Long-term Neurological Outcome and Neutralizing Antibody Titers against Parechovirus-A3 (PeV-A3) in Children who Developed PeV-A3-Related Diseases in Neonatal and Infantile Periods

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Abstract

Background: Parechovirus-A3 (PeV-A3) causes sepsis and meningoencephalitis in neonates and young infants. We previously reported that 45 neonates and infants had low neutralizing antibody titers (NATs) against PeV-A3 at the onset of disease but developed high NATs at 3 and 6 months of age. Subsequent changes in NATs against PeV-A3 in children who suffered from PeV-A3-related diseases are currently unknown. Additionally, their long-term neurological outcome is not well described in such population. We monitored NATs against PeV-A3 and evaluated their neurological development 3 years after infection who developed PeV-A3-related disease in their neonatal or young infantile periods.
Methods: Subjects were PeV-A3-infected infants less than 4 months in Niigata, Japan during 2013-2014, and follow-up serum samples were obtained longitudinally from the patients at 3, 6 months, 1 and 3 years after the infection. NATs against PeV-A3 were measured using LLC-MK2 cells. Neurological outcomes of the patients were evaluated by their pediatricians at their study visits.
Results: We evaluated 45, 34, 33, 26, and 16 serum samples at onset, 3, 6 months, 1 and, 3 years after the infection, respectively. All 45 serum samples at onset had low NATs against PeV-A3 less than 1:32 which was regarded as a cutoff to prevent PeV-A3 infection. Subsequently, the NATs had elevated to the high level (≥1:512) after the infection in all patients. Three years after the infection, all patients except one achieved normal neurodevelopmental milestones. Only one patient who was diagnosed as severe status epileptics due to meningoencephalitis had developmental delay with difficulties in sitting and walking with support.
Conclusions: This 3-year follow-up study showed that high NATs against PeV-A3 persisted in PeV-A3-infected patients. Except for 1 patient with encephalitis, neurological outcomes were excellent.

Background

- Parechovirus-A3 (PeV-A3) causes sepsis and meningoencephalitis in neonates and young infants (<4 months old).
- We previously reported that maternal antibodies against PeV-A3 may protect them from PeV-A3-related diseases.
- We also showed that all neonates and infants had low neutralizing antibody titers (NATs) against PeV-A3 at the onset of disease but subsequently developed high NATs at 3 and 6 months of age.
- Little data are currently available regarding long-term changes in NATs against PeV-A3 in such patients and their long-term neurodevelopmental outcomes.

Materials & Methods

Sample collection: From the patients who were diagnosed with severe PeV-A3 infection in their neonatal or young infantile periods, serum samples were collected at disease onset, 3 months, 6 months, 1 year, and 3 years after the infection.
Neutralizing antibody titers (NATs) measurement: NATs against PeV-A3 were measured using LLC-MK2 cells.
Virus strain: PeV-A3; A308/99.
Neurological evaluation: Evaluated by general pediatrician at a follow-up visit 3 years after onset.

Results

Table Demographics, diagnosis and neurological outcome of patients with 16 PeV-A3 infection

Case	Sex	Gestational age (weeks)	Birth weight (g)	Age at presentation (days)	Clinical diagnosis	CSF white blood cell count (/μL)	PeV-A3-RNA detection in CSF	3-year neurological outcome
1	M	40	3610	10	Sepsis-like illness	NA	NA	Normal
2	F	38	3156	12	Sepsis	6	Yes	Normal
3	M	39	3324	17	Sepsis	1	Yes	Normal
4	M	39	3574	18	Sepsis	11	Yes	Normal
5	M	38	3000	22	Sepsis	0	Yes	Normal
6	F	39	3038	22	Sepsis	9	Yes	Normal
7	M	42	3972	27	Sepsis	1	Yes	Normal
8	F	39	2984	32	Sepsis	25	Yes	Normal
9	M	38	3136	40	Sepsis-like illness	0	Yes	Normal
10	M	38	2745	48	Septic shock Encephalitis	3	Yes	Abnormal severe psychomotor retardation
11	F	40	3330	51	Sepsis	0	Yes	Normal
12	F	40	3520	51	Sepsis	4	Yes	Normal
13	F	39	3160	59	Sepsis	4	Yes	Normal
14	M	38	3248	66	Sepsis	3	Yes	Normal
15	M	27	916	81	Sepsis	2	NA	Normal
16	M	27	999	83	Sepsis	NA	NA	Normal

PeV-A3, parechovirus-A3; CSF, cerebrospinal fluid; NA, not available; M, male; F, female

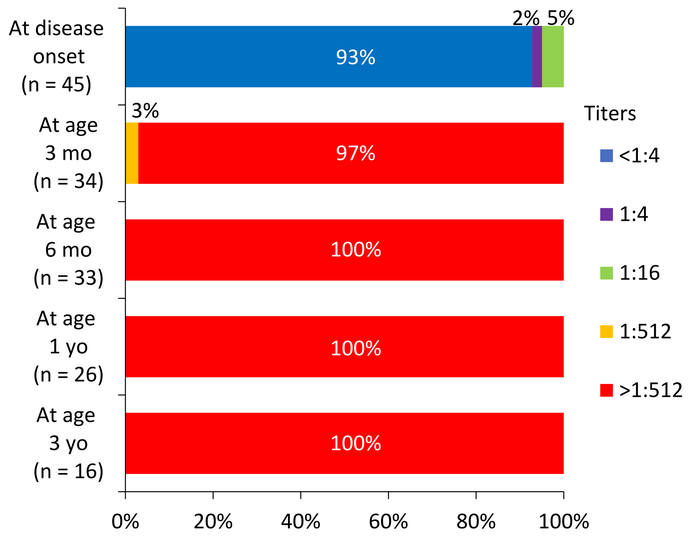

Figure Changes in neutralizing antibodies against parechovirus-A3 (PeV-A3) during the 3 years after the infection in neonatal or young infantile periods

Summary

- All 16 patients who were able to follow for 3 years had high NATs against PeV-A3 3 years after infection.
- Their neurological outcomes at the age of 3 years were age-appropriate except for 1 patient with septic shock and encephalitis who has a sever psychomotor retardation.

Conclusions

- Neutralizing antibody titers (NATs) against parechovirus-A3 (PeV-A3) remained high in PeV-A3-infected children for at least 3 years after infection.
- All patients thrived after infection, except for 1 patient with septic shock and encephalitis.
- Further follow-up of NATs and neurological development in this cohort will help clarify the changes of humoral immunity and the long-term outcomes of PeV-A3 infection.