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Retinopathy Surgery in Patients with Diabetic Ophthalmoplegia in the City of Kashan

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Diabetic ophthalmoplegia is a complication of diabetic mellitus. The purpose of this study was to examine the clinical characteristics and severity of retinopathy in diabetic patients with cranial nerve (CN) 3,4 and or 6 palsies involvement. This descriptive study included 96 patients with diabetic ophthalmoplegia who were treated in Matini hospital of Kashan, Iran during the years 2004-2012. Demographic and clinical data including type of DM, stage of diabetic retinopathy, involved cranial nerve, and duration of resolution were examined. Statistical analysis was performed by SPSS 16.0 Software. The result showed that 96 patients 54(56%) were male and 42 (44%) were female. The frequency of 6th nerve involvement was 50(52%), 3rd nerve 41(43%) , and 4th nerve 5(5.2%). There was no statistically significant association between the stage of diabetic retinopathy (DR) and diabetic ophthalmoplegia (P=0.92). Based on the result of this study, diabetic ophthalmoplegia more frequently involves 6th cranial nerve and rarely 4th nerve. Diabetic patients with cranial nerve palsies (3,4 or 6) may have mild retinopathy. This may imply a different pathophysiologic mechanism for these two microvascular complications of DM.

Key words: Diabetes Mellitus, ophthalmoplegia, Diabetic retinopathy.

Acquired diplopia, painful ophthalmoplegia and ptosis are relatively common manifestation of ocular motor nerves dysfunction in diabetic patients. However, in case of such incidence, they are associated with sever anxiety and fear in patients. Incidence of CN palsy in diabetics is 5 to 10 times higher than the non diabetics and is about 0.97% of diabetics comparing to 0.13% in non-diabetics[1,2]. Due to diffuse *microangiopathy* in diabetic patients, it seems like the prevalence of cranial nerve (CN) palsy and diabetic retinopathy are positively correlated. However, in few studies it has been showed that the stage of diabetic retinopathy in patients with CN palsy is relatively mild to rare[3-5]. The purpose of this study was to ophthalmoplegia evaluate the clinical characteristics of (DO) in addition to the duration, severity of DM and resolution times of retinopathy in patients with different types of CN palsies.

MATERIAL AND METHODS

In this prospective study, all of the diabetic patients with diabetic ophthalmoplegia who referred to Matini Eye Hospital of Kashan, Iran during the years 2004-2012 were examined. The inclusion criteria were DM as the cause of ophthalmoplegia. The criteria for diagnosis of DM was fasting plasma glucose level of e" 126mg/dl or Hb A/C level e" 6/5% or patients being a known

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case a DM on medications(Insulin or oral hypoglycemic agents[6]. The exclusion criteria were other causes of ophthalmoplegia including trauma, tumors, multiple sclerosis or secondary to surgery (iatrogenic). All patients underwent complete and ophthalmologic examination by fellowship of vitreo-retina and by a neurologist.

Demographic data in addition to the data such as the involved cranial nerve, date of onset of the palsy, and its resolution, duration and type of DM, level of blood glucose at or within one week of onset of palsy, presence or absence and stage of diabetic retinopathy on the basis of Early Treatment of Diabetic Retinopathy (ETDRS) staging[5] were collected. The presence of other systemic (vasculopathic) risk factors including high blood pressure ,hyperlipidemia and coronary artery disease was determined by asking the patients or if there was any evidence of active medical treatment. Diabetic type included non-insulin dependent DM (NIDDM), using only oral hypoglycemic agents (OH) or insulin dependent DM (IDDM), using insulin with or without OH. Neuroimaging of central nervous system (MRI or CT-Scan) was performed to rule out other causes of CN palsy. The data were analyzed by using SPSS: 16.0. Descriptive statistics including mean and standard deviation (SD) for continuous data and percent for the categorized data were calculated. Chi square test of significance was employed to compare the proportions. The level of significance was set to á=0.05.

RESULTS

The results of analysis for the demographics characteristics of the patients is presented in table 1. An eye inspection of this table reveals that the majority of the patients were suffering from type P DM NIDDM,(94%). The mean age and duration of disease of the patients were 62.9±3.3 and 10.3±2.6 years, respectively. The duration of DM to the onset of CN palsy was much longer in the type I (IDDM) compared to the type P (10 years to 7 years, respectively). In addition, blood glucose levels within 1 week of onset of palsy were less than 200 mg/dl in 68 percent of the patients. Forty-one (48%) patients were suffering from diplopia. The result also showed the presence of this risk in the patient as follow: vasculopathic hypertension in 64.5%, hyperlipidemia in 49% and coronary artery diseases in 21.8% of the patients, respectively. The result of chi-square indicated that there was a significant difference between the proportion of NIDDM and IDDM diabetic patients (p=0.0001, OR=15) and NIDDM were 15 times more at risk of affliction to the disease than the IDDM. However, no significant differences was found between the male and female patients (p=0.48). Further analysis revealed that the frequency of cranial nerve palsy in 6th nerve was 50(52%) , and in 3rd nerve with and without pupillary involvement was in 38(36%) and 4th nerve was 5(5.2%). None of patients had simultaneous or bilateral CN palsies. There was a complete resolution of CN palsy in 88 of patients less than 3 months. Mean time of resolution was 12 weeks and there were no significant differences between the two types of DM with respect to the resolution time (P=0.86). However, there was a significant difference between the proportion of the month of affliction to the disease (p=0.0001); higher proportion of patient showed 1 to 3 month of resolution than the other two time intervals.

DISCUSSION

This descriptive study was designed to examine the characteristics of 96 patients with retinopathy diabetic and cranial nerve (CN) 3,4 and or 6 palsies. The result indicated that NIDDM were 15 times more at risk of affliction to the disease than the IDDM (p<0.05). In addition, there was no significant association between the gender and affliction to the disease (p>0.05). These results were similar to what was reported by Wantabe and associates, Chih-Hsien and associates, Trigler and associates and Richards and associates who examined the retinopathy disease in diabetic patients[1-4]. Also, the results showed that the mean age of onset of cranial nerve palsy and duration of DM in present study was 62.9±3.3 years and 10.3±2.6 years, respectively. In this regard, the result of the study supports the findings of researches reported by Wantabe and associates, Chih-Hsien and associates, Jacobson and associates, American Diabetic Assocition(2014) and Greco and associates[1, 2, 5,7,8]. The result of the present study also showed the highest frequency of symptoms of CN palsy in diabetic patients in

diplopia (48%), ptosis(33.3%) , pain(9.4 %) and anisocoria (3.1%), respectively. These results were in agreement with the findings of studies reported by Chih-Hsien and associates, Richards and associates and Jacobson and associates[2, 4, 5]. In addition, nearly all of the patients in this study

Table 1. Demographics and Clinical data of patients with diabetic cranial nerve palsy

characteristics	number	percent	P-value
Sex			
Male	54	%56.2	0.48
Female	42	%43.8	
Age(years)			
mean		62.9±7.3	
Type of DM			
NIDDM	90	93.7	0.0001
IDDM	6	6.3	OR=15
Blood glucose(mg/dl)			
<200	65	68%	
201-250	23	24%	
e”251-300	8	8%	
Total number	96	100	

	No	Percent	P-value
Time of Resolution (month)			
< 1 mo	18	18.7	0.0001
1-3 mo	71	74	
>3 mo	7	7.3	
Duration of DM			
<5 years	15	15.6	0.03
6-15 years	50	52	
e”16 years	31	32.5	
Stage of Diabetic Retinopathy (DR)			
No Diabetic Retinopathy(NDR)	53	55.2	
Non Proliferative Diabetic Retinopathy (NPDR)	30	31.2	
NPDR + Diabetic Macular Edema (DME)	9	9.4	
Proliferative Diabetic Retinopathy (PDR)	4	4.2	

conditions	No	Percent
Hypertension	62	64.5
Hyperlipidemia	41	49
Coronary artery diseases	21	21.5
Initial presenting Symptom(S)		
Diplopia	41	48
Ptosis	32	33.3
Pain	9	9.4
Anisocoria	3	3.1
Combination of two or more symptoms	4	4.2
Involved Cranial Nerve		
3	41	42.7
4	5	5.2
6	50	52

experienced recovery during 1.5-3.5 months period. Other researchers also reported similar finding[5, 8].

The distribution of CN involvement in this study was similar to the research results reported previously[2, 3, 6] and in order of frequency were 6th, 3rd and 4th cranial nerves palsies. In a large clinical study of 4000 patients with CN 3, 4, or 6th nerve palsy regardless of their etiology, it was showed that 6th nerve was the most frequently involved nerve[3]

In the present study 5.2 percent of the patients developed 4th CN palsy, and reason that the trochlear nerve was involved remains unknown. After controlling for age and duration of DM, this study showed that type P DM patients (NIDDM) with ocular motor cranial neuropathies have a significantly lower prevalence of diabetic retinopathy (p=0.001). In review of the literature, no association between type of DM and occurrence of CN palsy was reported. In the present study as well no significant association was found (P>0.08). None of the patient had simultaneous or bilateral CN palsies, whereas Eshaugh C.G. *et al* reported 3 patients with simultaneous multiple diabetic cranial neuropathies with no retinopathy condition[8]. Batoechi Ap, *et al* reported 105 cases with CN palsies without any neurological diseases[9]. Zorrilla and Kozak reported 24 patients with diabetic ophthalmoplegia, 37.5% patients had non proliferative diabetic retinopathy (NPDR), 8.3% cases showed proliferative diabetic retinopathy (PDR), and 54% were free of any diabetic retinopathy[10]. In the present study, 55% of the patients had no DR , 41% had NPDR, and 4.2% had proliferative DR. Pupillary involvement is not a common finding in diabetic *ophthalmoplegia*. This condition was observed in (3.31% of the patients. In other studies, 14-18% of patients with diabetic *ophthalmoplegia* developed papillary dysfunction[11]. The differences in microvascular structure and function of extra ocular muscle nerves and retinal vessels may have been the causes of different susceptibility to injury. In one pathologic study, Zrustova *et al* showed that in diabetics' patients there is degenerative axonal changes and abnormal myelin sheath swelling compared to the non-diabetic controls[12]. These changes did not correlate with duration, severity (type of control) and stage of diabetic retinopathy. In some other histopathological studies, it has been shown that hyaline thickening of intraneural arterioles and localized nerve changes, compatible with ischemia including necrosis and interstitial edema was present[13-17]. The patients with coexistent vasculopathic risk factors such as hypertension, hyperlipidemia and coronary artery diseases were more susceptible to neuropathy than retinopathy. This finding is similar to what was reported by other research reports[13, 14]**.** Vascular supply to oculomotor CN in the brainstem and subarachnoid space is by *vertebrobasilar* artery not via the carotid circulation[17]. The result of early treatment diabetic retinopathy study (ETDRS) have showed that type of glycemic control account for different stages of retinopathy, however, in the present study and others[17, 18] no significant relationship between blood glucose levels and presence of diabetic ophthalmoplegia have been found (P=0.07).

Nearly all of patients in this study experienced spontaneous recovery during 1.5-3.5 months period, that result is compatible with the results of previous studies[4,8]. In summary, diabetic ocular motor palsies shows a propensity for CN 6 and 3, with relative sparing of CN 4 and stage of diabetic retinopathy has no association with the occurrence of CN palsies. A conceivable explanation for the findings of the present study is that ocular motor CN paresis imparts a protective effect against retinopathy (or is a marker for some protective effect) via as an undiscovered process at the genetic or cellular level[15, 19, 20].

For evaluation of effectiveness of tight control of blood glucose on systemic complications of diabetes mellitus including CN palsies a large case control study in multicenter is needed.

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