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Plasmatic neuroglobin during the primitive open-angle glaucoma

Intérêt de la neuroglobine plasmatique dans le glaucome primitif à angle ouvert

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Abstract. *Objective*: Elucidate the relation between neuroglobin and the primitive open-angle glaucoma. *Patients and methods*: This cross-sectional case-control study involved 64 patients with primitive open-angle glaucoma on 2 eyes and 64 control subjects. Glaucoma was classified as early, moderate or severe according to ophthalmological examination. Then we determined neuroglobin concentration and compared his ROC curve with characteristics of glaucoma. Chi-square test was used to compare proportions and spearman test for correlations between quantitative variables. *Results*: Neuroglobin concentrations were higher among patients with glaucoma compared to control's (4.7±4.6 ng/mL *versus* 0.9±1.1 ng/mL, p=0.0000). Neuroglobin concentration was related to visual acuity, to the cup/disc ratio (eye right: r=0.340, p=0.006 and left eye: r=0.413, p=0.001). In addition, neuroglobin concentration was correlated with duration (r=0.565; p=0.000) and glaucoma severity (r=0.506, p=0.000). The area under the curve of neuroglobin concentration was 0.82 compared to that of intra ocular pressure (0.70). *Conclusion*: This study suggests that neuroglobin could be used as biomarker for glaucoma diagnosis.

Key words: *neuroglobin, open-angle primitive glaucoma, visual acuity, cup/disc ratio, marker*

Résumé. *But*: Rechercher une relation entre la neuroglobine et le glaucome primitif à angle ouvert. *Patients et méthodes* : Il s'agit d'une étude ponctuelle, de type cas-témoins, qui s'est déroulée de janvier à décembre 2016. Elle était basée sur un échantillon de convenance de 64 sujets atteints de glaucome primitif à angle ouvert et de 64 témoins. Après le recueil des paramètres épidémiologiques des patients et des témoins, pour diagnostiquer et classer le glaucome, nous avons dosé la neuroglobine à l'aide d'un kit Elisa. La comparaison des proportions a été réalisée à l'aide du test du chi-2 ; le test de Spearman a permis d'étudier les corrélations entre variables quantitatives. Le seuil de significativité retenu était de 5 %. *Résultats* : La concentration de neuroglobine était en moyenne de 4,7 ± 4,6 ng/mL chez les malades et 0,9 ± 1,1 ng/mL chez les témoins (p = 0,0000). Chez les malades, la neuroglobine était associée à l'acuité visuelle d'une part et au rapport cup/disc (œil droit : r = 0,340 ; p = 0,006 ; œil gauche : r = 0,413 ; p = 0,001). Par ailleurs, la concentration de neuroglobine était reliée à la durée (r = 0,565 ; p = 0,000) et à la sévérité du glaucome (r = 0,506 ; p = 0,000). L'aire sous la courbe de la ROC de la neurglobine était de 0,82, contre 0,98 pour le champ visuel et 0,70 pour la pression intraoculaire. *Conclusion* : Ces résultats suggèrent que la neuroglobine pourrait être ajoutée à l'arsenal utilisé pour le diagnostic du glaucome primitif à angle aigu.

Mots clés : *neuroglobine, glaucome, acuité visuelle, rapport cup/disc, marqueur*

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Neuroglobin is a protein belonging to globin family. It owes its name to its preferential expression in the nervous system [1, 2]. The exact function of the neuroglobin, as well as its mechanisms of action are not yet known except neuroprotective role reported by authors [3, 4]. Thus, its plasma concentration increases with hypoxia and cerebral ischemia. Neuroglobin may be considered as a hypoxic sensor and initiator of signal transduction involving oxidative and hypoxic pathways, cellular apoptotic pathways, and cellular ATP pathways [5]. Present in mitochondria, neuroglobin protects neurons from bleeding by inhibiting mitochondrial apoptotic pathways [6]. In comparison with acute cerebral ischemia, neuroglobin expression would be 100-fold higher in retinal cases and 1000-fold more in ischemic optic nerve injury such as that seen in glaucoma [7-9]. Indeed, the pathophysiology of primary open-angle glaucoma (POAG) combines hypoxia, oxidative stress and sometimes chronic ischemia. Some studies have demonstrated a relationship between tissue expression of neuroglobin and acute forms of glaucoma [7, 8, 10]. Thus Shi SY *et al.* were able to monitor and early detect retinal and optic nerve ischemia in animals [7, 10-12]. Similarly, Rajendram *et al.* have found an increase in the expression of neuroglobin on retinal patches among patients with advanced glaucoma [13, 14]. However, we did not find any studies linking plasma concentration of neuroglobin with open-angle primary glaucoma. We therefore initiated this work to investigate a relationship between plasma concentration of neuroglobin and open-angle primary glaucoma.

Material and methods

Cross-sectional and case control study was conducted from 1st January to 1st December 2016. Enrollment of patient took place at the Ophthalmology Department of the *Centre hospitalier universitaire d'Angondjé*. The local ethic committee approved the study, which was carried out according to the recommendations of Helsinki declaration [15].

Two groups of population were involved POAG+ and POAG-. POAG+ were glaucoma patients on two eyes followed or newly discovered and POAG- were unaffected subjects. Enrollment took place at the ophthalmology consultation room. After an interview during which sociodemographic data, personal and family history and the duration of the POAG were collected, ophthalmological examination and blood test were carried out. Patients with glaucoma, discovered during the survey also had complementary examinations such as visual fields and pachymetry. Control group was own free will enrolled.

All patients aged from 15 to 80 years, with primary open-angle glaucoma on eyes (POAG+), were included, as well as all control subject (POAG-). Patients under treatment that may modify neuroglobin concentration (valproic acid, cinnamic acid, iron chelator) and those suffering of other disease were excluded. Ophthalmological examination was performed following visual acuity distance with a Monoyer scale placed 5 meters from the patient. Intraocular pressure (IOP) in mmHg, using GoldmannTM applanation tonometer was measured. Values between 9 to 21 mmHg were considered normal [16]. The IOP measurement was correlated with central corneal thickness (CCT) using Nidex NT-530PTM pachymeter. CCT was normal for values between 527 µm to 560 µm [17]. The scanned field of view Octopus 900TM was used for deficits screening. Slit lamp biomicroscope (HAAG Streit 900TM) coupled with Goldman glass determine the cup/disc (C/D) ratio.

Variables studied were age, sex, family history of glaucoma, duration of glaucoma, visual acuity (VA), corrected IOP, central corneal thickness (CCT), ratio of C/D, visual field, plasma concentration of neuroglobin, glaucoma severity, intra ocular pressure and central thickness of the cornea (in mm). Primitive open-angle glaucoma was defined by a normal gonioscopy, associated with at least two of the following items: an IOP greater than 21 mmHg, a papillary excavation greater than 0.3 or a visual field with a lower mean deficit of 6 decibels. Visual field results classified glaucoma as early (mean deficit <6 dB), moderate (mean deficit <12 dB) and severe (mean deficit> 12 dB) [18].

Analysis was done using IBM® SPSS® Statistic 21. Standard descriptive analyzes with mean ± standard deviation for quantitative variables and frequencies for qualitative ones were used. Chi-2 test was used for proportions comparison and Spearman's test for correlations between quantitative variables. Relationships between qualitative and quantitative variables were studied with Pearson test. ROC curves allowed assessing area under the curve of neuroglobin concentration for glaucoma detection. The differences were statistically significant for p values less than 0.05.

Results

During the study, 153 patients with inclusion criteria were screened. Among them 80 glaucomatous (POAG+) and 73 controls (POAG-); 16 POAG+ and 9 POAG- were not willing to participate in the study. Therefore, study population was 128 with 64 glaucomatous (POAG+) and 64 controls (POAG-).

Socio-demographic parameters

Mean age of the general population (POAG+ and POAG-) was 42.3±13.7 years. Among subjects with POAG+ the

Table 1. Comparison of clinical variables between POAG+ and POAG-.

Variables	POAG+	POAG-	p
Age (years)	45.1±14.5	43.6±11.9	0.630
Glaucoma family antecedents (%)	45.9	54.1	0.243
Intra ocular pression (mmHg)			
Right eye	18.1±7.7	13.0±3.0	0.0000
Left eye	18.8±7.6	12.6±2.8	0.0000
Visual acuity			
Right eye	7.8±3.1	9.9±0.4	0.0000
Left eye	7.2±3.6	9.9±0.4	0.0000

average IOP in the right eye was 18.1±7.7 mmHg [7-44 mmHg] versus 12.6±2.8 in the control group (p=0.000). Similarly, visual acuity was for the right eye of POAG+ subjects, of 7.8±3.1, versus 9.9±0.4 for control subjects (p=0.0000) (*table 1*).

The central thickness of the cornea was between 527 and 560 µm in both eyes among 39.9% of POAG+ subjects. The visual field was severe in both eyes (n=128) and in 16.4% of POAG+ subjects. The majority of POAG+ patients had a C/D ratio less than 0.6 (*table 2*).

The mean concentration of neuroglobin found in POAG- subjects was 0.9±1.1 ng/mL [0-6.3 ng/mL], compared to 4.7±4.6 ng/mL [0.9-23.9 ng/mL] for POAG+ subjects (p=0,000).

The concentration of neuroglobin was 2.6±1.5 ng/mL, 4.8±5.4 and 7.7±4.6 ng/mL among patients with early, moderate and severe glaucoma respectively. Similarly, depending on the duration of glaucoma, neuroglobin concentration increased from 2.7±1.6 to 10.8±4.8 ng/mL among patients with glaucoma less than 5 years and over 15 years respectively (p=0.000) (*table 3*).

On the ROC curves for detecting glaucoma, the area under the curve was 0.98 for visual field and 0.82 for neuroglobin. That of IOP and visual acuity were 0.70 and 0.45 respectively (*figure 1*).

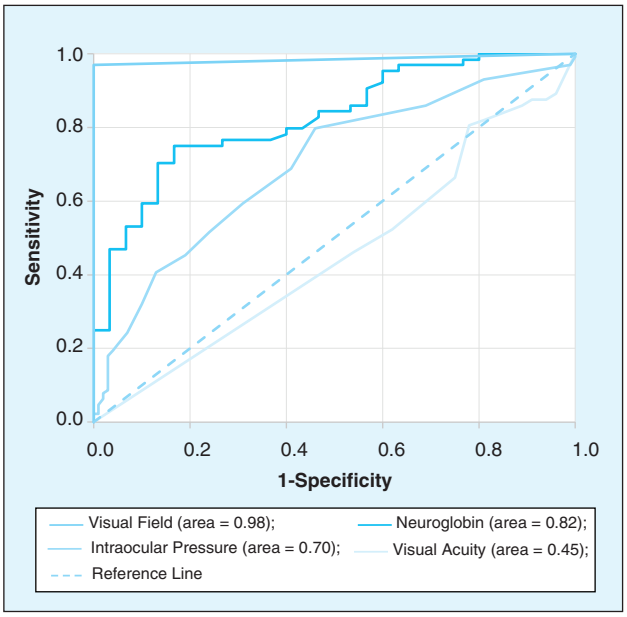

Figure 1. Roc curves for neuroglobin, visual field, intraocular pressure and visual acuity for the diagnostic of primitive open-angle glaucoma.

Discussion

Primary open-angle glaucoma is a neurodegenerative situation of the optic nerve head whose pathophysiology and management remains complex. The aim of this work was to investigate the existence of a relationship between the mean plasma concentration of neuroglobin with duration, and severity of open-angle primary glaucoma. For that, cross-sectional observational study was performed among glaucomatous and controls patients. Despite the small size sample, we found some very relevant results. Average of age for POAG+ population was relatively young (45.1±14.5 years). This result is similar to that of other studies [19, 20]. Indeed, several authors in the literature agree that primary open-angle glaucoma occurs earlier in melanoderm subjects [21, 22]. Female population was mostly represented in glaucoma population. This female predominance varies from one study to another [20, 23, 24]. Moreover, sex is not a risk factor for POAG. Among POAG+ population, control of glaucoma evolution was the most frequent reason for consultation (65.6%). This result differs from that of Moukouri *et al.* [25], who found that reduction of visual acuity was the primary reason for consultation (67.54%).

This study shows that 56.3% of patients with POAG+ have a family history of glaucoma. Most studies have shown that family history of glaucoma is a predisposing factor that is strongly associated with the onset of glaucoma [21]. In fact, it has been clearly demonstrated that some genetic factors are involved in the onset of glaucomatous disease [21, 26]. In this study, we found mean values of left and

Table 2. Ophthalmologic examination among POAG+ POGA-.

Parameters	POAG+	POAG-	p
Visual acuity (right eye)			0.000
< 3/10	7 (100)	0 (0)	
4 – 7/10	16 (94.1)	1 (0.9)	
8 – 10/10	41(39.4)	63 (60.6)	
Visual acuity (left eye)			0.000
< 3/10	11 (100)	0 (0)	
4 – 7/10	12 (92.3)	1 (7.7)	
8 – 10/10	41 (39.4)	63 (60.6)	
Central thickness of the cornea for right eye (µm)			0.000
< 527	26 (21.7)	64 (53.3)	
527 – 560	26 (100)	0 (0)	
> 560	12 (100)	0 (0)	
Central thickness of the cornea for left eye (µm)			0.000
< 527	25 (28.1)	64 (71.9)	
527 – 560	27 (100)	0 (0)	
> 560	12 (100)	0 (0)	
Glaucoma severity			
Early	59 (46.1)	-	-
Moderate	48 (37.5)	-	
Severe	21 (16.4)	-	
Ratio C/D (right eye)			
0.3 – 0.5	38 (37.3)	64 (62.7)	0.000
0.6 – 0.7	15 (100)	0 (0)	
0.8 – 1.0	11 (100)	0 (0)	
Ratio C/D (left eye)			0.000
0.3 – 0.5	38 (37.3)	64 (62.7)	
0.6 – 0.7	12 (100)	0 (0)	
0.8 – 1.0	14 (100)	0 (0)	

right IOP respectively of 18.8±7.6 mmHg and 18.1±7.7 mmHg. These average values are lower than those found by Ellong *et al*. and Sounouvou *et al.* [23, 24]. Indeed, these two studies concerned patients whose glaucoma was recently discovered and therefore untreated. In contrast, ours included treated and untreated patients, which explains a lower mean IOP among this population. The mean value of neuroglobin concentration among control population aged 16 to 60 years was 0.9±1.1 ng/mL. This neuroglobin concentration is not different from that found by Ovono (0.5±0.2 ng/mL) [27]. This means that in healthy subjects (free from all ischemic pathologies), the average concentration of neuroglobin is low. Among the POAG+ population, mean of plasma neuroglobin level was 4.7±4.6 ng/mL 8-fold higher than that found by Ovono *et al.* (0.5±0.3 ng/mL) in neonates with acute fetal distress [27]. Difference in neuroglobin concentrations between the two studies could be explained by the fact that the former study conducted by Ovono mainly treated for hypoxic and ischemic encephalopathies and not for ischemia of the optic nerve. In fact, study carried out on retinal histological specimens of post-mortem glaucomatous subjects showed that the expression of neuroglobin was 100 times higher in the retina than in the brain. In the same study, neuroglobin concentration was 10-fold higher in the optic nerve than in the retina [9]. On an animal model, Lechauve *et al*. drove the same conclusions [28].

Plasma neuroglobin concentration among POAG+ was 5 times higher than that among POAG-. Difference was found between these two averages, which reinforced the idea of neuroglobin level rising among primary open-angle glaucoma. Rajendram *et al*. made the same finding at the tissue level in a study [13]. The fact that neuroglobin is elevated in GPAO+, suggests the involvement of this protein in the processes of degeneration of the peripheral nervous system (visual pathways) compared to the central nervous system (brain). Indeed, the ischemia described during the pathophysiology of glaucoma by Weinreb *et al.*, in 2015, occurred to be responsible of increase expression of neuroglobin in the optic nerve [29]. This increased could lead, according to Chan *et al*. to optic nerve oxygenation, inhibit oxidation and apoptotic stress responsible of optic nerve ischemia. This may have neuroprotective effect [10]. Knowing that neuroglobin is detectable in plasma and can be higher among POAG+ shows that passage of this protein in blood was linked to an alteration of optic nerve. Therefore, its dosage could be of interest approach for glaucomatous subjects' diagnosis.

Table 3. Relationship between neuroglobin concentration, clinical and paraclinical parameters of (POAG+) patients.

Variables	Numbers (%)	Neuroglobin (mean±SD)	p
Visual acuity (right eye)			0.02
≤ 3/10	8 (12.5)	7.3±3.3	
4/10 – 7/10	16 (25.0)	3.9±3.7	
8/10 – 10/10	40 (62.5)	4.4±5.0	
Visual acuity (left eye)			0.01
≤ 3/10	10 (15.6)	8.5±3.9	
4/10 – 7/10	12 (18.8)	3.3±2.3	
8/10 – 10/10	42 (65.2)	4.1±4.8	
Central thickness of the cornea (right eye)			0.9
< 527	26 (40.6)	4.6±4.1	
527 - 560	26 (40.6)	5.1±5.5	
≥ 560	12 (18.8)	4.0±4.6	
Central thickness of the cornea (left eye)			0.7
< 527	25 (39.1)	4.7±4.1	
527 - 560	27 (42.1)	4.5±5.1	
≥ 560	12 (18.8)	5.1±4.8	
Ratio C/D (right eye)			0.006
0.3 – 0.5	38 (59.4)	3.7±3.2	
0.6 – 0.7	15 (23.4)	5.1±6.1	
0.8 – 1	11 (17.2)	7.7±3.2	
Ratio C/D (left eye)			0.001
0.3 – 0.5	38 (59.3)	3.3±2.7	
0.6 – 0.7	12 (18.8)	5.3±6.0	
0.8 – 1	14 (21.9)	7.9±4.8	
Glaucoma severity			0.001
Beginner	22 (34.4)	2.6±1.5	
Moderate	28 (43.8)	4.8±5.4	
Severe	14 (21.8)	7.7±4.6	
Glaucoma duration (years)			0.000
< 5	39 (60.9)	2.7±1.6	
[5 – 10[	17 (26.6)	7.7±6.1	
[10 – 15[	6 (9.4)	7.0±6.0	
≥ 15	2 (3.1)	10.8±4.8	

Neuroglobin concentration and age of POAG+ patients were not correlated (p=0.08). This result is similar to those of Ovono *et al.* [27]. However, it is different from those of Sun *et al.*, who found that neuroglobin expression declined in the oldest rat populations compared to younger ones [30]. These results could be explained by the difference among species. No relationship between sex and mean plasma neuroglobin has been found (p=0.65). This result was different from that of Szymanski *et al*. who in their study of neuroglobin and Alzheimer's disease found lower neuroglobin levels among women [31].

Differences was found between left and right papillary excavation size and mean plasma neuroglobin level (p=0.001 and p=0.006). During glaucoma, the widening of the papillary excavation is related to the destruction of the optical fibers. By analogy, a large excavation would correspond to large loss of optical fibers and therefore to higher elevation of neuroglobin concentration. There was a negative correlation between mean neuroglobin concentration and far left (p=0.01) and right (p=0.02) visual acuity in POAG+ patients. In fact, concentration of neuroglobin was inversely proportional to the value of visual acuity. This means that lower the visual acuity (sign of the severity of glaucoma) higher the neuroglobin concentration was.

There was a correlation between neuroglobin concentration and the severity of POAG. In fact, more POAG was severe, higher the mean plasma neuroglobin level was (p=0.001). This result corroborates that of Rajendram *et al.* in his post mortem study on histological features of eyes of patients with advanced glaucoma [13]. In this study, they found that the higher the level of neuroglobin was in retina more glaucoma was serious. This elevation suggests the presence of hypoxia and an increase in oxidative stress depending on the degree of progression of glaucoma. A strong statistical

relationship between neuroglobin concentration and POAG duration was observed (p=0.000). The older the glaucoma was the higher the rate of neuroglobin was. This could be explained by the fact that during chronic glaucoma the mechanisms of hypoxia and ischemia were permanently active, with a chronic character, thus resulting in a permanent rise of neuroglobin concentration. This chronic expression would help to improve oxygenation of the optic nerve. Neuroglobin is present in the retinal mitochondria, in the matrix and the matrix side of the inner membrane. Thus the neuroglobin could be considered as a new mitochondrial protein, involved in the functioning of the respiratory chain, by activation of complexes I and III [32]. This protein is also present in the nuclei of the optic nerves but also in astrocytes [11]. Chan *et al*. showed that during retinal ischemia, neuroglobin inhibits mitochondrial oxidative stress, activates caspase-3 [10], and then would reduce the severity of retinal lesions [5, 6, 33, 34]. Therefore, in the absence of neuroglobin, the retina and the optic nerve would degenerate, leading to glaucoma. The exact mechanism by which neuroglobin acts is not determined, due to its many factors [35, 36].

The mechanism underlying the growth of neuroglobin during glaucoma is unknown. Indeed, Cwerman-Thibault *et al*. demonstrated a decrease in the intra retinal concentration of neuroglobin in rats with induced glaucoma [37]. The increase of neuroglobin concentration highlighted here could be due to its capacity to be inducible. Firstly, neuroglobin could rise in case of decrease of the oxygenation in retina, as stated some authors [5, 11, 36]. Secondly, cell necrosis would then cause a release of this neuroglobin from mitochondria to peripheral blood, allowing the detection.

Whatever the mechanism involved, neuroglobin also appears to be a better marker of glaucoma than visual acuity or intra ocular pressure. In addition, neuroglobin could serve as a marker for monitoring glaucoma. However, its relation to cerebral ischemia reduces its specificity in case of glaucoma.

Conclusion

This study shows that the average concentration of neuroglobin rises at the plasma level in the case of open-angle primary glaucoma. This increase depends not only of the severity but also of the duration of this pathology. The relation between the mean plasma concentration of neuroglobin and gravity factors shows the involvement of this protein in the process of chronic ischemia of visual pathways, thus suggesting neuroglobin as a prognostic biomarker of glaucomatous neuropathy. However, in front of our small population, these results suggest a larger population, to validate our data, and better specify the diagnosis and prognostic performance of this marker during primitive open-angle glaucoma.

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