

# Weak Association Between Retinopathy of Prematurity and Neurological Disorders in Childhood

Saki Sugimoto,\* Ayako Furukawa,\*  
Yoshikazu Hatsukawa,\* Keiko Yanagihara<sup>†</sup> and Yoshihiro Saito<sup>‡</sup>

\**Department of Ophthalmology and <sup>†</sup>Department of Pediatric Neurology, Osaka Medical Center and Research Institute for Maternal and Child Health, Izumi, Osaka 590-02, Japan;*  
*<sup>‡</sup>Department of Ophthalmology, Osaka University Medical School, Suita, Osaka 565, Japan*

---

**Abstract:** An attempt was made to elucidate the association between retinopathy of prematurity (ROP) and neurological disorders in infants of very low birth weight. In this retrospective study, 1081 Japanese children weighing less than 1500 g at birth were classified into four subgroups according to birth weight. In each subgroup, the association among cerebral palsy (CP) or mental retardation (MR) and ROP, treated ROP, and cicatricial ROP was analyzed statistically. In the population as a whole, CP and MR were positively associated with ROP. However, in the birth-weight subgroup analysis, no significant association was found. We can conclude that there is a weak association between ROP and CP or MR. **Jpn J Ophthalmol 1998;42:142–145** © 1998 Japanese Ophthalmological Society

**Key Words:** Cerebral palsy, mental retardation, neurological disorders, retinopathy of prematurity, very-low-birth-weight infants.

---

## Introduction

Recent advances in neonatal care have increased the survival of very-low-birth-weight infants (<1500 g).<sup>1</sup> However, severity of retinopathy of prematurity (ROP) is increasingly being encountered in these premature infants. There have been reports on the surgical outcome of ROP,<sup>2–5</sup> and the perinatal risk factors have been discussed.<sup>6–10</sup>

Neurological disorders are frequently associated with very low birth weight.<sup>11–16</sup> Ophthalmologists often notice that infants with severe ROP also have neurological disorders. The present study tried to elucidate the association between ROP and cerebral palsy (CP) or mental retardation (MR) to determine whether the incidence, severity, and cicatricial findings of ROP in the neonatal period may perhaps predict the development of neurological disorders in later years.

## Subjects and Methods

Data were collected on 1081 Japanese children with birth weights below 1500 g who were treated in the neonatal intensive care unit of our institution and discharged alive between 1981 and 1993. The fundus of each premature infant was examined by a pediatric ophthalmologist. The severity of ROP was classified according to the International Classification of Retinopathy of Prematurity.<sup>17</sup> Patients born before 1991 were treated by cryotherapy,<sup>18</sup> and those born after 1991 were treated mainly by argon laser photocoagulation with or without cryotherapy under general anesthesia, referred to hereafter as treated ROP.

The patients were regularly followed until they were 5 years old. For this study, CP and MR were chosen as the neurological disorders of interest. Cerebral palsy included spastic and athetotic CP, according to the criteria of Illingworth,<sup>19</sup> and mental retardation was diagnosed when the intelligence quotient was 70 or lower at the corrected ages of 10 months, 18 months, and 36 months.

## Data Analysis

The children were divided into four subgroups according to birth weight: below or equal to 749 g, 750 g–

---

Received: April 18, 1997

Address correspondence and reprint requests to: Yoshikazu HATSUKAWA, MD, Department of Ophthalmology, Osaka Medical Center and Research Institute for Maternal and Child Health, Murodo, Izumi, Osaka 590-02, Japan

**Table 1.** Incidence and Severity of Retinopathy of Prematurity (ROP) in Very-Low-Birth-Weight Infants

Birth Weight (Grams)	Patients	No ROP	Total ROP	Treated ROP	Cicatricial ROP
≤749	126	5	121	42	14
750–999	273	35	238	31	5
1000–1249	325	171	154	6	1
1250–1499	357	280	77	1	0
Total	1081	491	590	80	20

999 g, 1000 g–1249 g, and 1250 g–1499 g. The associations among CP and ROP, treated ROP, and cicatricial ROP were analyzed statistically in each subgroup according to birth weight. The incidence of CP in each condition of ROP was compared with data on cases without ROP using chi-square test. If the number of cases was less than five in each subgroup, Yates' correction of continuity or Fisher's exact test was used. The same analyses were applied to MR. A level of  $P < 0.05$  was accepted as statistically significant.

### Results

Of the 1081 infants, 590 were found to have ROP,<sup>20</sup> with 80 patients exhibiting severe stage 3 or threshold ROP undergoing treatment (treated ROP).<sup>21</sup> Twenty patients developed cicatricial ROP<sup>20</sup> such as dragged disc, macular change,<sup>18</sup> or retinal detachment. Retinopathy of prematurity appeared more frequently in infants whose birth weight was equal to or less than 1249 g. Infants with treated ROP and cicatricial ROP generally weighed 999 g or less at birth (Table 1).

A total of 43 children were diagnosed as having CP. The incidence of CP in ROP, treated ROP, and

cicatricial ROP was, as a whole, significantly higher than that of CP in ROP-free cases ( $P = 0.012$ , 0.006, and 0.006, respectively) (Table 2). However, when analyzed in the subgroups of birth weight, there was no statistically significant association.

Mental retardation was diagnosed in 54 children. The incidence of MR in ROP, treated ROP, and cicatricial ROP was, as a whole, significantly higher than that of MR in ROP-free cases ( $P = 0.008$ , 0.032, and 0.026, respectively) (Table 3). However, when analyzed in the subgroups of birth weight, there was no statistically significant association.

### Discussion

The long-term neurological development of very-low-birth-weight infants is a major concern. A few reports have suggested the association between ROP and neurological development. Hack et al<sup>22</sup> compared children with birth weights below 750 g with those between 750 g and 1500 g, and they found a higher incidence of CP, MR, and blindness in the former group. Bowen et al<sup>23</sup> reported a significant association between severe CP and ROP. Greggard et

**Table 2.** Incidence of Cerebral Palsy (CP) in Infants With or Without Retinopathy of Prematurity (ROP)

Birth Weight (Grams)	CP/Total	CP/No ROP	CP/ROP	CP/Treated ROP	CP/Cicatricial ROP
≤749	10/126 (7.9%)	0/5 (0%)	10/121 (8.3%)	6/42 (14.2%)	3/14 (21.4%)
			NS	NS	NS
750–999	15/273 (5.5%)	1/35 (2.8%)	14/238 (5.9%)	1/31 (3.2%)	0/5 (0%)
			NS	NS	NS
1000–1249	8/325 (2.4%)	3/171 (1.7%)	5/154 (3.2%)	0/6 (0%)	0/1 (0%)
			NS	NS	NS
1250–1499	10/357 (2.8%)	7/280 (2.5%)	3/77 (3.9%)	0/1 (0%)	0/0 (0%)
			NS	NS	NS
Total	43/1081 (4.0%)	11/491 (2.2%)	32/590 (5.4%)	7/80 (8.8%)	3/20 (15.0%)
			$P = 0.012$	$P = 0.006$	$P = 0.006$

Incidence of CP in each condition of ROP was compared with that in cases without ROP. NS: not significant.

**Table 3.** Incidence of Mental Retardation (MR) in Infants With or Without Retinopathy of Prematurity (ROP)

Birth Weight (Grams)	MR/Total	MR/No ROP	MR/ROP	MR/Treated ROP	MR/Cicatrical ROP
≤749	16/126 (12.7%)	1/5 (20.0%)	15/121 (12.4%)	6/42 (14.3%)	3/14 (21.4%)
			NS	NS	NS
750-999	12/273 (4.4%)	1/35 (2.9%)	11/238 (4.6%)	0/31 (0%)	0/5 (0%)
			NS	NS	NS
1000-1249	12/329 (3.6%)	1/171 (0.6%)	11/154 (7.1%)	1/6 (16.7%)	0/1 (0%)
			NS	NS	NS
1250-1499	14/357 (3.9%)	12/280 (4.3%)	2/77 (2.6%)	0/1 (0%)	0/0 (0%)
			NS	NS	NS
Total	54/1081 (5.0%)	15/491 (3.1%)	39/590 (6.6%)	7/80 (8.8%)	3/20 (15.0%)
			<i>P</i> = 0.008	<i>P</i> = 0.032	<i>P</i> = 0.026

Incidence of MR in each condition of ROP was compared with that in cases without ROP. NS: not significant.

al<sup>24</sup> classified very-low-birth-weight infants into four subgroups according to birth weight and showed no association between CP, MR, or hearing loss and ROP. Greisen et al<sup>25</sup> suggested a possible association between ROP and CP between 1976 and 1987. Thus, previous studies disagree as to whether the incidence of neurological handicaps is associated with ROP.

We focused on the association of ROP with CP or MR. Significant associations were found when all cases were analyzed statistically, without regard to the severity of ROP. However, few positive associations were found in each subgroup when analyzed according to birth weight and severity of ROP (Tables 2 and 3). Our study showed weak associations between ROP and CP or MR, similar to those reported by Greggard et al<sup>24</sup> and Takahashi.<sup>26</sup>

Thus, we can conclude that there is a weak association between ROP and CP or MR. Treatment or cicatricial changes of severe ROP in the neonatal period are not necessarily indicative of the development of neurological disorders in childhood.

## References

- Hack M, Fanaroff AA. Changes in the delivery room care of extremely small infants (<750 g): effects on morbidity and outcome. *N Engl J Med* 1986;314:660-4.
- Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. *Arch Ophthalmol* 1990;108:195-204.
- Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: 3½-year outcome—structure and function. *Arch Ophthalmol* 1993;111:339-44.
- Nagata M, Terauchi H, Takeuchi A, et al. Multicenter prospective studies of retinopathy of prematurity. I. Incidence and results of treatment. *Nihon Ganka Gakkai Zasshi (Acta Soc Ophthalmol Jpn)* 1988;92:646-57.
- Reynolds J, Dobson V, Graham Q, Tung B, Robertson J, Flynn J. Prediction of visual function in eyes with mild to moderate posterior pole residua of retinopathy of prematurity. *Arch Ophthalmol* 1993;111:1050-6.
- Cho Y, Saito Y, Omoto T. Retinopathy of prematurity and perinatal factors (Apgar score, fetal distress, intrauterine infection). *Ganki (Folia Ophthalmol Jpn)* 1989;40:1933-8.
- Fielder AR, Robinson J, Shaw DE, Ng YK, Moseley MJ. Light and retinopathy of prematurity: does retinal location offer a clue? *Pediatrics* 1992;89:648-53.
- Flynn JT, Bancalari E, Bowel R, Goldberg R, Cassady J, Schiffman J. Retinopathy of prematurity: a randomized, prospective trial of transcutaneous oxygen monitoring. *Ophthalmology* 1987;94:630-8.
- Saito Y, Omoto T, Cho Y, Hatsukawa Y, Fujimura M, Takeuchi T. The progression of retinopathy of prematurity and fluctuation in blood gas tension. *Graefes Arch Clin Exp Ophthalmol* 1993;231:151-6.
- Shohat M, Reisner SH, Krikler R, Nissenkorn I, Yassar Y, Ben-Sira I. Retinopathy of prematurity: incidence and risk factors. *Pediatrics* 1983;72:159-63.
- Hack M, Fanaroff AA. Outcomes of extremely-low-birth-weight infants between 1982 and 1988. *N Engl J Med* 1989;321:1642-7.
- Hirata T, Epcar JT, Walsh A, et al. Survival and outcome of infants 501 to 750 gm: a six-year experience. *J Pediatr* 1983;102:741-8.
- Johnson A, Townsherd P, Yarkin P, Bull D, Wilkinson AR. Functional abilities at age 4 years of children born before 29 weeks of gestation. *BMJ* 1993;306:1715-8.
- Kitchen WH, Ford GW, Richards AL, Lissenden JV, Ryan MM. Children of birth weight <1000 g: changing outcome between ages 2 and 5 years. *J Pediatr* 1987;110:283-8.
- Saigal S, Szatmari P, Rosenbaum P, Campbell D, King S. Cognitive ability and school performance of extremely low birth weight children and matched term controlled children at age 8 years: a regional study. *J Pediatr* 1991;118:751-60.
- Vohr BR, Garcia Coll CT. Neurodevelopmental and school performance of very-low-birth-weight infants: a seven-year longitudinal study. *Pediatrics* 1985;76:345-50.
- The Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Arch Ophthalmol* 1984;102:1130-4.

18. Saito Y, Hatsukawa Y, Lewis JM, Kioke H, Omoto T, Tano Y. Macular coloboma-like lesions and pigment abnormalities as complications of cryotherapy for retinopathy of prematurity in very low birth-weight infants. *Am J Ophthalmol* 1996;122:299–308.
19. Illingworth RS. The diagnosis of cerebral palsy in the first year of life. *Dev Med Child Neurol* 1966;8:178–94.
20. Sugimoto S, Furukawa A, Hatsukawa Y, Fujimura M, Saito Y, Omoto T. Incidence and therapeutic outcome of retinopathy of prematurity in extremely- and very-low-birth-weight infants. *Rinsho Ganka (Jpn J Clin Ophthalmol)* 1995;49:1101–4.
21. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: one year outcome—structure and function. *Arch Ophthalmol* 1990;108:1408–16.
22. Hack M, Taylor HG, Klein N, Eiben R, Schatschneider C, Mercuri-Minich N. School-age outcomes in children with birth weights under 750 g. *N Engl J Med* 1994;331:753–9.
23. Bowen JR, Starte DR, Arnold JD, Simmons JL, Ma PJ, Ileslie G. Extremely low birth weight infants at 3 years: a developmental profile. *J Pediatr Child Health* 1993;29:276–81.
24. Greggard JB, Lindstrom DP, Parker RA, Culley B, Stahlman MT. Increased survival rate in very low birth weight infants (1500 grams or less): no association with increased incidence of handicaps. *J Pediatr* 1990;117:139–46.
25. Greisen G. ROP in three follow-up studies from Rigshospitalet during the period 1976–1987. *Acta Ophthalmol* 1993;210 Suppl:30–3.
26. Takahashi A, Majima A, Suzuki C, et al. The association between retinopathy of prematurity and chronic general complications. *Rinsho Ganka (Jpn J Clin Ophthalmol)* 1995;49:935–8.