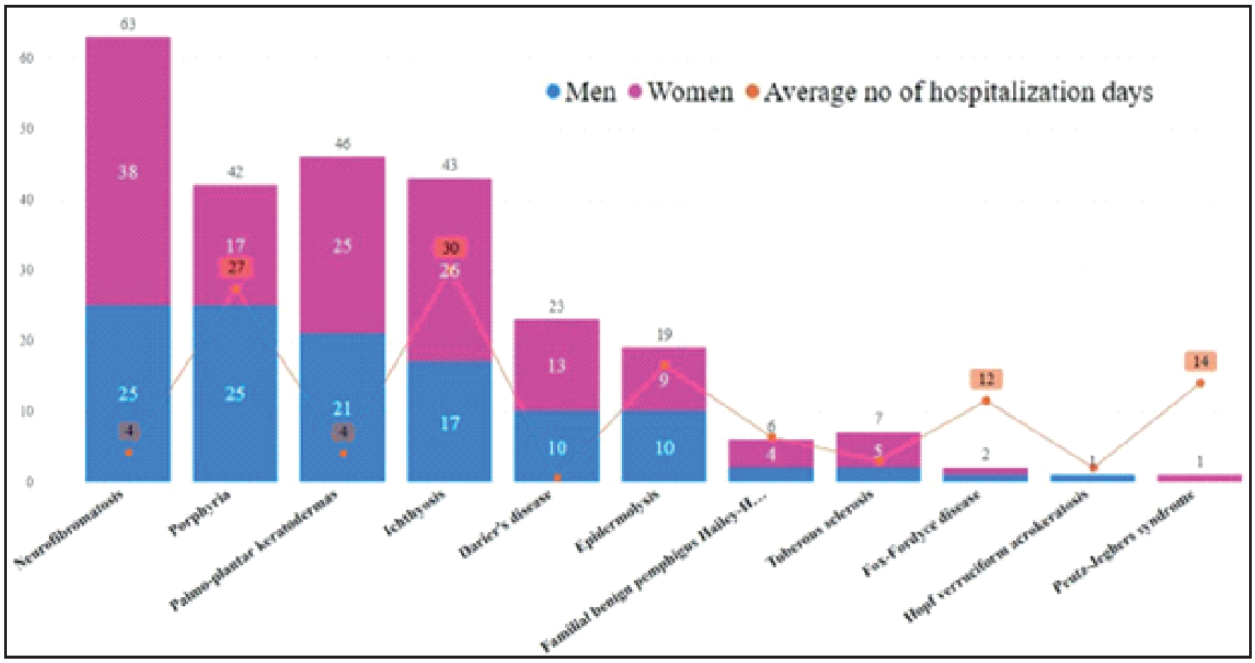

Figure 6. Distribution of various forms of genodermatoses according to the number of hospitalization days for the total number of discharged patients.

Discussions

Genodermatoses are chronic, incurable conditions, sometimes with severe clinical manifestations and potential for serious complications, so the main objectives of treatment for these diseases are to decrease the duration of flare-ups and increase the period of remission in cases where it is possible to achieve clinical remission, as well as to prevent complications, improve quality of life and reduce morbidity and mortality.

From this perspective, a major role is played by family investigation and genetic counseling, and prenatal diagnostic methods must be explained and used for all patients with a family or personal history of genetically determined conditions [1,8].

Genetic counseling provided by specialized teams aims to explain complex information regarding genetic risks, methods of anamnestic and clinical-paraclinical investigation, stages of diagnosis establishment and therapeutic options; it also has the role of providing psycho-emotional support and directing patients towards modern medical services that are specialized in this regard and tailored to individual needs.

Therapeutic options available for patients diagnosed with various clinical-etiopathogenic forms of genodermatoses are somewhat limited at present, so they are often disappointing for patients and clinicians, especially in severe forms of disease. In most cases, symptomatic dermatological treatment is instituted, associated as needed with treatment aimed at the complications and comorbidities frequently associated with this group of conditions. In mild or moderate forms of disease, the evolution of the condition is often favorable, especially in the short term, but without disease cure.

Following the clinical-epidemiological study conducted between 2013 and 2023, it was concluded that genodermatoses are rare conditions, with a low reported incidence during the period of the present study, in which a slight predominance of female patients was observed; this correlates both with the autosomal transmission model and the gonosomal type. Also, a predominance of patients from urban areas was observed, which can be attributed to better medical information among the population and easier access to medical services in urban areas.

Related to the etiopathogenic form of the disease, a heterogeneous distribution of the genodermatoses included in the study was noted, which were classified into the following categories: congenital keratinization disorders (ichthyoses, palmoplantar keratodermas, Darier's disease, acrokeratosis verruciformis of Hopf), bullous genodermatoses (epidermolysis bullosa, benign familial pemphigus Hailey-Hailey, porphyrias), congenital neurocutaneous syndromes (neurofibromatoses, tuberous sclerosis), chromosomal abnormalities with potential for malignant degeneration (Peutz-Jeghers syndrome) and conditions of uncertain etiology (Fox-Fordyce disease). Among these, the most frequent genodermatoses encountered between 2013 – 2023 are keratinization disorders (113 cases out of 253 patients, representing 44.66%).

Regarding the length of hospitalization for each clinical-etiopathogenic disease category, the highest number of hospitalization days was recorded among patients diagnosed with keratinization disorders (605 hospitalization days, representing 42.36% of the total of 1428 hospitalization days recorded for the 253 patients diagnosed with genodermatoses). Of the total keratinization disorders cases, the highest number of hospitalization days was recorded among patients diagnosed with ichthyoses (43 patients – 405 days, 28.36%). Other clinical-etiopathogenic categories with a high number of hospitalization days include porphyrias (42 patients – 380 days, 26.61%) and neurofibromatoses (63 patients – 261 days, 18.27%), which can be explained both by the therapeutic needs of the patients and by the increased number of patients. On the other hand, in terms of the average number of hospitalization days, Peutz-Jeghers syndrome (14 days of hospitalization for 1 single patient) and Fox-Fordyce disease (23 days of hospitalization for 2 patients) rank first, which is due to comorbidities that required surgical treatment (laparoscopic sigmoidectomy with mechanical end-to-end colorectal anastomosis for colonic polyposis with suspected malignant degeneration and histopathologically confirmed dysplasia and, respectively, total hysterectomy with bilateral anexectomy for uterine polyfibromatosis with foci of endometriosis).

With regard to the clinical manifestations, among the 253 patients diagnosed with genodermatoses included in the present study, predominantly mild or moderate forms of the disease were identified, with severe cases being extremely rare.

Paraclinical investigations played a significant role in establishing the clinical-etiopathogenic form of genodermatoses, and the histopathological examination served to highlight certain diagnostic criteria in accordance with the data found in specialized literature.

Conclusions

Genodermatoses represent rare conditions with multiorgan and multisystem involvement, manifesting in multiple clinical forms of variable severity. In severe cases, multidisciplinary collaboration is necessary for the accurate diagnosis and treatment of these chronic patients for whom curative therapeutic alternatives do not currently exist. Genodermatoses affect the patients' quality of life and can alter the vital prognosis in severe forms of the disease, which also constitutes a public health issue due to the increased number of hospitalization days and resources invested in these cases.

In this regard, therapeutic modalities that intervene in disease pathways are promising for the future and due to the fact that considerable progress has been reported in understanding the pathophysiological mechanisms of genodermatoses, the way has been paved towards innovative treatments aimed at correcting abnormalities in intercellular signaling pathways, inflammation suppression by replacing defective proteins or through cell therapy, and genetic engineering techniques that attempt genome editing (rearrangement, insertion or deletion of abnormal genes, insertion of a normal gene, manipulation of interfering RNA, and post-transcriptional gene repression) [9,10].

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This paper is part of a doctoral study entitled "Genodermatoses – Etiopathogenic, clinical, diagnostic and therapeutic considerations with practical applications in medical case studies" carried out by Silvia Popescu, PhD student at the "Carol Davila" University of Medicine and Pharmacy in Bucharest, Romania, under the guidance of university professor doctor Giurcăneanu Călin.

Conflict of interest
NONE DECLARED

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