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ORIGINAL RESEARCH ARTICLE

Aripiprazole-induced chorioretinopathy: multimodal imaging and electrophysiological features

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Abstract
Purpose To report the first documented case of aripiprazole-induced chorioretinopathy.
Methods and results A 47-year-old schizophrenic patient with loss of vision due to an atypical retinopathy was investigated. She had been treated with aripiprazole for 8 years. Multimodal imaging showed in the right eye a large area of retinal atrophy predominating in the outer retina, including the posterior pole up to the upper temporal periphery, and in the left eye a serous retinal detachment. The electroretinogram exhibited decreased and delayed responses of both the rod and cone systems; the electrooculogram showed no light peak.
Conclusion Aripiprazole, an atypical antipsychotic, was introduced more recently than the antipsychotics commonly incriminated in chorioretinopathies, such as thioridazine. Optical coherence tomography was not used to document former cases of antipsychotic-related chorioretinopathies. Although pathophysiological mechanisms are poorly understood, imaging of the present case points toward an involvement of the retinal pigmentary epithelium. Clinicians should be aware of the potential chorioretinal toxicity of new atypical antipsychotics.

Keywords Antipsychotic · Chorioretinopathy · Retinopathy · Spectral domain OCT · Aripiprazole · CYP2D6

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Introduction

Soon after phenothiazines were introduced as antipsychotics, a series of reports cast light on their ocular toxicity [1, 2]. Some drugs—notably thioridazine—, long-duration treatments and high daily doses were identified as risk factors, leading to maximal daily dose recommendations, and more recently withdrawal of thioridazine in many countries. The number of reported cases subsequently decreased, while evidence accumulated showing that thioridazine ocular toxicity could be seen after treatment of various durations at recommended doses [3–9] and could also progress more than 30 years after treatment discontinuation [10].

The ocular presentation of phenothiazine toxicity consists in anatomical and functional changes in the retina and choroid. Although it is now known to be progressive, the succession of well-described ophthalmic stages does not correlate with functional decline, hence the suggestion to avoid using the term "progressive chorioretinopathy" [11]. The first stage is a granular retinopathy, with peppery pigmentation of the posterior pole. The second stage is a patchy nummular chorioretinopathy, with areas of chorioretinal atrophy growing in size in the midperiphery, sometimes associated with large areas of pigment clumping, while the initial features tend to disappear. The third stage shows large geographic areas of chorioretinal atrophy. Since most descriptions preceded the optical coherence tomography (OCT) era, little is known about the associated structural changes in the retinal layers.

Other antipsychotics from various classes have also been incriminated in retinal toxicity: chlorpromazine [12] and fluphenazine [13, 14], both phenothiazines;

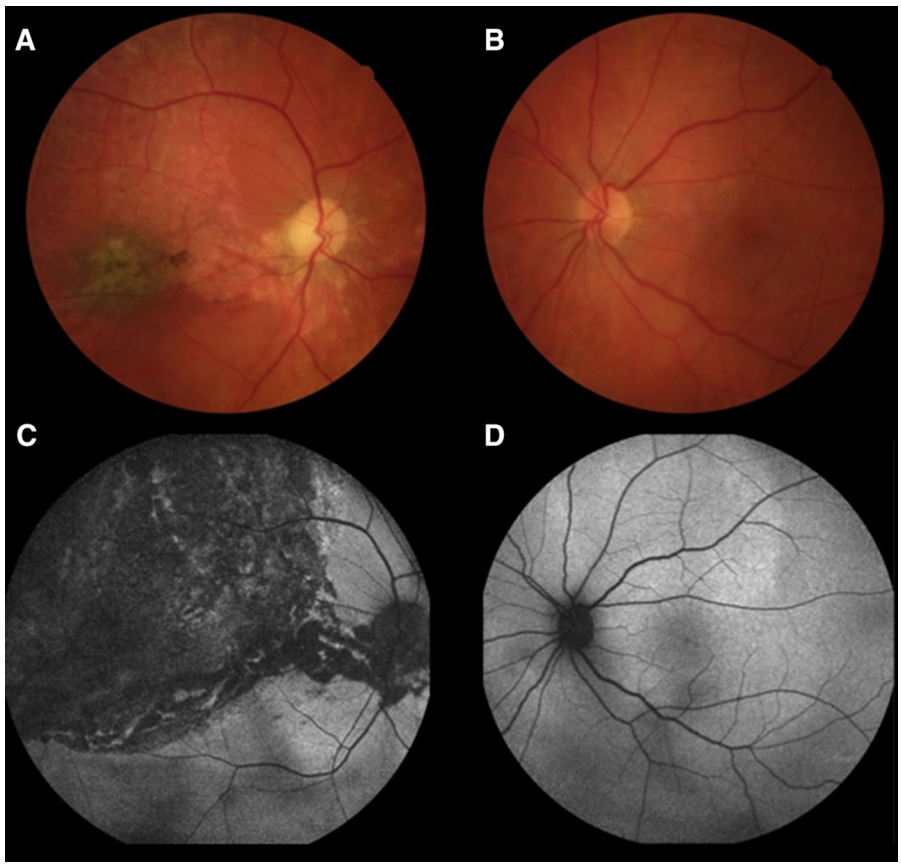

Fig. 1 **a** *Color photograph* shows a large area of chorioretinal atrophy of the posterior pole of the RE; **b** LE color fundus being unremarkable. **c** Fundus autofluorescence photograph displays a large loss of autofluorescence in the area of atrophy of the RE. **d** LE showing an increased autofluorescence at the posterior pole

and even, more recently, atypical antipsychotics such as clozapine [15]. Risperidone, another atypical antipsychotic, has also been incriminated in cystoid macular edema [16].

Here, we report a case of retinal toxicity secondary to aripiprazole intake and discuss potential pathophysiological mechanisms.

Case report

A 47-year-old schizophrenic woman was referred for bilateral visual loss. Best corrected visual acuity (BCVA) was counting finger in the right eye (RE) and 20/100 in the left eye (LE). She had not undergone ophthalmic examination over the five previous years. In her last medical record, 5 years before, RE BCVA was already counting fingers and LE BCVA was 20/30. No family history of hereditary retinal degeneration was found. Slit lamp examination was normal except for pigment in the vitreous. The RE fundus showed a large area of chorioretinal atrophy from the upper temporal periphery to the posterior pole with involvement of the peripapillary area. The posterior pole of the LE was unremarkable. On fundus autofluorescence imaging of the RE, the area of chorioretinal atrophy manifested with irregular loss of autofluorescence, while the LE revealed only subtle changes with mild autofluorescence, in particular along the superior vascular arcade (Fig. 1). Spectral domain OCT (SD-OCT) of the RE confirmed the global retinal atrophy, with major thinning of the outer retinal layer, associated with a few tubular lesions. The RE choroid showed the presence of large, irregular hyporeflective cavities, probably indicating advanced choroidal degenerescence. Left-eye SD-OCT revealed a diffuse shallow serous retinal detachment (Fig. 2). Fluorescein angiography showed a hyperfluorescence by window defect in the area of retinal atrophy of the RE (Fig. 3). In the LE, only minimal changes were seen in the periphery (Fig. 3). Indocyanine green angiography (ICG) emphasized the areas of chorioretinal atrophy at the posterior pole and in the periphery of the RE (Fig. 3).

Full-field electroretinogram (ERG) was recorded after a minimal dark adaptation of 10 min and after a light adaptation of 10 min, with skin electrodes, due to the impossibility for the patient to tolerate corneal electrodes. Responses recorded after both dark and light adaptation were decreased and delayed compared to controls, with responses from the RE being more severely abnormal than from the LE and responses of the rod system being more affected than of the cone system (Fig. 4). No light peak was identified on the electrooculogram (EOG), resulting in severely reduced Arden ratio (Fig. 5).

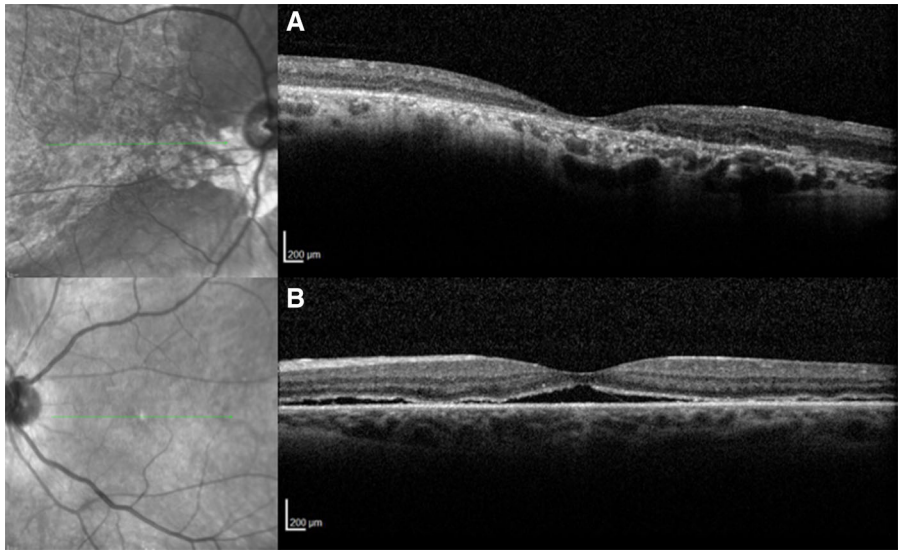

Fig. 2 **a** Spectral domain OCT (SD-OCT) underlines the atrophy of the posterior pole of the RE. Tubulations can be seen at the level of the interdigitation zone. **b** LE SD-OCT shows a large serous retinal detachment of the entire posterior pole

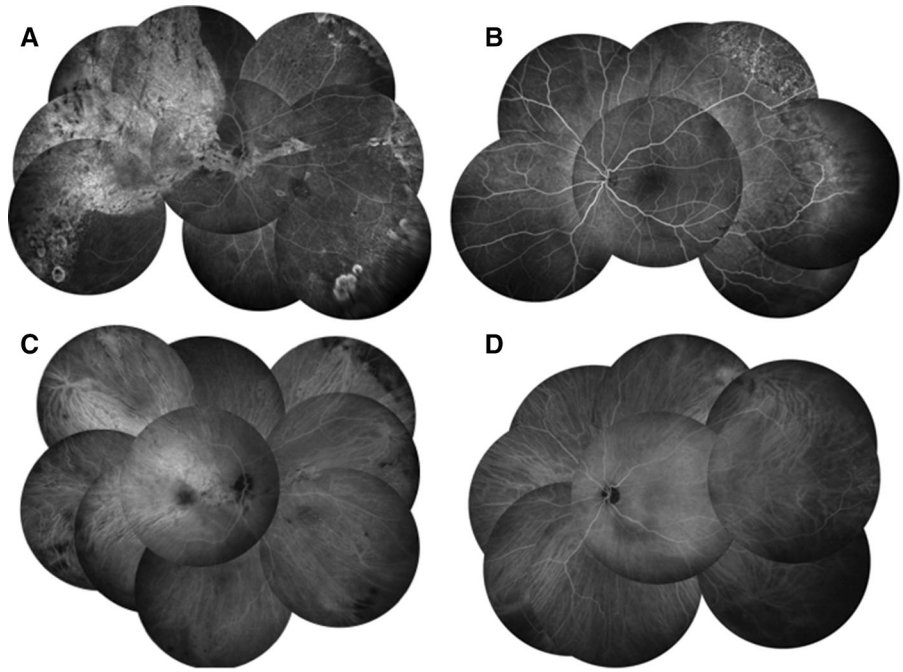

Fig. 3 **a** Fluorescein angiography shows a large window defect from the upper temporal periphery to the posterior pole of the RE. **b** Fluorescein angiography shows no vascular leakage on the LE. **c**, **d** Midphase ICG shows no choroidal hyperpermeability in either eyes

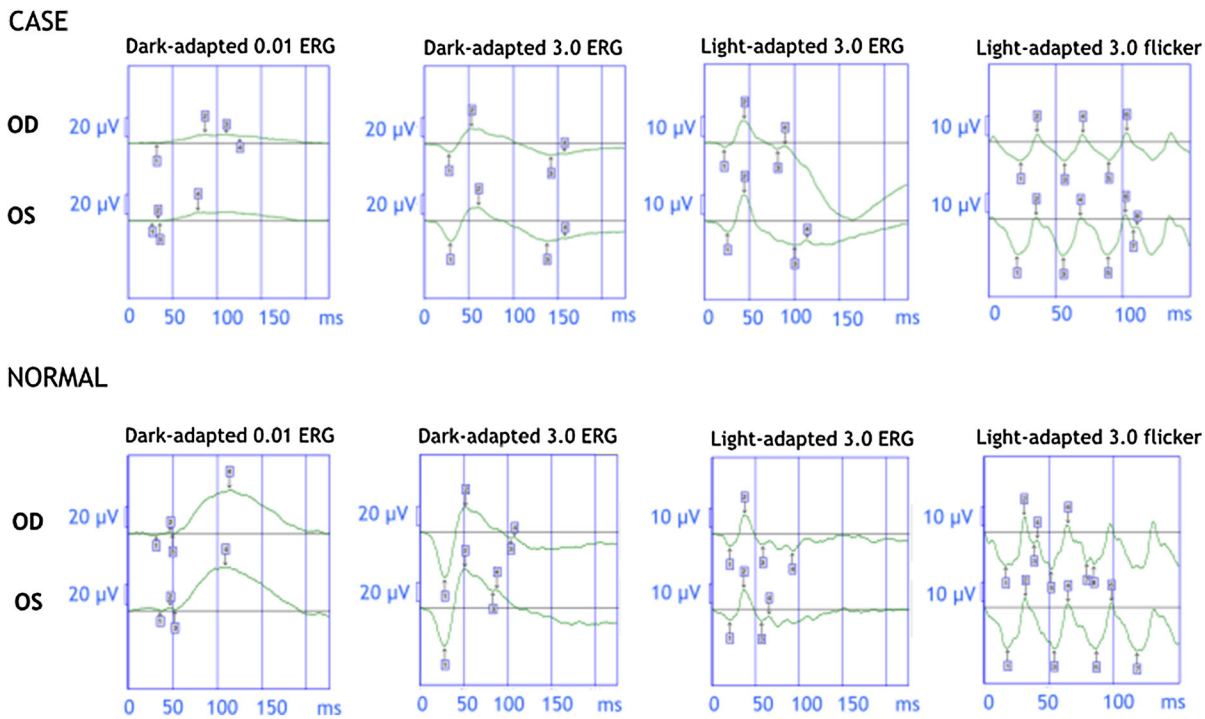

Fig. 4 Short ISCEV full-field ERG recorded with skin electrodes (Metrovision^{TM}, Perenchies, France). Scotopic and photopic responses of the right eye (first trace) and of the left eye (second trace) are both abnormal

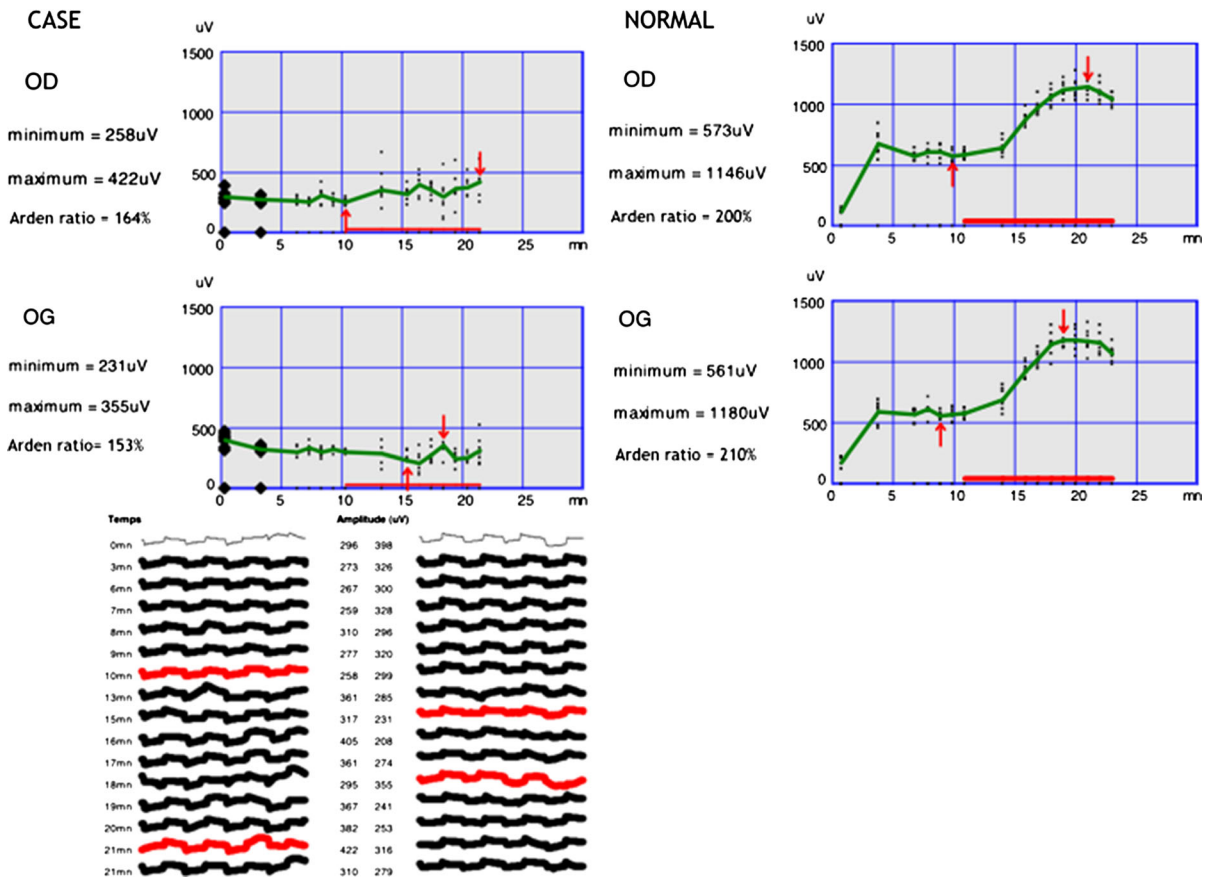

Fig. 5 EOG showing no light peak

Syphilis retinopathy was ruled out; VDRL (Venereal Disease Research Laboratory) and TPHA (*Treponema pallidum* hemagglutination) assay were negative. Direct Sanger sequencing of exon and exon boundaries of BEST1 (Ref Seq: NM 001300787.1) did not reveal any pathogenic variant, excluding a putative diagnosis of bestrophinopathy. A iatrogenic cause was therefore suspected. The patient had been treated with antipsychotics only over the previous 10 years: haloperidol alone (15 mg/day) for 2 years; haloperidol (1 mg/day) plus aripiprazole (10 mg/day) for 2 years; and aripiprazole alone for 6 years (15 mg/day for 4 years, then 10 mg/day), corresponding to a cumulative dose of 60 g of haloperidol and 200 g of aripiprazole. A toxicity of aripiprazole was hypothesized. It was decided together with her psychiatrist to decrease the medication to half dose. Two months later, the patient was stable from a psychiatric point of view; BCVA had improved to 20/50 in the LE, and SD-OCT showed a drastic decrease in the serous detachment (Fig. 6). Genetic investigations on *CYP2D6* were subsequently performed in order to document a potential susceptibility to drug toxicity [17], but none of the most frequent mutations involved in slow acetylation (CYP 2D6*3-4-5-6) was found. Due to the favorable ophthalmic outcome, aripiprazole was discontinued but schizophrenic symptoms soon resumed, leading to the patient's hospitalization and the introduction of olanzapine. Successive follow-up examinations at 1 and 3 months after discontinuation of aripiprazole showed a stable visual acuity and a complete and persisting resolution of the serous detachment (Fig. 6).

Discussion

We report a case of antipsychotic chorioretinopathy, which characteristics add to the current knowledge in the matter. The drastic regression of the serous

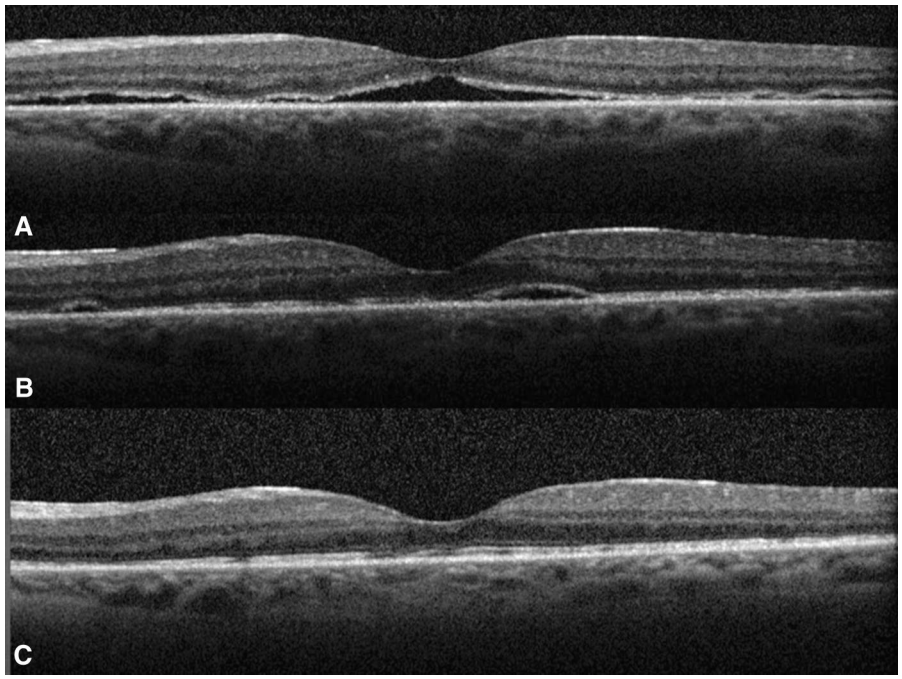

Fig. 6 Enhanced depth imaging OCT follow-up

detachment after the drug discontinuation makes the imputability level of aripiprazole probable, although the responsibility (or co-responsibility) of haloperidol in this chorioretinopathy cannot be fully excluded. This case is the first to incriminate aripiprazole in chorioretinal toxicity. Only one report of transient aripiprazole-induced myopia has been published [18]. Aripiprazole is among the most recently authorized atypical antipsychotics (approved in 2002 by the Food and Drug Administration and in 2004 by the European Medicines Agency). Our patient received this treatment for 8 years, i.e., a long period of time regarding the introduction date of the drug. This chorioretinal toxicity may be overlooked since psychotic patients often undergo ophthalmological screenings less frequently than the general population.

The search for *CYP2D6* mutations was motivated by the hypothesis of a slow metabolism of aripiprazole in this patient, which may have explained the occurrence of an ocular toxicity despite the use of standard doses [17]. The negative results do not, however, exclude this hypothesis, as only the most frequent mutations were screened.

Physiopathology remains unclear. Histopathologically, antipsychotics-related degenerative chorioretinopathy is characterized by loss of photoreceptors, retinal pigment epithelium and choriocapillaris [19]. Previous electrophysiological studies showed selective decrease in the red ERG components, which may indicate a disorder of the outer retinal layers [20]. It has been suggested that these retinopathies were due to drug absorption by the melanin of the eye, which would first damage the choriocapillaris and subsequently the photoreceptors and the retinal pigment epithelium, possibly through changes in the enzymatic activity of Müller cells and photoreceptors [21, 22]. An alternative explanation underlines the role of the drug effects on the activity of several retinal enzymatic systems [22]. Antipsychotics would induce blockade of retinal dopamine D4 receptors [22]. These dopamine receptors are involved in the synthesis of melatonin, a factor that regulates several aspects of retinal physiology and increases photoreceptors susceptibility to be damaged by light [23].

Former reports never mentioned OCT findings in antipsychotic chorioretinopathy. Here, in the LE, where pigmentary alterations were less advanced, SD-OCT revealed a large serous retinal detachment, but thin and diffuse and therefore unsuspectable through routine fundus examination. The large contiguous pigmentary alterations observed in the RE probably represent the later evolutive stage of a similar process, and may—at least partially—result from a

former long-lasting serous retinal detachment. Retinal tubulations were found in the RE, as already reported in association with outer retinal atrophy [24]. The presence of subretinal fluid on OCT, together with the complete lack of a light peak on EOG despite a persisting b-wave on the scotopic ERG, would point toward a mechanism primarily affecting the pigmentary epithelium.

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Conflict of interest None.

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