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Ocular Anomalies in Incontinentia Pigmenti: Literature Review and Meta-Analysis

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SUMMARY

Introduction Incontinentia pigmenti (IP) is an X-linked genodermatosis in which skin changes are combined with dental, eye and central nervous system anomalies.

Objective The goal of the study was to analyze ocular findings, IP minor criteria in available literature concerning IP cases published until now.

Methods We have done meta-analysis of 1931 IP patients found in 302 references published until 2010. Comparison of data published for the 1906-1976 and 1976-2010 periods was made. The collected data were mainly frequencies of ocular anomalies. Chi-square test was used to compare observed frequencies with their expectations.

Results Of total number of IP patients, 1,227 were ophthalmologically investigated. In 449 such patients 972 eye anomalies were registered, 2.16 anomalies per patient. Proportion of ophthalmologically investigated IP patients in the period 1906-1975 (70%) was higher than corresponding proportion (60%) for the period 1976-2010. For 1906-2010 period 36.5% IP patients with eye anomalies were diagnosed. The number of amaurotic eyes per patient did not significantly differ for the two periods ($p=0.50$; >0.05). The total number of eye anomalies per patient significantly differed for the same periods ($p=0.00005$; <0.05). Retinal anomalies were most frequent in both periods.

Conclusion This study suggests that IP is far more frequent than anyone could estimate. We believe that this study, covering 1906-2010 period, gives more reliable information about ophthalmological findings in IP; considering them as severe anomalies. Early detection and treatment of ophthalmological, neurological etc. findings may prevent severe consequences that IP may cause.

Keywords: Incontinentia pigmenti; ocular anomalies; retinal anomalies; meta-analysis

INTRODUCTION

Incontinentia pigmenti (IP), also known as Bloch-Sulzberger syndrome, is a rare X-linked genodermatosis in which skin changes are usually combined with anomalies of other organs mainly of ectodermal origin. It appears almost exclusively in females and is usually lethal in males [1]. The typical pattern of IP skin changes appears along Blaschko lines [2]. Mutations of the NEMO-gene localized on the Xq28 chromosomal region are responsible for IP [3]. NEMO (IKBKG) gene signalling pathway is a multicomponent pathway that regulates the expression of hundreds of genes that are involved in diverse and key cellular processes, including cell proliferation, cell survival, immunity and inflammation. Its misregulation is involved in many diseases [4, 5]. However, failure to identify a NEMO (IKBKG) mutation does not rule out the diagnosis of IP [6]. Affected females survive because of X-chromosome dizygozity and negative selection of cells carrying the mutant X-chromosome [7].

In routine practice from 1993, proposed criteria for IP have been Landy and Donnai's [8] (Table 1). The presence of other than skin changes is important if skin changes are discrete. They can be of great prognostic and diagnostic value, because unlike dermatological alterations that fade through years they will be present throughout the patient's whole life [9]. The prognosis of IP is generally good and depends on extracutaneous manifestations that may also affect patients' quality of life. According to Landy and Donnai criteria [8], ocular findings are classified as IP minor criteria. Nevertheless, the severity of IP is very often attributed to these findings.

From 1906, when the disease was described for the first time [10], there were numerous reports of ocular anomalies in IP. In 1976, Carney [11] reviewed 653 case reports of IP from 464 references published in 1906-1975 period, of which 455 provided enough information to evaluate possible ocular anomalies.

Ever since Carney [11] has published world statistics of IP, no such meta-analysis has been done. The only exception was Porteleone's et al. [12] meta-analysis of clinical data for 82 IP patients cited by MEDLINE in the European literature from 2000 to 2006. In this group, 21% of patients had ocular findings. Detailed information about the number and type of ocular anomalies was not available. There were also articles in which single cases or series of patients with IP have been presented, but they were usually approached from one aspect: genetical [13], ophthalmological [14], dermatological [15],

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Table 1. Proposed criteria for Incontinentia pigmenti (IP) according to Landy and Donnai [8]

Family history	Criteria	
No evidence of IP in the first degree female relative*	Major	Typical neonatal rash (erythema, vesicles, eosinophilia)
		Typical hyperpigmentation (mainly trunk, Blaschko's lines, fading in adolescence)
		Linear, atrophic, hairless lesion
	Minor (supportive evidence)	Dental involvement
		Alopecia
		Woolly hair/abnormal nails
		Retinal disease
Evidence of IP in a first degree female relative**	Major	Suggestive history or evidence of typical rash
		Skin manifestations of IP (hyperpigmentation, scarring, hairless streaks, alopecia and vertex)
		Anomalous dentition
		Woolly hair
		Retinal disease
		Multiple male miscarriages

* At least one major criterion is necessary to make a firm diagnosis of sporadic IP. The minor criteria, if present, will support the diagnosis but because of their high incidence, complete absence should induce a degree of uncertainty.
** The diagnosis of IP is likely in the first degree female relative of an affected female if any of these features are demonstrable, alone or in combination.

etc. Reported data concerning the number of diagnosed patients and description of anomalies are often unreliable due to a highly specialized approach. Some papers dealing with genetical issues of IP were lacking complete clinical findings concerning analyzed patients [13]. According to ophthalmological investigation of Holmström and Thorén [14], out of 30 patients with IP, 23 (77%) had ocular anomalies and 7 of them amaurosis (30%). Phan et al. [15] reported a general retrospective study of 53 female patients. They presented 19 (36%) patients with IP and ocular anomalies. Intriguingly, in a number of articles, even the ones published recently [12], there was a statement that the total of 700 or some extra cases of IP were published in the literature. The only exception was Scheuerle and Nelson's [6] estimation of approximately 900-1200 IP affected individuals, 60 of them males that have been reported in the literature.

The literature was lacking a broad approach since IP is an illness with diverse abnormalities. In order to obtain further relevant data, besides Carney's study [11] which covered 1906-1975 period, we made a meta-analysis of ocular findings in the available literature concerning IP cases published in 1976-2010 period.

OBJECTIVE

The goal of the study was to analyze ocular findings, IP minor criteria in the available literature concerning IP cases published until now.

METHODS

We analyzed the available literature data concerning IP cases published in 1976-2010 period. Carney's article [11] was accepted for publication in August, 1975 and published in 1976, so papers published after this date were not covered in his study. We found 302 references from the world literature published during 1976-2010 period with acceptable data to warrant inclusion in the analyses. The analyzed references were published in Europe, Asia, Africa, Australia, North and South America, and covered patients from all cited continents. These references were listed separately in the Additional reference list (see Note). The validity of analyzed articles was taken for granted and not assessed. The authors made a maximal possible effort to exclude multiplications of data, e.g. patients described in more than one reference. The data that we collected were mainly frequencies that we presented in tables. Chi-square test was used to compare the observed frequencies with their expectations [16].

We reviewed 1,278 IP diagnosed patients presented in the available literature in the period 1976-2010. Out of these, 772 patients provided enough information to evaluate possible ocular anomalies. In this analysis, we considered retinal, lens and vitreous anomalies, optical nerve atrophy, and microphthalmia, as serious vision threatening findings that can lead to blindness. Anomalies were counted per eye. We counted as retinal anomalies: retinal detachment, retinal vascular anomalies, retinal pigment epithelium anomalies and all other anomalies of the retina. Retinal vascular anomalies included telangiectasia, ectasia, haemorrhage, neovascularization, and avascularity of the retina. Lens anomalies included cataracts, and other lens anomalies. Amaurotic eyes (blindness) were analyzed as a separate entity. All further ocular anomalies, such as strabismus, nystagmus, refractory, iris, corneal anomalies found in small number, originally unspecified anomalies (e.g. ocular disorder, ocular anomaly or severe eye impairment), as well as frequent anomalies, such as retinal detachments, retinal vascular anomalies, cataracts and strabismus with uncertain numerical data were presented as unspecified anomalies. Quite often individual patients had more than one type of anomaly.

RESULTS

In meta-analysis we presented data in tables. In Table 2 we presented data from Carney's study [11] covering the period from first reported IP patient in 1906, until 1975, data from the literature we collected for 1976-2010 period concerning the number of IP patients, and cumulative data for the period 1906-2010. In Table 3 and Table 4 data on type of

Table 2. Number of IP patients according to observed period, gender, ophthalmological investigation and presence of ocular anomalies

Observed period	Number of all IP patients				Number of ophthalmologically investigated patients				Number of ophthalmologically investigated patients with eye anomalies			
	Total	NA	Female	Male	Total	NA	Female	Male	Total	NA	Female	Male
1906-1975	653	44	593	16	455	0	444	11	160	0	156	4
1976-2010	1278	17	1157	104	772	6	686	80	289	5	268	16
1906-2010	1931	61	1750	120	1227	6	1130	91	449	5	424	20

NA – not available

Table 3. Number of all and essential types of ocular anomalies in IP patients in observed periods

Observed period	Total number of anomalies	Serious vision threatening findings	Amaurotic eyes	Strabismus and nystagmus	Unclassified anomalies
1906-1975	286	135	34	83	34
1976-2010	686	412	53	89	131
1906-2010	972	547	87	172	165

Table 4. Number of different serious vision threatening findings and amaurotic eyes in IP patients

Observed period	Retinal anomalies	Optical nerve atrophy	Vitreous anomalies	Lens anomalies	Microphthalmus/ anophthalmos	Amaurotic eyes
1906-1975	75	18	11	18	13	34
1976-2010	321	15	33	26	17	53
1906-2010	396	33	44	44	30	87

ocular anomalies in IP patients in different observed periods were presented.

The total number of IP patients in 1906-2010 period we found in the literature was 1,931, of whom 1,750 females, 120 males, and 61 with unspecified sex. Of all registered IP patients 64% were ophthalmologically investigated.

Out of 653 cases in Carney's study [11] covering the period 1906-1976, 91% were female, 2% male and 7% of unspecified sex (Table 2). Only four of 160 IP patients with diagnosed ocular anomalies were male. Out of 1,278 IP patients in 1976-2010 period 90% were female, 8% male and 2% of unspecified sex. Considering 1906-2010 period, 91% were female and 6% were male.

There was a difference in the frequencies of conducted ophthalmological investigations for IP patients for 1906-1975 and 1976-2010 periods (Table 2). Proportion of IP patients that were ophthalmologically investigated in 1906-1975 period (70%) was higher than corresponding proportion (60%) for the period of 1976-2010.

Proportions of patients with eye anomalies out of ophthalmologically investigated IP patients do not significantly differ for the two periods (p=0.42; >0.05). In the period 1906-1975 there where 160 out of 455 patients (35.1%) and there were 287 out of 772 patients (37.4%) in 1976-2010. For cumulative 1906-2010 period there were 36.5% (449/1,227) diagnosed IP patients with eye anomalies.

In 1906-1976 there were 286 ocular anomalies present in 160 IP patients with ophthalmic findings, 1.79 anomalies per patient were registered (Tables 3 and 5). Among ocular anomalies, the most frequent were strabismus, retinal, optical nerve and lens anomalies (Tables 4 and 5). In the period 1976-2010, there were 686 ocular anomalies in 289 IP patients, 2.37 anomalies per patient. Among ocular anomalies, the most frequent were retinal anomalies, strabismus, vitreous, and lens anomalies. According to cumulative data for the period 1906-2010, there were total of 449 IP patients with ocular anomalies, 2.16 anomalies per patient. Among ocular anomalies, the most frequent were retinal anomalies, strabismus, vitreous, lens anomalies and optical nerve atrophy. The number of amaurotic eyes per ophthalmologically investigated IP patient with anomalies does not significantly differ for the two periods (p=0.50; >0.05). On the other hand, the total number of eye anomalies per ophthalmologically investigated IP patient with anomalies significantly differs for the two periods (p=0.00005; <0.05).

Table 5. Number of serious vision threatening findings and amaurotic eyes per patient in observed periods

Observed period	Total number of anomalies per patient	Number of serious vision threatening findings per patient	Number of amaurotic eyes per patient
1906-1975	1.79	0.84	0.21
1976-2010	2.37	1.42	0.18
1906-2010	2.16	1.22	0.19

Retinal anomalies were by far most frequent in both periods of investigation. Ocular malignancies were rarely registered, only six in 1906-2010. Some ocular anomalies like refractory, corneal and iris were not registered by Carney [11] in 1906-1975. In 1976-2010 we found registered 28 refractory anomalies, 20 corneal anomalies and 13 iris anomalies. We noted three nasolacrimal duct anomalies in IP patients.

There was a problem with counting and identifying anomalies in some references [15, 17], because there was only a list of observed anomalies with no exact number. These lists included frequent anomalies such as retinal detachments, retinal vascular anomalies, cataracts and strabismus. These serious vision threatening anomalies we classified as unspecified anomalies together with different anomalies presented

in a small number. Due to this, the exact number of retinal detachments, retinal vascular anomalies, cataracts and strabismus was actually higher than presented in Tables for 1976-2010 as well as for 1906-2010 periods.

DISCUSSION

Incontinentia pigmenti is a hereditary, X linked disease lethal in most but not all males, with skin, dental, ophthalmological and neurological manifestations. In neonates with obvious skin manifestations and heredity for IP, the diagnosis is easy to be made. In older children and adults, the constellation of skin manifestations, dental abnormalities, possible neurological problems and eye manifestations helps in the diagnosis.

Of 1,278 IP cases found in the literature for 1976-2010 period, for 1,261 patients gender could be determined out of whom 90% were female and 8% male. The number of male IP patients was higher in 1976-2010 period, 8% compared to 2% in 1906-1975 [11]. We supposed that the reason for this difference arose from the better knowledge and availability of information about IP.

The explanation for the lower frequencies of conducted ophthalmological investigations for IP patients of 1976-2010 period compared to 1906-1976 period may be that the number of ophthalmologically investigated IP patients without anomalies in 1976-2010 period was higher, but the authors [13] did not put any (even negative) statement or comment in their paper about ophthalmological findings.

For ophthalmologically investigated IP patients in 1906-1975 and 1976-2010 periods, there was no significant difference in the proportions of diagnosed patients with eye anomalies. Intriguingly, nearly the same percentage of IP patients with ocular anomalies was registered in Carney's [11], Phan et al. [15] articles and in the period 1976-2010 which we analyzed. There was a significant difference in the number of eye anomalies per IP patient – 1.79 for 1906-1975 and 2.37 for the period of 1976-2010. Retinal anomalies were by far most frequent in both periods of investigation.

The number of amaurotic eyes per patient was similar in both observed periods, while the number of serious vision threatening findings per patient was significantly higher in the period 1976-2010. We supposed that the reason for no significant difference in the proportions of diagnosed patients with eye anomalies and similar number of amaurotic eyes in both periods was that IP is a hereditary disease with limited possibility for therapy.

According to Landy and Donnai [8], ocular anomalies in IP were represented as minor criteria; we have seen in cumulative analysis that more than one third of ophthalmologically investigated IP patients had on the average 2.16 anomalies each. The most frequent were retinal anomalies. In addition to retinal anomalies, we found strabismus, vitreous and lens anomalies and optical nerve atrophy. These severe anomalies presented more than half of the total number of anomalies registered in IP patients. The quoted anomalies, as solitary or in combination with other anomalies, usually resulted in serious vision threatening conditions including blindness [11, 14].

Besides on the number of references dealing with ophthalmological problems in IP, little is known about its pathogenesis. It has been assumed that retinal IP affection begins with pigment epithelium changes and/or retinal vascular changes, followed by inflammatory response that may lead to retinal detachment. Retinal pathology was the most probable reason even for strabismus [14]. Nevertheless, the severity of IP is very often attributed to visual impairment including blindness. We wish to emphasize that beside diverse types of anomalies, a different intensity of specific anomalies was recorded. The explanations for such findings are probably in different NEMO gene mutations [18] as well as nonrandomed X-inactivation pattern in females [7].

We found in 1976-2010 period iris and corneal anomalies. These types of anomalies were not registered in the Carney's study [11], as well as ocular refractory anomalies. We supposed that ocular refractory anomalies were neglected by the authors in the description of IP patients and that they were more frequent than it was seen from the available data. As a rare finding in IP, we noted three nasolacrimal duct anomalies, not described previously in IP patients. Bilateral anophthalmia was found in a single patient. Malignant eye diseases in IP patients were rarely revealed. Carney [11] noted only two such anomalies diagnosed as metastatic ophthalmia. We found three patients in the analyzed literature with malignant eye diseases. Retinoblastoma was reported three times (in one case as a single and as bilateral in another), and tumour of the vitreous body in one case.

When discussing the appearance of different noncutaneous anomalies in IP patients with ophthalmological findings, we must bear in mind the fact that cutaneous IP patterns are along Blaschko lines. According to Rott [2] in other than skin like organs, lens, iris, retina, teeth and bones in different X-linked diseases also existed patterns of changes analogous to cutaneous Blaschko lines. For this reason, we believe that the pattern of retinal, iris, and lens anomalies also develope along analogues of Blaschko lines.

In our study, we found diagnosed corneal anomalies in a whorl-like pattern [19] or opacities with specific pattern [14, 20]. Using confocal microscopy a possible X-linked inactivation mosaic in the corneal epithelium was found [21]. Taking in account these facts, we hypothesized that it could be possible that Blaschko lines analogues also existed in the cornea as well as in other parts of the eye.

Cumulative statistical analysis of IP patients for the period of 1906-2010 gave us interesting results. IP was generally treated as a rare disease, but in the literature we found 1,931 patients, of whom 1,227 were ophthalmologically investigated. In 449 ophthalmologically investigated IP patients 972 ophthalmic anomalies were registered; 2.16 anomalies for each patient. The number and severity of ocular anomalies that we have recorded obviously proves the importance and influence of these clinical findings on the quality of life of these patients. Ocular lesions in patients with IP may be serious and lead to vision threatening manifestations or even blindness mainly because of retinal disease [14]. This study proves that dominant ocular findings were retinal findings. They included retinal vascular anomalies, retinal detachment

and retinal pigment epithelium anomalies. Early detection of the retinal disease and initiation of adequate treatment is very important. To achieve this, there is a need for a screening program for infants with IP and knowledge of natural history of the retinal disease and of different treatment modalities [14]. Regular visits to the paediatric ophthalmologist familiar with retinopathy of prematurity are essential during the first year of life.

CONCLUSION

We wish to emphasize that the total number of 1,931 IP patients in this meta-analysis was higher than any estimated number of IP patients presented so far in the literature [6]. We believe that this cumulative statistical study covering 1906-2010 period gives a more reliable source of information about ophthalmological findings, minor criteria of IP than previously published data. According to reported findings, epidemiological analyses of rare diseases, such as IP, would be more precise and reliable if authors and editors would pay more attention in collecting and presenting literature data. We would suggest that no matter which investigation approach for IP is chosen, it would be useful for further world statistics to give a precise list of all clinical findings. Further more, this study suggests that IP is far more frequent than anyone could have estimated before. Therefore, paediatricians should bear in mind this diagnosis, because early detection and treatment of some ophthalmological, neurological etc. findings may prevent severe consequences that IP may cause.

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NOTE

The Additional reference list is available upon request from the authors.

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Очне аномалије у инконтиненцији пигменти: преглед литературе и метаанализа

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КРАТАК САДРЖАЈ

Увод Инконтиненција пигменти (*incontinentia pigmenti – IP*) је генодерматоза везана за *X*-хромозом у којој су промене на кожи често удружене с поремећајима зуба, очију и централног нервног система.

Циљ рада Циљ рада је био да се испитају очни поремећаји и тзв. минор критеријуми *IP* у досад објављеној доступној литератури.

Методе рада Извршена је метаанализа података о 1.931 болеснику са *IP* нађених у 302 референце публиковане до 2010. године. Упоређени су резултати за периоде 1906-1976. и 1976-2010. године, а углавном је била реч о учесталости очних поремећаја. За поређење забележене и очекиване учесталости коришћен је χ^2-тест.

Резултати Од укупног броја болесника са *IP* 1.227 је било подвргнуто офталмолошком прегледу. Код 449 болесника су установљене 972 очне аномалије (2,16 аномалија по болеснику). Пропорција офталмолошки прегледаних болесника са *IP* у периоду 1906-1976. године (70%) је већа него у периоду 1976-2010. године (60%). У периоду 1906-2010. године очне аномалије су забележене код 36,5% болесника са *IP*. Број слепих очију по болеснику се не разликује значајно за испитиване периоде (p=0,50; >0,05). Укупан број аномалија очију по болеснику за исте периоде се, међутим, значајно разликује (p=0,00005; <0,05). Најчешће аномалије у оба посматрана периода биле су на ретини.

Закључак Студија показује да је *IP* много чешће обољење него што се досад процењивало. Период 1906-2010. године пружа много поузданије податке о очним аномалијама у *IP*, разматрајући их као тешке поремећаје. Рано откривање и лечење офталмолошких, неуролошких и других пратећих поремећаја могу да спрече озбиљне последице које може да изазове *IP*.

Кључне речи: инконтиненција пигменти; очне аномалије; аномалије ретине; метаанализа

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