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Testing for Herpesvirus Infection Is Essential in Children with Chromosomal-Instability Syndromes

Petra Lankisch,[a] Heiko Adler,[b] Arndt Borkhardt[a]

Department of Pediatric Oncology, Hematology, and Clinical Immunology, Medical Faculty, Center of Child and Adolescent Health, Heinrich Heine University, Dusseldorf, Germany[a]; Research Unit Gene Vectors, Helmholtz Zentrum München—German Research Center for Environmental Health, Munich, Germany[b]

In a set of very elegantly performed experiments, applying infection of ataxia-telangiectasia (A-T)-mutated kinase (ATM)-deficient mice with murine gammaherpesvirus 68 (MHV-68), Kulinski et al. (1) have demonstrated that the function of ATM is necessary for an optimal adaptive immune response against gammaherpesvirus infection. Their data provide excellent experimental evidence for a long-standing clinical observation, namely, the puzzling fact that children with ATM deficiency (A-T disease) often show high copy numbers of Epstein-Barr virus (EBV) in their peripheral blood. We support the interference of the authors that ATM might be relevant not only for controlling EBV replication but also for proper immune response against herpesviruses in general. Among our patients, EBV is demonstrated almost routinely but human herpesvirus 6 is also by no means rare (Table 1).

Ataxia-telangiectasia (A-T) is a rare disease, with an incidence of 1 in 40,000 to 100,000 people worldwide; however, many of these cases are concentrated in large pediatric centers where the staff gain extensive experience with this and similar syndromes. Thus, we would like to call attention to the existence of more literature on the investigation of herpesvirus infection in children with chromosomal instability syndromes (e.g., Masucci et al. [2], Okano [3], Okano and Gross [4], and Reyes et al. [5]) than just the one case report by Folgori et al. (6) which was cited by the authors.

Based on our own experience and that of other pediatricians well versed in this field, we would like to make three practical points.

1. While active EBV replication may obviously end up in significant clinical problems in patients with chromosomal instability syndromes, other herpesvirus infections may also become clinically relevant and should not be overlooked in the diagnostic workup.
2. In a considerable proportion of cases, however, the initial clinical signs of A-T are so mild that they can be missed. Therefore, all patients with unexplained EBV lymphoproliferation should be investigated for A-T so that those in whom it is detected can be invited to attend the recommended cancer surveillance program at appropriate intervals.
3. If a child with A-T develops a lymphoma or other cancers, careful histopathological and virological evaluation of the tumor sections should be performed. This may help to gain deeper insight into the role of herpesviruses in cancer development, particularly in those with a DNA-damage-response-deficient background.

Address correspondence to Petra Lankisch, petra.lankisch@med.uni-duesseldorf.de.

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TABLE 1 Cases of herpesvirus infection in children with chromosomal instability syndromes, diagnosed since 2006 at the Department of Pediatric Oncology, Hematology, and Clinical Immunology, Dusseldorf[a]

Patient no.	Disease	Gender	Age (yr) at time of diagnosis of herpesvirus infection	Demonstration of viral load	
				EBV (k/μg DNA)	HHV6 (k/ml)
1	A-T	Female	12	Positive (75–197)	Positive (62,000–112,000)
2	A-T	Male	7	Positive (10–28)	Positive (1,820,000–52,800)
3	A-T	Female	13	Positive (153)	Negative
4	A-T	Female	14	Positive (289–107)	Positive (190)
5	A-T	Male	18	Positive (14–78)	Negative
6	NBS	Male	11	Positive (143)	Not tested

[a] Abbreviations: A-T, ataxia-telangiectasia; EBV, Epstein-Barr virus; HHV6, human herpesvirus 6; NBS, Nijmegen breakage syndrome.

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