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Ophthalmic Features in Prader-Willi Syndrome Patients with Type-2 Diabetes Mellitus

Tetsuya Muto[1)], Yuji Oto[2)], Nobuyuki Murakami[2)], Shigeki Machida[1)]

[1)] *Department of Ophthalmology, Dokkyo Medical University Saitama Medical Center, Koshigaya, Japan*
[2)] *Department of Pedatrics, Dokkyo Medical University Saitama Medical Center, Koshigaya, Japan*

SUMMARY

Purpose : To investigate and compare features of diabetic retinopathy (DR) in patients with Prader-Willi Syndrome (PWS) and those without PWS.

Methods : Overall, 33 PWS patients with type-2 diabetes mellitus (T2DM) secondary to PWS (65 eyes) and 55 age-matched patients with T2DM (109 eyes) without congenital heredity diseases were reviewed. Medical records of 65 eyes with PWS (PWS group : mean age 24.7±5.9 years) and 109 eyes without PWS (control group : mean age 22.9±6.2 years) were acquired and compared from January 2000 to November 2018. Best-corrected visual acuity (BCVA) was determined and DR scores were assigned.

Results : BCVA was significantly low in PWS group compared with the controls ($P<0.001$). Pseudophakia was frequently observed in patients in the PWS group ($P=0.024$). No significant differences were found with respect to cataract ($P=0.065$) and DR score ($P=0.77$) between patients in the PWS and control groups. Investigations into the possible causes of the low BCVA in the PWS group found no significant difference regarding strabismus ($P=0.065$). However, significant differences were found between both groups with respect to amblyopia ($P<0.01$). Visual acuity examinations were incomplete in some patients with PWS because of their inability to concentrate ($P<0.01$).

Conclusions : There was no correlation between DR progression and PWS. Lower BCVA in PWS patients was likely owing to amblyopia and incomplete visual acuity examination owing to inability of patients with PWS to concentrate.

Keywords : diabetic retinopathy, Prader-Willi Syndrome, amblyopia, visual acuity

INTRODUCTION

The estimated prevalence of Prader-Willi Syndrome (PWS) is 1 in 10,000－30,000 with males and females being equally affected[1)]. PWS was first described by Prader et al. in 1956[2)] and the clinical manifestations of PWS include hypotonia, early childhood-onset hyperphagia, characteristic facial appearance, hypogonadism, growth hormone deficiency, mild-to-severe mental retardation, and behavioral disturbance[3)]. Although patients with PWS are characterized by feeding difficulties and poor growth until 9 months of age, they tend to be obese thereafter owing to hyperphagia and lack of satiety caused by the dysregulation of hypothalamic pituitary. PWS is often complicated by severe obesity and type-2 diabetes mellitus

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Reprint requests to : Tetsuya Muto, MD, PhD
Department of Ophthalmology, Dokkyo Medical University Saitama Medical Center 2-1-50 Minamikoshiagya, Koshigaya, 343-8555, Japan

(T2DM)[4] and the latter often leads to diabetic retinopathy (DR). The rate of T2DM incidence is 26.2% (17/65 patients) in Japanese PWS patients aged >10 years[5].

Strict control of blood sugar is difficult for patients with PWS owing to their mental retardation and abnormal behavior. Hori et al. reported that diagnosing and treating DR in patients with PWS is challenging owing to low levels of cooperation[6]. It may thus be hypothesized that diabetic retinopathy (DR) in PWS patients is more severe and visual acuity is poorer than in diabetic patients without PWS. Owing to the scarcity of studies regarding DR in PWS patients, we aimed to advance knowledge in this area by comparing DR in T2DM patients with PWS to that in age-matched T2DM patients without PWS.

METHODS

The study was approved by the Institutional Review Board of Dokkyo Medical University Saitama Medical Center and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

The medical records of 33 patients (65 eyes) who were diagnosed with T2DM secondary to PWS (PWS group : 25 males and 8 females) between January 2000 and November 2018 in the pediatrics division of Dokkyo Medical University Saitama Medical Center were reviewed in this study. The PWS group comprised 25 males and 8 females with a mean age of 24.7 ± 5.9 years. Two eyes in the PWS group were vitrectomized under local anesthesia at another clinic in this study. Overall, 55 age-matched T2DM patients without PWS (109 eyes) comprising 35 males and 20 females (22.9 ± 6.2 years) identified during the same time period formed the control group ; patients in the control group were not diagnosed with other congenital diseases or mental retardation. Diagnostic methods employed for T2DM and PWS were as previously reported[5]. PWS was diagnosed by polymerase chain reaction (PCR) analysis ; abnormal methylation was observed. The 15q11-q13 deletion was detected by fluorescence in situ hybridization using specific probes. Uniparental disomy (UPD) was detected by PCR using established methods targeting polymorphic DNA microsatellites in the chromosomal 15q11-q13 region. T2DM was diagnosed according to the criteria established in the Classification and Diagnostic Criteria of Diabetes Mellitus by the Committee of the Japan Diabetes Society in 1999. In brief, a diagnosis of T2DM was made if any of the following criteria were met : 1) fasting plasma glucose (FPG) ≥126 mg/dl and/or a plasma glucose level in the 2-hour oral glucose tolerance test (2hPG) ≥200 mg/dl (with 75 g glucose), and/or casual plasma glucose (CPG) ≥200 mg/dl detected on ≥2 occasions ; 2) FPG ≥126 mg/dl, and/or 2hPG ≥200 mg/dl, and/or CPG ≥200 mg/dl are measured at least once, accompanied by typical diabetic symptoms, and/or HbA1c ≥6.5% , and/or DR[7].

At the initial examination, all patients underwent comprehensive ophthalmologic examinations, which included standardized refraction, measurement of best-corrected visual acuity (BCVA) using a Landolt ring, slit-lamp biomicroscopy, and fundus examination after mydriasis. Color fundus photography and fluorescein angiography were performed as needed. Eyes with DR were classified according to Fukuda's new classification[8]. For convenience, we assigned non-DR a score of 0, simple DR (Fukuda A1 and A2) was assigned 1, interrupted proliferative DR (Fukuda A3-A5) as score 2, mild malignant DR (Fukuda B1 and B2) as score 3, and severe malignant retinopathy (Fukuda B3-B5) as score 4[8]. Complications, such as macular edema, tractional retinal detachment, neovascular glaucoma, and ischemic optic neuropathy were not assigned any scores[8]. Decimal VA data were converted to a logarithm of the minimum angle of resolution (logMAR). Objective refractive status was measured using autorefractometers. The manifest spherical equivalent (SE) value was calculated as the spherical power plus half the cylindrical power.

All data were expressed as mean ± standard deviation. Differences between the PWS and control groups in the variables of age, logMAR BCVA, DR score, spherical power, cylindrical power, and SE were compared using unpaired *t*-tests. Discrete variables between the 2 groups were compared using the chi-square test or Fisher's exact probability test. Statistical analyses were performed using StatMate version V for Macintosh (ATMS, Tokyo, Japan). A P value of <0.05 was considered statistically significant.

Table 1 Age and sex distribution of patients with Prader-Willi Syndrome and controls

Factor	PWS (n=33)	Control (n=65)	*P* Value
Age (years)	24.7±5.9	22.9±6.2	0.17*
Sex (Male, Female)	25, 8	35, 20	0.24†

PWS : Prader-Willi Syndrome
Data are shown as means±SDs.
* Unpaired *t*-test, † chi-square test.

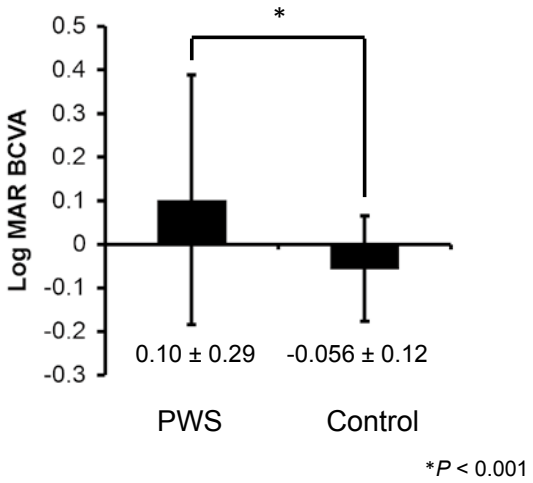

Fig. 1
LogMAR best-corrected visual acuity (BCVA) is significantly better ($P<0.001$ in the control group than in the PWS (Prader-Willi Syndrome) group.

Table 2 Ophthalmic factors of patients with Prader-Willi Syndrome and controls

Factor	PWS (n=65)	Control (n=109)	*P* Value
IOL/pseudophakia (Y, N)	3, 62	0, 109	0.024†
Cataracts (Y, N)	2, 63	0, 109	0.065†
‡, **Strabismus (Esotropia) (Y, N)	2, 31	0, 55	0.065†
‡, **Nystagmus (Y, N)	1, 32	0, 55	0.19†
‡Amblyopia (Y, N)	9, 56	2, 107	<0.01†
Concentration deficiency (Y, N)	5, 60	0, 109	<0.01†
Spherical power	−2.66±3.76	−1.81±2.89	0.098*
Cylindrical power	−1.61±1.45	−0.89±1.02	<0.001*
SE	−3.47±3.99	−2.26±3.06	0.042*

PWS : Prader-Willi Syndrome, IOL : intraocular lens, Y : yes, N : no
SE : manifest spherical equivalent
*Unpaired *t*-test, † chi-square test.
‡Overlaps included.
**PWS (n=33), Control (n=55)
Data are shown as mean±SD.

RESULTS

Patient demographics are summarized in Table 1. There were no statistically significant differences in the age and sex distributions between T2DM patients with PWS and those without PWS. Complications such as macular lesions, tractional retinal detachment, neovascular glaucoma, or ischemic optic neuropathy were not reported in any patient.

Log MAR BCVA was significantly worse in the PWS group than in the control group ($P<0.001$, Figure 1). Among T2DM patients in the PWS group, 3 eyes had pseudophakia ($P=0.024$, Table 2) and 2 eyes had slight cataracts ($P=0.065$, Table 2) compared with none in the control group. The DR score was 0.12±0.42 for the PWS group and 0.15±0.64 for the control group ; no significant differences in DR scores were observed between the 2 groups ($P=0.77$, Figure 2). Although there were no differences in the DR scores between PWS patients and controls, there was a significant difference in BCVA.

We further analyzed the factors contributing to this

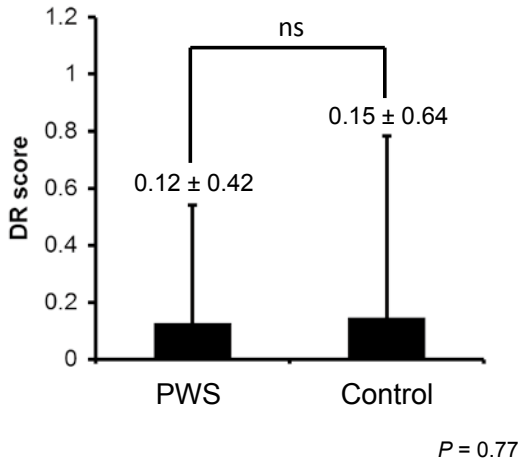

Fig. 2
Diabetic retinopathy (DR) score was not significantly different ($P=0.77$) between PWS and controls.

contradiction. Two eyes had esotropia and one had nystagmus in the PWS group, but no eyes with strabismus and nystagmus were observed in the control group ($P=0.065$ and $P=0.19$, respectively, Table 2). Nine eyes had amblyopia that in the PWS group, whereas only 2 eyes had amblyopia in the control group and reached statistical significance ($P<0.01$, Table 2). Of the 9 amblyopic eyes in the PWS group, 4 had ametropic amblyopia, 3 had anisometropic amblyopia, and 2 had strabismic amblyopia, whereas both amblyopic eyes in the control group had anisometropic amblyopia (Table 3). Examination of visual acuity was incomplete for 5 eyes in the PWS group owing to patient's lack of concentration during the procedure, whereas it was completed for all eyes in the control group ($P<0.01$, Table 2). Refraction, except pseudophakia, was analyzed and significant differences were observed between the PWS and control groups with respect to SE (-3.47 ± 3.99 and -2.26 ± 3.06, respectively ; $P=0.042$) and cylindrical power (-1.61 ± 1.45 and -0.89 ± 1.02, respectively ; $P<0.001$) (Table 2). However, spherical power (-2.66 ± 3.76 and -1.81 ± 2.89 for the PWS and control groups, respectively) was not significantly different ($P=0.098$, Table 2).

Table 3 Detail of amblyopia in both groups

Type of amblyopia	PWS	Control
Ametropic	4	0
Anisometropic	3	2
Strabismic	2	0

DISCUSSION

It is difficult for patients with PWS to cooperate during the ophthalmological examinations and treatments owing to mild-to-severe mental retardation. Therefore, it is believed that the diagnosis and initiation of the treatment of DR generally tends to be late in patients with PWS[6]. However, the progression of DR in PWS patients in this study was similar to that of control patients with T2DM who did not have PWS and mental retardation. At least, the discovery of DR in PWS was not delayed. However, some patients with PWS could not complete the visual acuity examination and faced challenges in performing fundus check, fluorescein angiography, laser treatment, intravitreal injection of anti-vascular endothelial growth factor or vitrectomy in such situations. Nevertheless, laser treatment[9] and vitrectomy under local[6] or general[10] anesthesia for proliferative DR in PWS have been previously reported.

Although the lifespan of patients with PWS is not well understood owing to limited studies, the severity of obesity and diabetes may affect it[11]. Severe obesity sometimes causes Pickwickian syndrome and the patient might die of heart failure at a young age[12~14]. Advances in PWS therapy may, in future, increase the lifespan of patients with PWS. Conversely, living longer may increase the chance of DR progression ; therefore, ophthalmological examination and treatment are essential and cooperation from patients is critical. Despite the availability of simple and rapid ophthalmological examination and treatments, problems may arise if ophthalmologists and ophthalmological assistants fail to elicit cooperation and communicate effectively with non-cooperative patients.

Amblyopia is generally diagnosed during childhood and can be treated using eyeglasses and eye patches, however, mental retardation of patients restricts the use of eyeglasses and eye patches. Significant differences in cylindrical power and SE, but not in spherical power, were observed between the PWS and control groups likely because 2 eyes in the PWS group had ametropic amblyopia caused by high astigmatism. This observation concurs with the findings of Hered

RW et al. who reported that 7 patients (15%) with PWS had a myopia refractive error of >-3.75 diopters (D), and 19 (41%) had astigmatism of >1.25D[15]. The prevalence of strabismus is 2.1%－3.3% in the normal population[16]. Strabismus (esotropia) was noted in 2 of the 65 eyes (3.1% of PWS group) in this study. Although we only analyzed patients with PWS and T2DM, further analysis should be performed in all patients with PWS regardless of their diabetic status. The prevalence of strabismus ranges from 16.7% to 95% in patients with PWS[15,17~20]. Taken together, strabismus generally seems to be more frequent in patients with PWS than normal individuals. Creel et al. reported that nystagmus was a characteristic feature in PWS[21]. Hered et al. did not find nystagmus in 46 patients with PWS[15], and Roy et al. observed 2 cases of nystagmus in 10 patients with PWS[20]. Nystagmus was observed in only 1 of the 33 patients in the PWS group in this study and no significant difference was observed between the 2 groups. Therefore, based on our results, a definite correlation between nystagmus and PWS cannot be derived. To the best of our knowledge, there are no reports about the reason about amblyopia, strabismus and nystagmus are frequent in patients with PWS than normal individuals.

In this study, 2 eyes had cortical cataracts and 3 eyes had pseudophakia in the PWS group. Among these, one eye received cataract surgery alone, whereas the remaining received vitrectomy and cataract surgery simultaneously under local anesthesia at another clinic. Although it is difficult to draw a conclusion because DM sometimes causes cataracts in young age, the correlation between PWS and cataracts observed in this study is plausible and is supported by published reports on PWS and cataracts[20, 22].This study has several limitations. First, the sample size was relatively small. Only 33 patients who had T2DM secondary to PWS underwent ophthalmological examinations. Because young T2DM patients were rare, only 55 patients were included as controls. Second, the limited observation period in this study may have obscured clinically important findings that may be unmasked in an extended study.

Although the diagnosis and treatment of DR in patients with PWS are thought to be late in general, we found that the diagnosis of DR was not late in this study. Because visual acuity examinations were incomplete in some cases owing to the lack of concentration during ophthalmological examination and treatment, non-invasive and rapid procedures and therapies are warranted for patients with PWS.

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