Ophthalmological Findings in Series of Incontinentia Pigmenti Patients from Serbia

Snežana Minić, Gerd E. K. Novotny, Ivan Stefanović, Miljana Obradović, Dušan Trpinac

1Institute of Dermatology, Clinical Centre of Serbia, Belgrade, Serbia; 2Medizinische Einrichtungen, Institute of Anatomy I, University of Düsseldorf, Düsseldorf, Germany; 3Institute of Ophthalmology, Clinical Centre of Serbia, Belgrade, Serbia; 4Institute of Histology and Embryology, School of Medicine, University of Belgrade, Belgrade, Serbia

SUMMARY

Introduction Incontinentia pigmenti (IP) is a rare complex X-linked genodermatosis in which skin changes are combined with anomalies of other organs. Mutations of the NEMO gene localized on chromosome Xq28 are responsible for IP. Clinical manifestations of IP according to evolution and prognosis can be considered as skin changes and dental, eye and central nervous system changes.

Objective The aim of our study was to investigate type and frequency of ocular features in Serbian population.

Methods We investigated the total of 9 families with 22 subjects, 20 females and 2 males, at the Institute of Dermatovenerology, Clinical Centre of Serbia, in the period from 1989 to 2009. Our subjects were diagnosed clinically by a dermatologist and the diagnosis confirmed by cutaneous histopathology and ultrastructural analysis. The pedigrees, karyotype analyses, routine laboratory findings, additional specialized clinical examinations were done for all subjects.

Results Among 22 IP patients from our study, different ophthalmological anomalies were observed in 16% of subjects. In female subjects, all of them with clinical characteristics of IP, we observed the following anomalies: retinal detachment, microphthalmia, cataract, strabismus and nystagmus.

Conclusion Compared to available literature data, our percentage of IP patients with anomalies was lower. It may be due to differences in examined populations or due to the fact that the patients in our study were firstly admitted to the Institute of Dermatology. Ophthalmological findings may be often considered as very severe anomalies in IP. It is very important to detect IP as early as possible, medically help and monitor these patients.

Keywords: incontinentia pigmenti; ocular anomalies; microphthalmia; cataract; nystagmus; strabismus

INTRODUCTION

Incontinentia pigmenti (IP), also known as Bloch-Sulzberger syndrome or Bloch-Simons syndrome, is a rare complex X-linked genodermatosis in which skin changes are combined with anomalies of other organs, and structures mainly of ectodermal origin [1]. It appears almost exclusively in females and is usually lethal in men [2]. Mutations of the NEMO gene (nuclear factor-KB essential modulator protein gene, IKBKG gene) localized on chromosome Xq28 are responsible for IP [3]. NEMO signaling pathway is a multi-component pathway that regulates the expression of a number of genes that are involved in cell proliferation, cell survival, immunity and inflammation. Its mis-regulation is involved in many diseases [4, 5]. However, failure to identify an NEMO mutation does not rule out the diagnosis of IP [6].

Landy and Donnai criteria [7] were used for the clinical diagnosis of IP. The clinical diagnosis of IP can be made in the presence of at least one major criterion. Major criteria are typical skin changes developing through four stages [2, 7]: erythema followed by vesicles usually in a linear distribution; hyperpigmented streaks and whorls that respect Blaschko lines; pale, hairless, atrophic, linear streaks or patches. The presence of minor criteria, teeth, hair, nails, retina, supports the clinical diagnosis and the complete absence of minor criteria should raise doubt about the diagnosis [7]. Family history of the IP or a history of multiple miscarriages is also supportive for IP diagnosis [7].

The presence of other than skin changes is sometimes of great importance if skin changes are discrete. It can be of great prognostic and diagnostic value because unlike dermatological alterations, they may be present throughout the patient’s whole life [7, 8, 9]. Among patients with IP, 79.9% have one or more anomalies of other organs besides skin changes [1]. Dental changes are the most frequent, present in 60% of the patients [10].

There have been numerous case reports of ocular abnormalities in IP. In 1976 Carney [1], in his world statistic study, reviewed 653 case reports of IP taken from literature, of which 455 provided enough information to evaluate possible ocular abnormalities. Ophthalmic features were present in 35% of patients. Strabismus was the most common ocular abnormality (18%). Besides Carney’s [1] classical review that covered cases from all over the world until 1977, ophthalmologic findings in series of IP patients were published in several retrospective studies from Scandinavia [11], France [12], Australia [13], Korea [14], and Spain [15]. In Holmström and Thorén’s [11] investigation, out of 30 patients...
with IP, 77% had ocular manifestations, some of them very severe. From 34 IP patients, Hadj-Rabia et al. [12] found ocular abnormalities in 20%. In 53 IP patients, Phan et al. [13] determined ocular anomalies in 37%. Of 30 IP patients, Kim et al. [14] found ocular anomalies in 66.7%, 56.3% with retinopathy and 16.3% strabismus. Pascual-Castroviejo et al. [15] presented a series of 12 IP patients, 25% of whom had both serious neurological and ophthalmological disorders.

**OBJECTIVE**

The aim of our study was to investigate type and frequency of ophthalmological features among 22 subjects from our study of IP in Serbian population.

**METHODS**

We investigated the total of 9 families with 22 subjects, 20 females and 2 males, in the period from 1989 to 2009. The patients were examined at the Outpatient Unit of the Institute of Dermatovenerology, Clinical Centre of Serbia. Selection of families was done according to Landy and Donnai criteria [7]. Our subjects were diagnosed clinically by a dermatologist and the diagnosis confirmed by cutaneous histopathology and ultrastructural analysis. The pedigrees (Figure 1), karyotype analyses and routine laboratory findings were done for all subjects. Depending on the presence of extracutaneous manifestation, they were referred to specialists for further examination.

**RESULTS**

Out of our 22 subjects, ophthalmological findings were present in four subjects from two families. One refers to a single female proband and the rest to a family where, out of four examinees, three had ophthalmological findings. Facts concerning basic subjects’ data, onset and key clinical findings are presented in Table 1.

**Family 1**

Proband 1, besides classical skin findings that had started the third day after birth and had expected evolution from vesiculobullous, through verrucolichenoid to hypopigmented maculas, had neurological and ophthalmological findings. Neurological examination revealed that the ability to follow features in the eye site was insecure. Both eyeballs were slightly deviated towards left. The left rima oculi was slightly narrower than the right one; only the left eye was occasionally shut. When testing iris, while one eye was shut the other had nystagmus, or not coordinated movements. Both irises were isochoric. The test with light showed a slow and insufficient reaction. The diagnosis was horizontal nystagmus. Examination of fundus revealed clearly distinguished papilla which was vaguely reddish in the retinal level. Retinal arteries and venulas had normal caliber. Maculas were normal as well. Due to the lack of retinal pigment, chorioidal vessels were visible. Diagnosis of fundus subalbinoticus was made.

Proband’s mother had only typical IP skin changes.

**Table 1. Facts concerning basic subjects’ data (all females)**

<table>
<thead>
<tr>
<th>Family</th>
<th>Subject</th>
<th>Age</th>
<th>Onset</th>
<th>Retina</th>
<th>Cataract</th>
<th>Microphthalmia</th>
<th>Nystagmus</th>
<th>Strabismus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>Proband</td>
<td>35 days</td>
<td>1 month</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>27 years</td>
<td>Uncertain</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Family 2</td>
<td>Proband</td>
<td>39 days</td>
<td>1 month</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Mother</td>
<td>20 years</td>
<td>First few months</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Grandmother</td>
<td>46 years</td>
<td>Early childhood</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Grandmother’s sister</td>
<td>49 years</td>
<td>First few months</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Family 2**

Proband 2 had classical clinical skin findings ever since she was four days old. Her skin changes had well known evolution. There were no other findings.

Proband’s mother had no skin changes but her ophthalmological findings were present since birth leading to vision threatening features. When examined, she had microphthalmic right eye with cataract and synechiae between iris and front lens capsule in the lower part. The diagnoses were amaurosis, microphthalmia, complicated cataract, hypotonia bulbi, esotropia, and strabismus. The left eye was normal. She had numerous carious teeth.

Proband’s grandmother had no skin changes. She complained about her eyes since early childhood. Her ophthalmological findings showed stronger arterial retinal reflex. Since youth, she had no teeth due to extremely bad quality and numerous carious problems.
Proband grandmother’s sister had retinal detachment in early childhood. Ever since then, she was nearly blind.

Frequencies of different ocular findings in investigated subjects are presented in Table 2.

<table>
<thead>
<tr>
<th>Finding</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal lesions</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Microphthalmia</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Strabismus</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

DISCUSSION

IP is a hereditary, X-linked disease lethal in most but not all males, with basically skin, dental, ophthalmological and neurological features. 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 are of help in making diagnosis.

We observed 22 IP patients from Serbia. Ophthalmological findings were present in four of them; all four females from two families. In our group of IP patients, different ophthalmological anomalies were observed in 16% of investigated subjects.

Carney [1] reviewed 455 IP cases with sufficient information to evaluate possible ocular abnormalities. Ophthalmic features were present in 35% of patients. Strabismus was the most common ocular abnormality (18%), different retinal findings were present in 10.1%, while microphthalmia was diagnosed in 2.9%. In our study one patient had unilateral microphthalmic eye, one retinal detachment and strabismus.

According to in-depth ophthalmological data by Holmström and Thorén [11], 77% of Scandinavian IP patients had ocular manifestations. The most frequent ophthalmological features were strabismus, nystagmus, cataract, pseudoglioma, retrolental fibroplasia, retinal atrophy and retinal detachment [11]. Hadj-Rabia et al. [12] found ocular abnormalities in 20% of French IP patients; the problems were severe in 8%. Unilateral microphthalmia was found in 6% of their patients. Phan et al. [13] determined ocular anomalies in 37%. The four Australian IP patients with intellectual deficit also had ocular abnormalities, suggesting that abnormalities of retinal vascularization may be the marker for other neurological abnormalities [13]. Kim et al. [14] found retinopathy in 56.3% and strabismus in 16.3% of Korean IP patients with ocular anomalies. Pascual-Castroviejo et al. [15] found ocular anomalies only in IP patients with serious neurological disorders. One of the patients had unilateral microphthalmia.

In our study, out of 22 examined subjects, four had ocular findings (16%). Compared to available data from other populations [1, 11-15], our percentage is lower. It may be due to differences in examined populations, or due to the fact that patients in our study were admitted firstly to the Institute of Dermatology. On the other hand, the investigation that had the highest percentage of ocular findings was coming from the Department of Ophthalmology [11].

In our study, proband 1 was a single positive member from family 1. Other three patients were from family 2. Ocular findings, apart from proband 2, in family were the strongest clinical finding of IP. Three patients had retinal findings, and one patient had cataract and microphthalmia.

Nystagmus may be approached in two ways: ophthalmological and neurological. It was present in two patients. It was the only neurological finding among all investigated subjects.

CONCLUSION

In our study, out of 22 examined IP patients from Serbian population, 4 had ocular findings (16%). Compared to available data, our percentage is lower. It may be attributed to differences in examined populations. The other reason may be the fact that our patients were firstly diagnosed by a dermatologist. Ocular lesions in patients with IP may be serious and lead to vision threatening manifestations or even blindness because of retinal disease. It is therefore essential to refer neonates to an ophthalmologist as soon as the diagnosis is made. They must be familiar with the disease and schedule these children for screening and regular follow-ups, preferably as recommended.

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Ofthalmološki naplati bolosnika s inkontinencijom pigmenti iz Srbije
Snježana Minić1, Gerd E. K. Novotny2, Ivan Stefanović3, Mišana Bradovic4, Dusana Trpinač4

3Институт за очне болести, Клинички центар Србије, Београд, Србија;
2Medizinische Einrichtungen, Институт за анатомију, Универзитет у Диселдорфу, Диселдорф, Немачка;
1Институт за дерматологију, Клинички центар Србије, Београд, Србија;
4Институт за хистологију и ембриологију “Проф. др Александар Ђ. Костић”, Медицински факултет, Универзитет у Београду, Београд, Србија

КРАТАК САДРЖАЈ
Увод
Инkontinencija pigmenti (Incontinentia pigmenti – IP) je retka složena genodermatoz vazena za X-hromozom u kojoj su promene na koji ceo udružene s poremećajima drugih organa. Za nećenastanack odogovore su mutacije gene NEMO, koji se nalazi na hromozomu Xq28. Kliničke manifestacije IP su promene na kojim koji mogu biti udružene s poremećajima Zuboa, očiju i centralnog nervnog sistema.

Циљ рада
Циљ рада je bio da se ispija tip i učestalost poremećaja očkih kod bolesnika sa IP u Srbiji.

Методе рада

Резултати
Аномалије на очима су установљене код четири бо- lesnice (16%). Дијагностиковане су: аблиција ретине, микрофталмија, катаракт, страхибзам и нистагмус.

Закључак
Процетат болесника са IP и poremećajima на очима је био највећи у описиваној групи која је ниска. Од поређењу са подацима из литература, разлике могу бити разлике у посматраним популаци- јама или чињеница да су болесници право дошли в Институт за dermatovenerologiju. У IP очи поремеćао се често представљају врло тешке аномалије. Због тога је веома важно да оф- талмолог код особа оболелих од IP што раније откриje могуће поређење, примени лечење и дање их надгледа.

Кључне речи:
инконтиненција pigmenti; очне аномалије; микро- фталмија; катаракта; нистагмус; страхибзам

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