Diagnostic Methods for and Clinical Pictures of Polyomavirus Primary Infections in Children, Finland

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We used comprehensive serodiagnostic methods (IgM, IgG, and IgG avidity) and PCR to study Merkel cell polyomavirus and trichodysplasia spinulosa-associated polyomavirus infections in children observed from infancy to adolescence. Comparing seroconversion intervals with previous and subsequent intervals, we found that primary infections with these 2 viruses were asymptomatic in childhood.

Two novel human polyomaviruses can cause skin diseases that are predominant in immunosuppressed persons. Merkel cell polyomavirus (MCPyV) is associated with Merkel cell carcinoma, which is an uncommon aggressive skin cancer, and trichodysplasia spinulosa-associated polyomavirus (TSPyV) is associated with trichodysplasia spinulosa, which is a rare skin disorder (1–3). In contrast with nulosa, which is a rare skin disorder (1–3), TSPyV is associated with trichodysplasia spinulosa, and trichodysplasia spinulosa-associated polyomavirus infections in children observed from infancy to adolescence. Comparing seroconversion intervals with previous and subsequent intervals, we found that primary infections with these 2 viruses were asymptomatic in childhood.

Of the 144 children, 45 (31%) showed IgG seroconversion for MCPyV and 39 (27%) for TSPyV. Before they were 1 year of age, 4 children showed IgG seroconversion for MCPyV at 0.68–0.94 year of age, 1 child showed seroconversion for TSPyV at 0.80 year, and another child showed MCPyV IgG, IgM, and low avidity of IgG in the first sample, which was collected at 0.63 year (online Technical Appendix Table 2). None of these children who
seroconverted early in life showed maternal IgG to the corresponding virus. Comparing participants at 0–1 year of age with those at 9–13 years, the seroprevalence for MCPyV caused by acquired infections rose from 3.4% to 65% and for TSPyV, from 0.7% to 53%. Seroconversions for each virus continued throughout the study (Figure).

Of the 45 children who seroconverted for MCPyV, 28 (62%) showed additional markers of primary infection at the time of IgG seroconversion: IgM was present in 15 (33%), and low avidity of IgG was detected in 23 (51%). Of the 39 TSPyV–seroconverted children, 32 (82%) showed corresponding markers: IgM in 30 (67%) and low avidity of IgG in 13 (29%). Samples did not show MCPyV viremia at or flanking the seroconversion, and TSPyV viremia was observed at low quantity (<10⁴ copies/mL) in the samples of 2 who seroconverted. Except 4 seroconverters for MCPyV and 1 for TSPyV, all showed long-term maturation of IgG avidity to the corresponding virus.

Maternal IgG showed in 10 (22%) of the 45 who seroconverted for MCPyV and in 12 (31%) of the 39 for TSPyV at sampling ages of 0.23–0.62 year; these maternal IgGs were no longer discernable at 0.49–1.07 year. After the first year of life, the age at seroconversion with either virus did not appear to correlate with the presence or absence of maternal antibodies.

To determine clinical correlates of MCPyV and TSPyV primary infections, all infection-related symptoms and illnesses during the seroconversion interval were compared with those during the previous or subsequent interval for each patient who seroconverted (Table). Infection-related symptoms during the seroconversion interval were reported for 73% of children who seroconverted for MCPyV and for 82% of those who seroconverted for TSPyV. The occurrences of symptoms, however, were not notably different from those during the previous or subsequent intervals. Exanthema was reported in 7 (15.9%) children at the MCPyV seroconversion interval and in 1 child in each of the adjacent periods (2.2% before, 2.3% after). However, the differences were not statistically significant (p = 0.0703).

Conclusions

The seroprevalence of MCPyV and TSPyV among children ≤13 years of age increased because of acquired infections, a finding consistent with reports that primary infections with these 2 viruses are ubiquitous in childhood (5, 7). The seroprevalence of these viruses had not reached a plateau by the end of study; thus, some infections are expected to occur later than 13 years of age. We expect that some children have become infected with these viruses after exiting the study.

For both viruses, prevalence of maternal antibodies during infancy was high, supporting recent findings by Martel-Jantin et al. (10). Although the age of the child at seroconversion did not appear to correlate with the presence of maternal antibodies, these antibodies were absent from children who showed viral infection during infancy, raising the possibility that maternal immunity may protect infants from infection by these viruses. However, the prevalence of MCPyV infection among infants was higher than that of TSPyV, possibly caused by MCPyV shedding from parental skin (10–12).

We did not observe any symptom associated with the time of seroconversion for these 2 viruses, which implies that primary exposures to these viruses during childhood cause no symptoms. When studying MCPyV infections in adult men who seroconverted, Tolstov et al. also found no clinical associations (13). Their observations and ours in the current study of MCPyV and TSPyV support...
the common notion that the prototypic human PyVs, BKPyV and JCPyV, also establish persistence without initial signs (14,15).

Exanthema, a common sign of skin infection, did not appear infrequently during MCPyV seroconversion; however, the rate did not reach statistical significance (p = 0.0703), which might be related to our limited cohort size. We cannot rule out that data for some transient skin-related signs may not have been captured during periodic patient interviews. Last, we do not believe that our study represents polyomavirus infections during childhood worldwide. Larger studies of more geographically diverse populations are needed to determine whether primary infection with MCPyV or TSPyV is always asymptomatic.

Although IgM and low-avidity IgG were observed in more than half of the seroconversion samples, the frequency of viremia was extremely low, indicating serodiagnosics as the strategy of choice in diagnosing primary infections with MCPyV and TSPyV. Our study suggests that these ubiquitous polyomaviruses circulate silently among children.

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Ms Chen was a PhD student at the University of Helsinki when conducting this study, and is now a postdoctoral researcher at Albert Einstein College of Medicine, Bronx, New York, USA. Her research interests are development of comprehensive diagnostics for the emerging human DNA viruses, including polyomavirus and anellovirus.

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Technical Appendix

Distribution of Outcomes of Serodiagnostic Methods

Technical Appendix Table 1. Distribution of outcomes of serodiagnostic methods used to detect polyomavirus primary infections in children, Finland, January 2011–July 2013

| Sample parameters | All participants, N = 144 | MCPyV, n = 45 | TSPyV, n = 39 | Total, n = 74 |
|-------------------|---------------------------|---------------|---------------|--------------|
| Serum samples, no. per child | 1,929 | 665 | 563 | 1,081 |
| Mean | 13 | 15 | 15 | 15 |
| Median | 12 | 15 | 13 | 13 |
| Range | 8–27 | 8–24 | 8–27 | 8–27 |
| Age at sampling initiation, y | | | | 0.37 |
| Mean | 0.36 | 0.36 | 0.37 | 0.37 |
| Median | 0.31 | 0.32 | 0.30 | 0.32 |
| Range | 0.20–0.91 | 0.22–0.79 | 0.20–0.60 | 0.20–0.79 |
| Age at sampling end, y | | | | 6.48 |
| Mean | 5.77 | 6.50 | 6.03 | 6.03 |
| Median | 5.07 | 6.03 | 6.03 | 5.98 |
| Range | 2.56–12.48 | 3.46–10.51 | 3.46–12.48 | 3.46–12.48 |
| Sampling interval, age <2 y, mo. | | | | 3.73 |
| Mean | 3.65 | 3.74 | 3.68 | 3.73 |
| Median | 3.23 | 3.27 | 3.23 | 3.25 |
| Range | 1.5–16.13 | 2.03–16.13 | 2.03–8.53 | 2.03–16.13 |
| Sampling interval, age >2 y, mo. | | | | 6.35 |
| Mean | 6.35 | 6.24 | 6.41 | 6.35 |
| Median | 6.03 | 6.00 | 6.10 | 6.03 |
| Range | 2.13–28.3 | 2.77–18.20 | 2.47–19.40 | 2.47–19.40 |

Technical Appendix Table 2. Serologic data of children showing or TSPyV primary infections before 1 year of age, Finland, January 2011–July 2013

| Subject no. | Sample no. | Age, y | IgM | IgG | IgG avidity |
|-------------|------------|-------|-----|-----|-------------|
| MCPyV       |            |       |     |     |             |
| #47         | 1          | 0.27  | 0.010 | 0.045 | ND          |
|             | 2          | 0.87  | 0.021 | 2.003 | 24.1        |
| #118        | 1          | 0.41  | 0.009 | 0.012 | ND          |
|             | 2          | 0.80  | 0.251 | 2.697 | 19.4        |
| #147        | 1          | 0.42  | 0.064 | 0.009 | ND          |
|             | 2          | 0.68  | 0.026 | 0.516 | 14.9        |
| #186        | 1          | 0.48  | 0.009 | 0.013 | ND          |
|             | 2          | 0.74  | 0.482 | 0.021 | ND          |
|             | 3          | 0.94  | 0.222 | 1.386 | 13.5        |
| #167        | 1          | 0.63  | 0.320 | 0.568 | 4.5         |
|             | 2          | 1.10  | 0.054 | 0.652 | 26.5        |
| TSPyV       |            |       |     |     |             |
| #157        | 2          | 0.49  | 0.023 | 0.010 | ND          |
|             | 3          | 0.80  | 0.071 | 2.317 | 54.7        |

*MCPyV, Merkel cell polyomavirus; TSPyV, trichodysplasia spinulosa-associated polyomavirus; ND, not detected.