ARTICLE ORIGINAL

Clinical patterns of third nerve palsies in diabetic patients

Caractéristiques cliniques de la paralysie de la troisième paire crânienne chez les patients diabétiques

Ghada Saad, Asma Ben Abdelkrim, Amel Maaroufi Beizig, Maha Kacem Njah, Molka Chadli Chaieb, Koussay Ach

Service d'endocrinologie et de diabétologie, Hôpital Farhat Hached de sousse, Faculté de Médecine de Sousse, Université de Sousse.

RÉSUMÉ

Introduction : La neuropathie est une complication fréquente du diabète, sa présentation clinique et son évolution sont imprévisibles

Objectifs : Etudier les caractéristiques cliniques de la paralysie du nerf III d'origine diabétique, d'identifier les facteurs de risque et d'analyser son évolution

Méthodes : Nous rapportons les cas de 11 patients diabétiques hospitalisés pour mononévrite du III d'origine diabétique au service d'endocrinologie et de diabétologie à l'hôpital Farhat Hached de Sousse entre 1996 et 2005.

Résultats : Notre étude a porté sur 6 femmes et 5 hommes âgés en moyenne de 63,6 ± 13,7 ans. Tous les patients avaient un diabète de type 2. Huit patients présentaient une diplopie, trois avaient une douleur périoculaire et six se plaignaient de céphalées. La paralysie du nerf oculomoteur était unilatérale chez tous les patients : du côté droit chez 7 patients et du côté gauche chez les 4 autres. Tous les patients présentaient un déséquilibre glycémique au moment du diagnostic du ptôsis et avaient un risque cardiovasculaire élevé. L'évolution sous équilibre optimal du diabète et contrôle des facteurs de risque cardiovasculaires a été marquée par une régression et une disparition chez 4 patients, une récidive homo ou controlatérale chez 4 patients et une persistance de la paralysie chez 1 patient.

Conclusion : L'équilibre glycémique et les phénomènes ischémiques dus aux facteurs de risque cardiovasculaires sont à l'origine des paralysies oculomotrices chez les patients diabétiques. L'évolution de la mononévrite diabétique reste imprévisible malgré le contrôle de la glycémie et des facteurs de risque cardiovasculaires.

Mots Cles : Diabète sucré, Paralysie oculomotrice, Mononévrite diabétique

SUMMARY

Background: Neuropathy is a frequent complication in diabetic patients with variable clinical presentations and evolutions.

Aim: To specify the clinical features of diabetic third nerve palsy, to assess the risk factors and to observe its evolution.

Methods: We report a series of 11 diabetic patients with oculomotor paralysis collected in the department of endocrinology and diabetology of Farhat Hached Hospital of Sousse between 1996 and 2005.

Results: Our study was about 6 men and 5 women with an average age of 63.6 ± 13.7 years. All patients had type 2 diabetes. Eight patients presented with diplopia, three with periocular pain and 6 with headache. The oculomotor palsy was unilateral in all cases. All patients were in glycemic imbalance at the time of the diagnosis of ptosis and they were at high cardiovascular risk. The evolution under optimal equilibrium of diabetes and control of cardiovascular risk factors was marked by regression and disappearance in 4 patients, homo or contralateral recurrence in 4 patients and persistence of the palsy in 1 patient.

Conclusion: Glycemic equilibrium and ischemic phenomena due to cardiovascular risk factors are at the root of these oculomotor paralyses in diabetic patients. The evolution of diabetic mononevritis remains unpredictable despite the control of blood glucose levels and cardiovascular risk factors.

Keys Words: Diabetes mellitus, nerve palsy, Diabetic mononeuropathy

Correspondance
Ghada Saad
Hôpital Farhat Hached de Sousse / faculté de Médecine de Sousse,
ghada.saad6587@gmail.com

INTRODUCTION

Neuropathy is a frequent complication in diabetic patients, and its clinical presentations are variable. Its incidence increases with the duration of the disease, poor glycemic control and age of the patient (1).

Data shows that it affects 1 to 14% of the diabetic patients, it is 7 to 8 times more frequent in the diabetic subjects than the non-diabetics (2).

Diabetic peripheral neuropathy may take the form of polyneuritis or mononeuritis. Diabetic mononeuropathy is an uncommon form of neuropathy, which often appears to be a serious problem from a diagnostic and therapeutic point of view (2).

Although different incidences of cranial nerve palsies in diabetic patients have been reported, such abnormalities are seen relatively rarely in the general population. As regards to cranial nerve palsy caused by diabetes, it is generally accepted that the external ophtalmic muscles are the most frequently involved (3). Third nerve palsy has been reported in association with diabetes as early as 1866 (4) but localization of the causative lesion remained controversial for many years. The aim of our study is to describe clinical and evolving characteristics of diabetic third nerve palsy.

METHODS

Eleven diabetic patients enrolled in our retrospective study were admitted to our department between 1996 and 2015 with unilateral third nerve palsy.

In order to set proper diagnosis of diabetic mononeuropathy and to exclude other possible causes for the impairment of this nerve, all the patients were referred to a neuroophthalmologist; magnetic resonance imaging (MRI), MRI angiography and computed tomography (CT) were performed when necessary.

We have identified for each patient the parameters of glycaemic control: HbA1c and fasting blood glucose had been determined in the acute stage of the palsy. The ophtalmoscopic examination was done and diabetic retinopathy was classified according to simplified diagnosis classifications of DR (ALFEDIAM) (5). Diabetic nephropathy was defined as albuminuria rate > 30 mg/day. A diagnosis of diabetic neuropathy was made when subjective sensory disturbance was disclosed. Cardiovascular risk factors associated with diabetes were also screened (blood pressure, LDL-cholesterol, body mass index (BMI), smoking status). Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg.

All patients were treated with insulin for gradual and optimal blood glucose balance.

The evolution of the ptosis was evaluated on ophthalmic exams every month.

RESULTS

Six men and 5 women were included, mean age: 63.6 ± 13.7 years (41 – 81 years); the mean duration of diabetes was 11.8 ± 9.2 years (0 – 30 years).

The initial clinical symptoms included the inability to open the eye in all patients. Eight out of 11 patients complained of diplopia. Six patients presented with Headache, and periocular pain was noted in three cases.

The pupils examination was normal in all patients. The direct and the consensual pupillary light reflex were also normal in all cases. Third nerve palsy was complete in all patients: we noted a eye deflection in primary position and limitation of eye movements in the territory of the third nerve.

Lancaster test was not performed in all patients.

The diabetes control before palsy was fair in all patients (table1): HbA1c above 8% (8.4-14%), and an average fasting plasma glucose level of 13.32 ± 4.04 mmol/l (7.8 to 21.1 mmol/l).

The balance of diabetes of the 11 patients is summarized in Table 1.

Diabetes was on the average for 11.8 years and was already at the stage of degenerative complications in all patients. The search for these complications revealed that each patient had at least one diabetic microangiopathy at the time of diagnosis: Diabetic retinopathy was present in 5 patients; 2 patients had diabetic nephropathy. Diabetic neuropathy was diagnosed in 5 patients: distal symmetric polyneuropathy (DPN) in 3 patients, fifth nerve palsy in 3 patients and none had autonomic neuropathy (table2).

Table 1: The diabetic control before palsy of the 11 patients

Case	FPG* (mmol/l)	HbA1c (%)	Treatment
1	12,4	----	Oral drug
2	21,1	----	Insulin
3	12,6	9,7%	Oral drug
4	11,9	11,2%	None
5	12,2	9,1%	Oral drug
6	14,4	14%	Oral drug
7	7,8	10,6%	Insulin
8	11,4	8,4%	Oral drug
9	19	13%	None
10	15,5	8,8%	Insulin
11	8,2	9,7%	Oral drug

*FPG : fast plasma glucose

Table 2. Microangiopathic complications at the time of diagnosis.

Case	Diabetic Retinopathy	Microalbumlinuria (mg/day)	Diabetic Neuropathy
1	PDR[a]	200	DPN Fifth nerve palsy
2	DR[b] absent	16	Fifth nerve palsy
3	Mild NPDR[c]	30	DPN[d]
4	Bilateral PDR	9	None
5	DR absent	7	Fifith nerve palsy
6	DR absent	50	None
7	DR absent	20	None
8	PDR	8,5	None
9	DR absent	23	None
10	Mild NPDR	32	None
11	DR absent	12	DPN

[a]PDR : proliferative diabetic retinopathy, [b]DR : diabetic retinopathy, [c]NPDR : non-proliferative diabetic retinopathy, [d]DPN : distal symmetric polyneuropathy

In addition to diabetes, the study of cardiovascular risk factors showed hypertension in all patients, including 4 in imbalance at the time of diagnosis, overweight or obesity were found in 8 patients. No patient had LDL-cholesterol in the therapeutic goals (LDL-cholesterol < 0,7 g/l). Only one was a smoker. All patients except one were in primary prevention.

All patients were under insulin therapy sometimes intensified for an optimal balance of diabetes.

Specialized treatment such as occlusion or prismation has not been performed in our patients since the involvement is unilateral. They did not also have surgery.

The progression of diabetic mononeuritis was different from patient to another; In fact, mononeuritis evolved towards regression and disappearance in 4 patients, towards the homo or contralateral recurrence in 4 patients and towards the persistence in 1 patient; 2 patients were lost to follow-up.

DISCUSSION

Third nerve palsy was reported in association with diabetes as early as 1866 (4). It has been described as the first sign of type 2 diabetes by Laaribi et al (6).

Diabetic mononeuropathy of the cranial nerves has been reported to affect about 1% of diabetic patients (3), it is generally thought to arise most frequently in the external ophtalmic muscles (3). Indeed, Lajmi et al reported a Tunisian series of 24 diabetic patients who presented a sixth, a third and a fourth nerve palsies in respectively 50%, 37.5% and 12.5% of cases (7)

Third nerve palsy typically manifests as diplopia and ptosis : the pupil may be unaffected (8). The incidence of ophthalmoplegia in diabetics has been reported to be 0.4% by Waite and Beetham (9), 0.5% by Rose (10), and 0.7% by Fukuda (11). Higher incidences were reported by Rucker (12) and Leopold (13) at 4.5 and 5 % respectively. Simultaneous bilateral occulomotor nerve parlysis in diabetes mellitus is even more unusual and has rarely been reported in literature (13).

Green et al (14) and Pfeiffer et al (15) have reported different causes of the third nerve palsy:

- An aneurysm of the posterior communicating artery may compress the oculomotor nerve, leading to third nerve palsy; pupil constriction is typically impaired.

- A microvascular infarction of the blood supply to the oculomotor cranial nerve may cause diabetic third nerve palsy with inferolateral deviation of the eye, diplopia and ptosis.

- A myasthenia gravis ptosis caused by autoimmune destruction of postsynaptic acetylcholine receptors may manifest as pupil sparing third nerve palsy with ptosis but usually also affects multiple other nerves.

- An Orbital myositis may manifest as orbital pain, diplopia, and conjunctivitis.

- A Vertebrobasilar occlusion may affect the oculomotor nucleus located in the midbrain, resulting in nausea, dizziness and other cranial nerve deficits; bilateral ptosis also occurs.

The cause of the ophthalmoplegia occurring in diabetics has not been clarified yet.

Ischemic vascular origin is established but the location of this ischemia (central or peripheral) remains controversial

Dreyfus et al. (16) and Asbury et al. (17) found a focal zone of myelin sheath and axonal destruction in the intracavernous portion of the oculomotor nerve displaying fusiform enlargement as well as proliferation of connective tissue in diabetic cadavers. They also reported thickening and narrowing of the supplying vessels of the oculomotor nerve, and assumed that ischemic changes in these vessels played an important role in ophthalmoplegia.

The usual presentation is an old patient with vascular risk factors (17,18). The mean age in our series (63 years and 6 months) seems to correspond to the data of many authors (2) but this pathology is not specific to the elderly: 6 patients in our series had less than 65 years.

The onset of ophthalmoplegia was brutal in all the patients of our study, which is, without doubt in favor of an ischemic etiology.

The pain was present in 9 among our patients: 6 had headaches associated with the clinical presentation, 3 others complained of retro-orbital pain. In literature, diabetic palsies of the third cranial nerve (diabetic ophthalmoplegia) are painful in about 50% of cases (19). Some observations have hypothesized that the ischemic damage of trigonominal fibers contained in the oculomotor nerve is the origin of pain in ischemic-diabetic third-nerve palsies (20). Moreover, any headache in a diabetic should seek an infra-clinical oculomotor paralysis especially if it is associated with unexplained visual disturbances (2).

The duration of diabetes seems to be a more important risk factor than the age of onset of oculomotor paralysis (OMP) (2), indeed the average duration of diabetes evolution in our patients was 11 years. The occurrence of third nerve palsy can also inaugurate diabetes or occur after the first months of diabetes, as in one case of our series. Azaiez et al. have found that the duration of diabetes constitutes a statistically significant risk factor for both insulin-dependent and non-insulin-dependent diabetic patients (21). Watanabe et al. (3) observed that the duration of the diabetes was longer and the incidence of diabetic complications higher in the ophthalmoplegia group than in the facial palsy group. Thus, the ophthalmoplegia is more closely associated with diabetes than the facial palsy.

In addition, the association with high blood pressure (7 cases in our series), obesity (8 cases in our series), dyslipidemia (9 cases in our series) or vascular disease suggests the vascular origin of the pathogenesis of diabetic OMP. These factors have also been observed as a risk factor for the occurrence of diabetic OMP (18,19).

The diabetic OMP observed in our patients was associated in 100% of the cases with type 2 diabetes, type 1 diabetes was also associated with a OMP according to some authors (1). The insulin-dependent character of diabetes does not seem to be an added risk factor, in our series 3 out of 11 patients were already treated with insulin.

The microvascular ground is also a predictor of the diabetic ischemic origin of paralysis of the oculomotor nerve. In our series all the patients had already at least one diabetic micro angiopathy.

Magnetic resonance imaging should be performed if the diagnosis is unclear or if symptoms persist (17). In addition, it eliminates neurosurgical causes (vascular aneurysm), especially since pupillary involvement is not always present in carotid aneurysm. The diagnosis is therefore based on a set of clinical arguments and the elimination of other diagnoses with MRI.

Oculomotor findings reach their nadir within a day or at most a few days, persist for several weeks and then begin gradually to improve. Full resolution is the rule and generally takes place within 3 – 5 months (19).

Diabetic third nerve palsies usually occur in isolation and recover completely. These characteristics suggest peripheral nerve injury rather than brainstem infarction.

Jacobson, in a comparative study, showed that the more sudden the installation of the paralysis, the more rapid the resolution, which makes it possible to prognosticate this type of attack (22). In our study, the disappearance of the symptomatology after equilibration of the diabetes and control of the cardiovascular risk factors was observed in 6 patients, the recurrence (homo or contralateral)

was observed in 4 patients. One patient had persistent ophthalmoplegia.

Patient management in our study was a gradual but optimal control of blood glucose with control of other cardiovascular risk factors. The treatment proposed in the literature includes anti-platelet therapy and control of diabetes and blood pressure. Most patients had a history of malignancy (14). The anti-ischemic preventive effect of aspirin was tested by Johnson et al. (23) in diabetic patients with cranial nerve palsy, the rate of occurrence of cranial nerve palsy was not significantly different between patients in the aspirin group and patients in the non-aspirin group.

The treatment of symptomatic diabetic neuropathy should be directed toward long-term normalization of blood glucose until more specific therapies become available (24).

It will be very interesting to complete this work by studying the paralysis of other cranial pairs and to compare them with those of non-diabetic patients. Other biological studies looking for genetic polymorphisms associated with this type of paralysis will help us to find a clearer pathogenesis so as to a better prevention of this complication in exposed patients.

CONCLUSION

Diabetic mononevritis is a rare form of diabetic neuropathy. Oculomotor nerve palsy is the most frequent manifestation of diabetic mononevritis. Paresia may go unnoticed if not revealed by a diplopia that is disturbing to the patient; therefore a careful examination of ocular motility must be systematically carried out. MRI can eliminate the neurosurgical causes of OMP and must therefore be performed in a systematically. Several cardiovascular risk factors associated with old diabetes are arguments in favor of the diabetic ischemic origin of OMP. The evolution is usually spontaneously resolutive, the management is then preventive and consists of a good glycemic balance and a control of cardiovascular risk factors.

REFERENCES

1. Said G, Bigo A, Améri A et al. Uncommon early-onset neuropathy in diabetic patients. J Neurol,1998;245(2):61–8.
2. EL mansouri Y, Zaghloul K, AMRAOUI A. Oculomotor paralyses in the course of diabetes: about 12 cases. *J Fr ophtalmol,*2000;23(1):14–18.
3. Tankova T, Cherninkova S, Koev D. Treatment for diabetic mononeuropathy with a-lipoic acid. *Int J Clin Pract,2005;59(6):*645–650.
4. Watanabe K, Hagura R, Akanuma Y et al. Characteristics of cranial nerve palsies in diabetic patients. *Diabetes Res Clin Pract,1990;*10(1):19–27.
5. Collier J. Paralysis of the oculomotor nerve-trunks in diabetes. Proc R Soc Med,1930;23(5):627-30.
6. Laaribi N., Khlifi A., Ajhoun Y. et al. Extrinsic paralysis of the common motor ocular nerve revealing a type 2 diabetes. Presse Med. 2017;46(6 Pt 1):630-33
7. Lajmi H., Hmaied W., Ben Jalel W. et al. Oculomotor palsy in diabetics. Journal Français d'Ophtalmologie, 2018;41(1):45-9
8. Massin P, Angioi-Duprez K, Bacin F *et al*. Recommandations de l'ALFEDIAM pour le dépistage et la surveillance de la rétinopathie diabétique. Diabetes Metab, 1996;22:203-9.
9. Keane JR and Ahmadi J. Most diabetic third nerve palsies are peripheral. *Neurology,*1998;51(5):1510.
10. Waite JH and Beetham WP. The visual mechanism in diabetes mellitus (a comparative study of 2002 diabetics and 457 non-diabetics for control). N Eng J Med,1935;212:429-443.
11. Rose FC. The neuro-ophthalmological complications of diabetes. Proc R Sot Med,1965;58:537-538.
12. Rucker CW. Paralysis of the third, fourth and sixth cranial nerves. Am J Ophthalmol,1958;46:787-794.
13. Leopold I.H. Diabetes mellitus as observed in 100 cases for 10 or more years. Am J Med Sci,1945;209:16-23.
14. Green WR, Hackett ER, Schlezinger NS. Neuro-ophthalmologic evaluation of oculomotor nerve paralysis. Arch Ophthalmol,1964;72:154-67.
15. Pfeiffer KJ, Ropers SK, Short MW. Diplopia and Ptosis. Diagnosis: Diabetic third nerve palsy. *Am Fam Physician*,2010;82(2):187–8.
16. Dreyfus PM, Hakim S and Adams RD. Diabetic ophthalmoplegia. Arch NeurPsych,1957; 77(4):337-349.
17. Asbury AK, Aldredge H, Hershberg R, Miller Fisher C. Oculomoter palsy in diabetes mellitus: a clinico-pathological study. Brain,1970;93:555-566.
18. Yanovitch T, Buckley E. Diagnosis and management of third nerve palsy. *Curr Opin Ophthalmol,*2007;18(5):373–8.
19. Ziegler D. Diabetic Peripheral Neuropathy. in: Textbook of Diabetes, Blackwell Publishing Ltd, UK, 2010;38:615–32.
20. Bortolami R, D'Alessandro R, Manni E. The origin of pain in ischemic-diabetic third-nerve palsy. *Arch Neurol*,1993;50:795.
21. Azaiez A, Marrakchi S, Rezgui H et al. Les paralysies oculomotrices chez le diabétique. *Tunis Med*,1996;74(11):489–91.
22. Jacobson DM. Pupil involvement in patients with diabetes-associated oculomotor nerve palsy. *Arch Ophthalmol*,1998;116(6):723–727.
23. Johnson LN, Stetson SW, Krohel GB, Cipollo CL, Madsen RW. Aspirin use and the prevention of acute ischemic cranial nerve palsy. *Am J Ophtalmol*,2000;129(3):367–371
24. Brown MJ and Asbury AK. Diabetic neuropathy. *Ann Neurol*,1984;15(1):2–12.