Clinical report

Corneal changes in long-term chlorpromazine therapy

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Objective: To study ocular manifestations in patients who were on long-term use of chlorpromazine.

Methods: A retrospective observational case study was made. Three patients, who were diagnosed as Schizophrenia and on long-term use of chlorpromazine for more than 20 years, were examined retrospectively. The examinations included clinical history, physical examination, slit-lamp biomicroscopy, and fundus examination. Confocal microstructure analyses of corneal changes were also performed on two cases.

Results: A series of three cases, a 52-year-old woman, and two men of 45-year-old and 56-year-old, had a history of prolonged chlorpromazine use and presented with gradual onset of blurred vision in their both eyes for years. Slit-lamp biomicroscopy revealed multiple yellowish-white granular deposits on posterior stroma and corneal endothelium. Stellate yellowish-brown pigments deposited in the anterior subcapsular areas were also found. Fundus examination showed neither pigment epithelial mottling nor maculopathy. Confocal microscopic examination of two patients revealed numerous hyper-reflective deposits on the posterior stroma and corneal endothelium. There were no abnormalities in both endothelial cellular morphology and density.

Conclusion: We reported ocular manifestations of three patients who were on long-term chlorpromazine therapy. Confocal imaging is useful for detection of abnormality in the corneal structure. Microstructure changes revealed numerous hyper-reflective deposits on the posterior stroma and endothelium without any changes in cellular morphology and density.

Keywords: Confocal microscopy, Chlorpromazine, Pigment deposit.

Long-term chlorpromazine therapy has been reported to cause numerous side effects involving many systems, i.e., hepatic disorders, extrapyramidal symptoms, and blood dyscrasias. Deposits in cornea and lens are known complication. This is a case-series to describe pigmentary deposits on the cornea using in vivo confocal microscopy.

Materials and methods

Three patients, who were diagnosed as schizophrenia and on long-term use of chlorpromazine for more than 20 years were retrospectively examined. The examinations included clinical history, physical examination, slit-lamp biomicroscopy and fundus examination. Confocal microstructure analyses of corneal changes were also performed on two cases using in vivo confocal microscopy (ConfoScan 4.0, NIDEK; Padova, Italy).

Results

Case 1

A 52-year-old woman presented with gradual onset of blurred vision for two years. She was diagnosed as schizophrenia. She had been taking chlorpromazine 200 mg per day for 28 years. Her psychotropic medications consisted of chlorpromazine 100 mg per day for 33 years and trifluoperazine 5 mg twice a day, modicate when necessary.

Her best-corrected visual acuities were 20/40 bilaterally. Slit-lamp biomicroscopy revealed multiple fine yellowish-brown deposits on her corneal stroma, endothelium (Fig.1) and anterior crystalline lens capsule bilaterally (Fig. 2). Fundus examination showed no maculopathy.
Fig. 1 Slit-lamp biomicroscopic image revealing multiple fine yellowish-brown deposits on corneal stroma and endothelium.

Fig. 2 (a, b) Slit-lamp biomicroscopic images revealing multiple fine yellowish-brown deposits on anterior crystalline lens capsule bilaterally (a), and Retroillumination technique (b).
Confocal microscopic examinations demonstrated irregular well-defined, hyper-reflective deposits on the posterior stroma and corneal endothelium (Fig. 3 a-d). Endothelial morphology was normal bilaterally. The endothelial density in both eyes were within the normal age-adjusted range (right eye 2835 cells/mm² and left eye 2897 cells/mm², normal range 1695-3221 cells/mm²) and there was no endothelial pleomorphism or polymegathism.
The second case, a 56-year-old man presented with gradual onset of blurred vision for 2 years. He was diagnosed as schizophrenia. He had been taking chlorpromazine 400 mg per day for 33 years. His psychotropic medication consisted of lithium, diazepam, benzhexol, and chlorpromazine.

His best-corrected visual acuities were 20/30 in the right eye and 20/20 in the left eye. Slit-lamp biomicroscopy revealed multiple fine creamy-white deposits on his corneal stroma, endothelium and anterior crystalline lens capsule bilaterally (Fig. 4). Fundus examination showed no maculopathy.

Confocal microscopic examinations showed numerous irregular hyper-reflective deposits on the stroma and corneal endothelium (Fig. 5a, b). There were no abnormalities in both endothelial cellular morphology and density within the age-adjusted range like the first case.

Fig. 3 (a-d) Confocal microscopic examinations of the cornea identified irregular hyper-reflective, well-defined edges deposits on the posterior corneal stroma and endothelium.

Fig. 4 Slit-lamp biomicroscopic image revealing multiple fine creamy-white deposits on corneal stroma and endothelium.
Case 3

The third case, a 45-year-old man presented with gradual onset of blurred vision for 2 months. He was diagnosed as schizophrenia. He had been taking chlorpromazine 800 mg per day for 20 years. His psychotropic medication consisted of triflazine (10) 1 tab pox qid, benzhexol (2) 1 tab pox qid, and chlorpromazine.

His best-corrected visual acuities were 20/40 in the right eye and 20/30 in the left eye. Slit-lamp biomicroscopy revealed multiple fine brown deposits on his corneal stroma, endothelium and anterior crystalline lens capsule bilaterally (Fig. 6a, b). Fundus examination showed no maculopathy.

Discussion

Chlorpromazine is an aliphatic phenothiazine used in manic-depression, psychosis, especially schizophrenia. The adverse effects include lethargy, postural hypotension, anticholinergic side-effects, infertility and extrapyramidal symptoms, which are dose-related. The hypersensitivity reactions are cholestatic jaundice, skin rashes, photosensitivity, and agranulocytosis. Pigmentation of exposed skin, corneal and lenticular opacities, and retinal degeneration occur rarely after long-term use of high doses chlorpromazine [1].

The most prevalent ocular side-effect associated with chlorpromazine therapy is pigmentation of anterior capsular and subcapsular of the lens, followed by corneal pigmentary changes [2, 3]. Even though all corneal layers involvement has been reported, the corneal changes usually occur in endothelium, Descemet's membrane, and posterior stroma respectively [4]. These pigmentary deposits have been found to be dose-dependent and usually irreversible [4, 5]. Deposits in the lens occur in most patients with a cumulative chlorpromazine dose of more than 1,000 gram, and corneal deposits occur at higher levels [4]. On the other hand, pigmentary retinopathy has been reported with higher dose (2400 mg/day) [6, 7].

Fig. 5 (a, b) Confocal microscopic examinations of the cornea showed irregular hyper-reflective deposits on corneal stroma and endothelium.
In our case series, the patient’s cumulative chlorpromazine dose was more than 1,000 gram as shown in Table 1. When compare to clinical presentations, we found that the more cumulative doses used, the more corneal deposits found. In the third case, which had the maximal cumulative dose, the cornea showed more density of pigmentary deposit, more diffuse to anterior corneal stroma, and the color of deposit changed to brown pigmentation.

Table 1. Summary of mean and cumulative chlorpromazine dose in three patients.

<table>
<thead>
<tr>
<th>Summary dose</th>
<th>Case 1 (Male 56 years)</th>
<th>Case 2 (Female 52 years)</th>
<th>Case 3 (Male 45 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose (mg/day)</td>
<td>100</td>
<td>200</td>
<td>800</td>
</tr>
<tr>
<td>Duration (year)</td>
<td>33</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>Total dose (gram)</td>
<td>1174</td>
<td>1433</td>
<td>5696</td>
</tr>
</tbody>
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Fig. 6 (a, b) Slit-lamp biomicroscopic images revealing multiple fine brown deposits on corneal stroma, endothelium and anterior crystalline lens capsule bilaterally.
The precise nature of the pigmentary granules in the cornea and lens is unknown. There is a general knowledge that the pigment deposited is melanin, probably combined with the neuroleptic or its metabolites. They assumed that the pigmentary changes is likely to result from drug interactions with ultraviolet light as it passes through the cornea and lens, causing exposed anterior segment proteins to denature, opacify, and accumulate in the anterior subcapsular region of the lens as well as in the conjunctiva and corneal stroma [7, 8]. However, the use of spectacle, to reduce the amount of ultraviolet light entering the eye, has been unsuccessful in reducing the prevalence of ocular toxicity [9].

There are many reports using specular microscopy analysis of chlorpromazine deposit in the cornea, especially endothelium. Brooks and his coworkers [10] showed numerous discrete clumped, irregular appearance, and variable size against the background of the normal corneal endothelial mosaic. Nowadays, we have in vivo confocal microscopy to analyze corneal cells more precise layer by layer. Yun SP et al. first reported deposits using this instrument. He revealed no abnormalities in cellular morphology resulting from these deposits in one patient [11]. Our findings also confirm his report.

The co-management between the psychiatrist and ophthalmologist in patients on long-term chlorpromazine treatment is essential. We hypothesized that microstructure analysis by confocal microscopy is useful in early detection of drug deposit in the cornea as it is more sensitive for the detection of pigmentary granule deposit in the lens by slit-lamp biomicroscopy. Although the pigmentary change of the cornea and lens causes minimal visual acuity loss, there is no study showing the effect of these deposits on the quality of vision, such as glare, decrease contrast sensitivity, reduce color perception, and recurrent corneal epithelial erosion in more severe cases. This may need further investigation and study.

The authors have no conflict of interest to report.

References