Electrophysiological assessment of glaucomatous visual dysfunction during treatment with cytidine-5′-diphosphocholine (citcicoline): a study of 8 years of follow-up

Vincenzo Parisi
Fondazione per l'Oftalmologia G.B. Bietti-ONLUS, Roma, Italy

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Abstract
In this study we assessed, by simultaneous recordings of visual evoked potentials (VEPs) and pattern-electroretinograms (PERGs), the effects cytidine-5′-diphosphocholine (citcicoline) on retinal function and/or visual cortical responses in glaucoma patients. Thirty glaucoma patients were randomly divided into two age-matched groups: patients in group GC (15 patients) were treated with citicoline (1000 mg/die intramuscularly) for 2 months; patients in group GP (15 patients) were treated with placebo for 2 months. After 4 months of wash-out (month 6), GC patients underwent a further 2-month period of citicoline treatment (months 7–8) followed by another 4-month period of wash-out (months 9–12). In GP patients the wash-out was extended for a further 6 months (months 7–12). During the following 13–96 months, GC patients received additional 2-month periods of treatment with citicoline (each period followed by 4 months of wash-out) for a total of 16 periods in 8 years. GP patients were also examined at months 24, 26, 48, 60, 72, 84 and 96. In GC patients the first two treatments with citicoline induced a significant \( (p < 0.01) \) improvement of VEP and PERG parameters with respect to pre-treatment conditions. VEPs and PERGs recorded in GC patients after the first wash-out revealed that, although there was a worsening trend, the electrophysiological improvement was still maintained with respect to baseline conditions. The additional periods of citicoline treatment in GC patients during the subsequent 13–96 months induced a greater \( (p < 0.01) \) improvement of VEP and PERG parameters with respect to pre-treatment conditions and when compared to GP patients. Thus, we observed that citicoline significantly improves retinal and cortical bioelectrical responses in glaucoma patients, suggesting a potential use of this substance in the medical treatment of glaucoma, as a complement to hypotensive therapy.

Introduction
It is known that patients affected by open-angle glaucoma (POAG) develop a visual dysfunction that can be revealed by psychophysical methods such as visual field analysis [1, 2], colour vision [3] and contrast sensitivity [4–6]. The visual impairment develops together with clinical signs such as ocular hypertension (intracocular pressure, IOP, > 21 mmHg) and characteristic optic nerve head cupping.

In the management of glaucoma, an important goal of ophthalmologists is represented by the possibility of influencing visual function. In this regard, Pecori Giraldi et al. [7] suggested the use of cytidine-5-diphosphocholine (CDP-Choline or citicoline) to improve glaucomatous visual field defects. They observed that 75% of POAG showed a better perimetric condition after treatment with citicoline [7].
Even though perimetric analysis gives a psychophysical assessment of visual function, it has been observed that citicoline increases the level of consciousness [8–12 and see 13 for a review], and thus it was unclear whether the observed changes in glaucomatous visual field [7] could be ascribed to a better performance during the visual field examination and/or to therapeutic effects on impaired retinal and postretinal visual structures.

It was recently suggested that glaucomatous visual field defects might be ascribed to two sources of functional impairment. One, at the retinal level, can be revealed by impaired pattern-ERG (PERG) responses that reflect the bioelectrical activity of ganglion cells and their fibers [14–17], and the other, at the postretinal level, can be revealed by abnormal visual evoked potential (VEP) responses and by a delay in ‘retinocortical time’ (RCT) [15–17]. RCT represents an index of neural conduction in postretinal visual pathways, derived by simultaneous recordings of VEPs and PERGs [18]. Indeed, a postsynaptic degeneration at the level of the lateral geniculate nucleus (LGN) was suggested [19–23].

Since 1994 we studied the effects of citicoline on glaucomatous retinal and postretinal visual structures by electrophysiological examinations (PERG and VEP) and we found that a 2-month period of treatment with citicoline may induce improvement in both ganglion cell function (PERGs with increase in amplitudes and shortening in times-to-peak) and in neural conduction along postretinal visual pathways (VEPs with increase in amplitudes and shortening in times-to-peak and reduced RCT) [24]. The effects of citicoline on glaucomatous retinal and postretinal structures were not present 8 months after the end of treatment [24]. However, a second 2-month period of treatment with citicoline induced an additional improvement of the glaucomatous retinal and postretinal impairment [24].

In this paper we describe data from our previous study [24] regarding the effects of two periods of citicoline treatment and, since citicoline treatment was continued for the following 13–96 months using the same therapeutic protocol (see below), we present the data of the effects on retinal (PERG) and cortical (VEP) bioelectrical responses obtained during 14 additional periods of treatment. Thus, we present data regarding 8 years of follow-up and the use of PERGs and VEPs in monitoring the therapeutic effects of citicoline on the glaucomatous visual dysfunction.

Materials and methods

Thirty volunteer patients with open-angle glaucoma (OAG) took part in our study.

At the time of diagnosis of glaucoma, IOP was greater than 21 mmHg in the absence of topical treatment in all patients (range 23–27, mean 25.10 ± 1.55 mmHg). All patients thus received topical monotherapy with beta-blockers, inducing an IOP less than 21 mmHg, that remained stable throughout the study (mean 17.5 ± 1.3 mmHg). None of the patients enrolled were subjected to filtration surgery. Other inclusion criteria were: glaucomatous optic nerve head cupping (cup/disc ratio > 0.5), glaucomatous visual field defects (Humphrey 24–2 perimetry–HFA– with mean deviation (MD) between −3 and −6 dB), best corrected visual acuity of 20/20 or better; mean refractive error, when present, between −0.50 and +0.50 spherical equivalent; no other ocular, neurological or systemic diseases. None of the patients underwent systemic pharmacological therapy that could potentially influence retinal function and/or neural conduction along visual pathways. Mean age was 45.6 ± 4.3 years.

The 30 patients with glaucoma were randomly divided into groups on the basis of age and MD in order to obtain two age-matched groups: 15 patients were treated with citicoline (GC, 15 eyes) and 15 patients were treated with placebo for the first period of treatment (GP, 15 eyes). No differences in IOP or MD measurements were found between GC and GP patients (GC: 17.4 ± 1.3 mmHg; GP: 17.5 ± 1.5 mmHg).

During the entire study period (96 months, see below), three GP patients and three GC patients were considered as ‘drop-out’ patients, since they received additional medical treatment or they showed an increase in IOP requiring other topical treatment. We therefore considered 12 GP and 12 GC patients for all statistical analyses.

Informed consent was obtained from each patient enrolled in the study and the research followed the tenets of the Declaration of Helsinki.