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The Prevalence of Brain Abnormalities in Japanese Patients with Optic Nerve Hypoplasia

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ABSTRACT

The purpose of this study was to investigate the clinical characteristics of Japanese patients with optic nerve hypoplasia (ONH), with particular attention to the prevalence of brain abnormalities. We retrospectively analysed the medical charts of 16 patients who were diagnosed with ONH and who underwent magnetic resonance imaging (MRI) at Niigata University Medical and Dental Hospital. We recorded the age, sex, laterality, initial eye and visual symptoms, best-corrected visual acuity, and brain abnormalities on MRI (excluding ONH). The median age at the first visit to the Ophthalmology Clinic was 2.4 years old. Four patients were male and 12 were female. ONH was bilateral in 11 patients and unilateral in five. Best-corrected visual acuity ranged from no light perception to 20/20. Seven patients (43.8%) had brain abnormalities including agenesis of the septum pellucidum, pituitary gland hypofunction, cerebral dysplasia, and West syndrome. Five of these seven patients had general manifestations since the neonatal or infantile period. Our study revealed the prevalence of brain abnormalities associated with optic nerve hypoplasia in Japanese patients at a single institute. Because two of 11 patients had no general manifestations since the neonatal or infantile period but demonstrated brain abnormalities, MRI should be performed to investigate all patients with ONH.

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Optic nerve hypoplasia; magnetic resonance imaging; brain abnormality; septo-optic dysplasia; pituitary hypofunction

Introduction

Optic nerve hypoplasia (ONH) is the most common congenital optic disc anomaly.[1] In Europe, its prevalence is 7.1 to 10.9 per 100,000 births.[2,3] Brain abnormalities have been reported in patients with both bilateral and unilateral ONH,[4] and include cerebral palsy, epilepsy,[5] cortical heterotopias, schizencephaly, periventricular leukomalacia, diffuse encephalomalacia, septo-optic dysplasia (SOD),[6] and arachnoid cyst.[7] SOD is a syndrome diagnosed by the presence of at least two of the following triad of features: ONH; midline brain structure abnormalities, including agenesis of the septum pellucidum and/or corpus callosum; and pituitary hormone abnormalities.[8–11] Although studies have been published in Europe and the United States regarding the prevalence of brain abnormalities in ONH patients from the viewpoint of ophthalmologists, there have been no detailed reports in Japan. The purpose of this study was to investigate the prevalence of brain abnormalities in Japanese patients with ONH.

Materials and methods

We retrospectively reviewed the records of 20 patients who were diagnosed with ONH at the Ophthalmology Clinic, Niigata University Medical and Dental Hospital, between 2004 and December 2015. Four patients who did not undergo brain magnetic resonance imaging (MRI) were excluded. We recorded the age, sex, laterality, initial eye and visual symptoms, best-corrected visual acuity, and brain abnormalities on MRI (excluding ONH). The diagnostic criteria for ONH were as follows: either or both of a small papilla and a double-ring sign completely surrounding the papilla revealed by ophthalmoscopic examination (Figure 1). These findings were confirmed by two or more ophthalmologists. A thin optic nerve revealed by MRI supported the diagnosis of ONH (Figure 2). Brain magnetic resonance images were assessed by neuro-ophthalmologists and radiologists, focusing on the following: pituitary abnormalities; midline cerebral structure abnormalities, including agenesis of the septum pellucidum and corpus callosum; and

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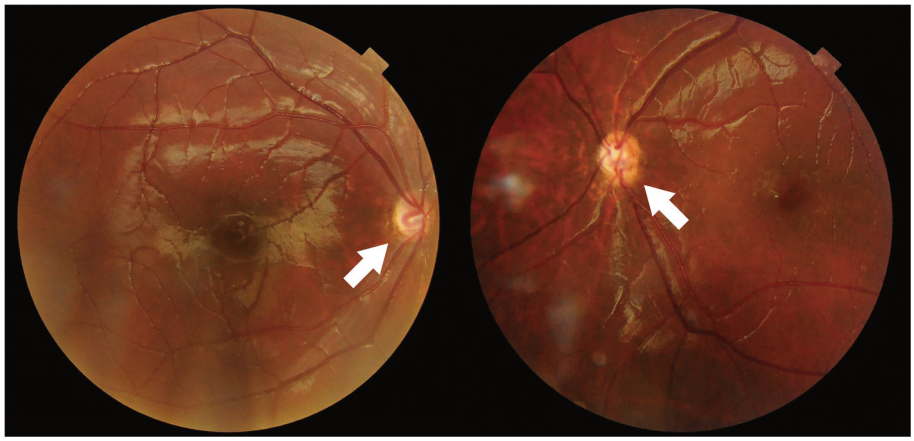

Figure 1. Fundus photographs of a patient with ONH (Number 15). Both a small papilla and a double-ring sign (white arrows) are observed.

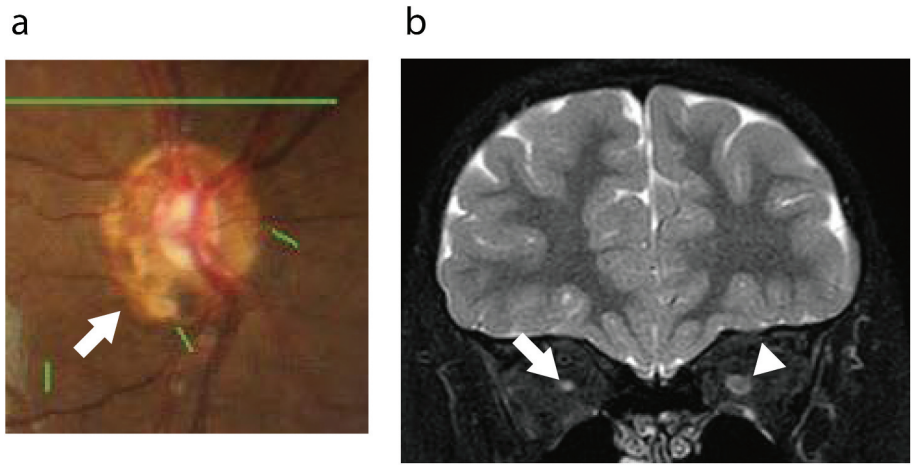

Figure 2. Fundus photograph (a) and coronal MRI (b) of a patient with ONH (Number 10). (a) Both a small papilla and a double-ring sign (white arrow) are observed. (b) The right optic nerve (white arrow) is very thin compared with the normal left optic nerve (white arrowhead).

cerebral hemisphere abnormalities. When structural or functional abnormalities of the pituitary gland and/or abnormalities of midline cerebral structures were present, we diagnosed the patient with septo-optic dysplasia (SOD). Based on the diagnostic criteria of SOD in previous studies,[8–11] we diagnosed a flat optic chiasm as ONH rather than a midline cerebral structure abnormality. This retrospective study was approved by our Institutional Review Board/Ethics Committee at Niigata University (Registration No. 2019–0335) and followed the tenets of the Declaration of Helsinki.

Results

ONH was present in 27 eyes of 16 patients, being bilateral in 11 patients and unilateral in five patients. The age at the first visit to the Ophthalmology Clinic was 4.7 ± 7.3 years (mean ± standard deviation) (range, 0 months to 28.5 years; median 2.4 years). Four patients were male and 12 were female. Eye and visual symptoms at the first visit to the Ophthalmology Clinic comprised poor vision in 11 patients, heterotropia in eight patients, and nystagmus in five patients. Two patients were asymptomatic. The two asymptomatic patients were referred to the Ophthalmology Clinic for examination of optic disc abnormalities. The results of best-corrected visual acuity ranged from no light perception to 20/20. Brain abnormalities were seen in seven out of the 16 patients (43.8%) (Table 1). Three had agenesis of the septum pellucidum, two had agenesis of the corpus callosum, three had pituitary hypofunction, two had severe cerebral dysplasia with neurodevelopmental

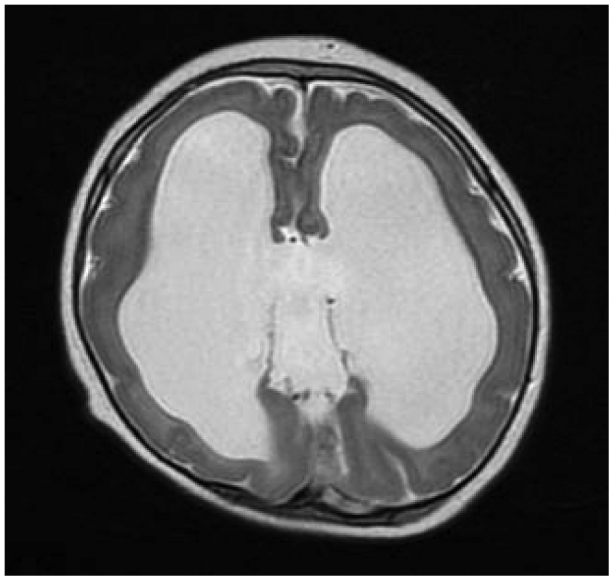

Figure 3. Axial brain MRI of a patient with ONH and cerebral dysplasia as well as ventricular enlargement (Number 2).

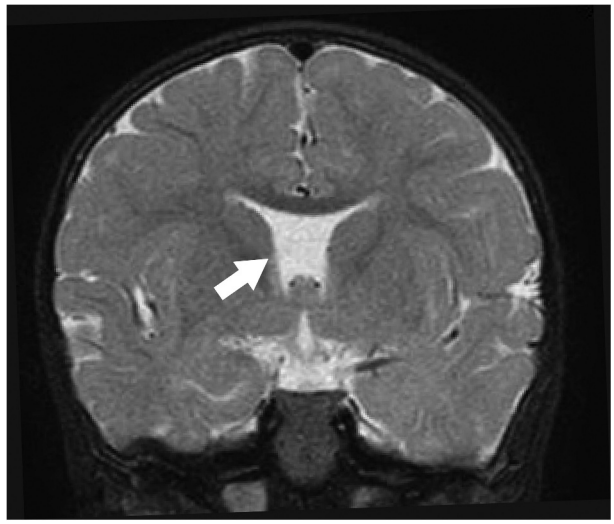

Figure 4. Coronal MRI of a patient (Number 4) with ONH and a brain abnormality (agenesis of the septum pellucidum, white arrow) without general manifestations since the neonatal or infantile period.

abnormalities since birth (Figure 3), and two had West syndrome. All three patients with pituitary hypofunction were treated with hormone replacement therapy. Six patients underwent a blood test for pituitary function. Five of the seven patients with brain abnormalities had general manifestations since the neonatal or infantile period. Two of the 11 patients (18.2%) without these early manifestations had brain abnormalities, specifically agenesis of the septum pellucidum. Six of the 16 patients (37.5%) were diagnosed with SOD. In addition to ONH, two of these had pituitary abnormalities, three had midline cerebral structural abnormalities, and one had both pituitary and midline cerebral abnormalities.

Case report

A 5-month-old female patient (Number 4) with ONH and a brain abnormality (agenesis of the septum pellucidum) without general manifestations since the neonatal period was brought to our Ophthalmology Clinic by her parents, who reported heterotropia and nystagmus. Esotropia and binocular nystagmus were observed. Her visual acuity was NLP OD and 20/180 OS by Teller acuity cards. Fundus examination with an ophthalmoscope revealed bilateral ONH with a small papilla and a double-ring sign. Further investigation by MRI at 1 year of age revealed agenesis of the septum pellucidum (Figure 4), and the patient was diagnosed with SOD. During follow-up, we have checked height and weight to avoid overlooking growth hormone deficiency.

Discussion

In this study, we investigated brain abnormalities in Japanese patients with ONH at a single institute. The abnormalities found in this study were West syndrome, cerebral dysplasia, pituitary hypofunction, and agenesis of the septum pellucidum and corpus callosum. These diseases have been reported in previous studies. Based on the morphological abnormalities observed by brain MRI and the functional abnormalities identified through clinical examination and past medical history, the prevalence of brain abnormalities was 43.7% (7/16 patients). Brodsky et al. reported that the prevalence of brain abnormalities in American patients with ONH was 75%,[6] which is considerably higher than that in this study. This discrepancy may be due to non-identical inclusion criteria and racial differences. It is presumed that the study by Brodsky et al. excluded patients diagnosed with mild ONH or partial hypoplasia based on funduscopic examination, and also those with good visual acuity. This study enrolled patients with mild ONH as well as those with good visual acuity. A study of Taiwanese patients with ONH by Cheng et al. reported that all eight ONH patients had midline brain abnormalities,[12] although the number of

Table 1. Clinical characteristics and brain abnormalities in 16 patients with ONH.

Patient number	Age at first visit to the Ophthalmology Clinic	Sex	Laterality	Best-corrected visual acuity	Eye and visual symptoms at the first visit to the Ophthalmology Clinic	Brain abnormalities (excluding ONH)	General manifestations since the neonatal or infantile period
1	13 Y, 10 Mo	F	B	RV = 20/20 LV = 20/20	Asymptomatic; referred for evaluation of optic disc abnormality	Pituitary hypofunction with MRI abnormality	Apnoea
2	3 Y, 6 Mo	M	B	RV = NLP LV = NLP	Poor vision	Cerebral dysplasia, agenesis of the corpus callosum	Apnoea, hypotonia
3	6 Mo	F	B	RV = LP LV = LP	Poor vision	Cerebral dysplasia, agenesis of the corpus callosum, agenesis of the septum pellucidum, pituitary hypofunction without MRI abnormality, West syndrome	Diabetes insipidus
4	5 Mo	F	B	RV = NLP LV = 20/180	Heterotropia, nystagmus	Agenesis of the septum pellucidum	-
5	4 Mo	M	B	RV = HM LV = 20/100	Poor vision, heterotropia, nystagmus	Agenesis of the septum pellucidum	-
6	9 Days	F	B	RV = NLP LV = NLP	Poor vision	Pituitary hypofunction without MRI abnormality	Hypoglycaemia, spasms
7	10 Mo	F	B	RV = LP LV = LP	Poor vision, nystagmus	West syndrome	Seizure
8	1 Y, 7 Mo	M	B	RV = 20/2000 LV = 20/20	Poor vision, heterotropia	None	-
9	3 Y, 4 Mo	F	L	LV = 20/2000	Poor vision, heterotropia	None	-
10	5 Y, 4 Mo	F	R	RV = LP	Poor vision, heterotropia	None	-
11	3 Y, 2 Mo	M	B	RV = 20/20 LV = NLP	Poor vision, heterotropia	None	-
12	28 Y, 6 Mo	F	L	LV = 20/20	Asymptomatic; referred for evaluation of optic disc abnormality	None	-
13	3 Mo	F	B	RV = 20/630, LV = 20/500	Poor vision, nystagmus	None	-
14	7 Y, 6 Mo	F	L	LV = 20/100	Poor vision	None	-
15	7 Mo	F	B	RV = 20/40, LV = HM	Heterotropia, nystagmus	None	-
16	6 Y, 2 Mo	F	L	LV = 20/500	Heterotropia	None	-

Notes. B: bilateral; F: female; HM: hand motion; L: left; LP: light perception; LV: left visual acuity; M: male; Mo: months; MRI: magnetic resonance imaging; NLP: no light perception; ONH: optic nerve hypoplasia; R: right; RV: right visual acuity.

patients was small. Their inclusion criterion was a horizontal disc diameter/disc-macula ratio of ≤0.35. A study of American ONH patients by Skarf and Hoyt showed that 78% of ONH patients with bilateral involvement, poor vision, and nystagmus had non-ocular developmental abnormalities compared with 21% of ONH patients with good vision and either unilateral or bilateral segmental involvement.[13] The prevalence of non-ocular developmental abnormalities in all ONH patients in that study was 43/93 (46.2%).

From another point of view, if the patients in this study were limited to those with no general manifestations since the neonatal or infantile period, the prevalence of brain abnormalities was 18.2% (2/11 patients). This indicates that MRI examination to evaluate the possible presence of brain abnormalities should be performed in ONH patients even if they have no general manifestations. However, MRI examination in young children usually requires sedation which increases the risk of adverse reactions. In such cases, ophthalmologists should obtain help from experienced paediatricians.

The prevalence of SOD in this study was 37.5% (6/16 patients); three of the six patients with SOD had pituitary hypofunction and received replacement therapy. Two out of the three patients with pituitary hypofunction had no pituitary morphological abnormalities on MRI. Three studies that performed brain MRI in ONH patients with hypopituitarism reported a prevalence of pituitary morphological abnormalities of 96%,[14] 88%,[15] and 54%,[16] respectively. This indicates that pituitary morphological abnormalities are not always detected by brain MRI in patients with hypopituitarism. ONH patients with pituitary hypofunction have demonstrated growth hormone deficiency, hypothyroidism, adrenal hormone deficiency, diabetes insipidus, and reduced gonadotropic hormone.[16,17] Although most cases of growth hormone deficiency and hypothyroidism are diagnosed by age 2,[17] gonadotropic hormone deficiency does not manifest until adolescence.[16] Therefore, long-term follow-up is required in patients with SOD and pituitary hypofunction.

Poor vision was the most frequent initial symptom in patients in this study, followed by heterotropia and nystagmus. These symptoms are frequently observed in various childhood diseases that threaten vision, including optic disc anomalies. On the other hand, two patients (Number 1 and Number 12) aged 13 and 28 years were referred to our Ophthalmology Clinic for examination of optic disc anomalies, and they demonstrated no eye or visual symptoms at their initial visits. However, the first of these patients (Number 1) had pituitary hypofunction, which was detected during a neonatal apnoea evaluation, with associated MRI abnormalities. Accordingly, it is important to screen for brain abnormalities even in ONH patients with good visual acuity.

A limitation of this study is that the number of patients was small. Further studies that include more patients are warranted. However, this study revealed that the prevalence of brain abnormalities was not low, even in patients without general manifestations. In the management of ONH, it is important to identify such abnormalities, particularly pituitary hypofunction that requires treatment. However, long-term follow-up is necessary because brain MRI does not always detect pituitary abnormalities.

Declaration of interest statement

The authors report no conflicts of interest.

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