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Human parvovirus 4 (PARV4) in the blood supply and transmission by pooled plasma derived clotting factors: does it matter?

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The paper by Sharp et al in this issue of Transfusion reports the transmission of human parvovirus 4 (PARV4) by "virus-inactivated" plasma pool-derived clotting factors, demonstrating that infection by non lipid-membrane viruses continues to be a concern for hemophiliacs and other recipients of such products [1]. While the inactivation of lipid enveloped viruses such as HIV and HCV by solvent/detergent and/or heating now used in the manufacture of plasma derivatives is highly effective, such treatments (at least as performed before 1992) were not sufficient to prevent the transmission of PARV4 [1]. Recipients of non-pooled (from a single or few donors), non-inactivated, blood products such as plasma or platelets, while at lower risk of receiving a PARV4 containing transfusion, must also be exposed to this recently characterized virus.

B19V is the prototypic human parvovirus of concern for recipients of blood component transfusions and plasma derivatives. B19V is a known human pathogen capable of causing fetal hydrops and developmental abnormalities in children, arrest of erythropoeisis in patients with sickle cell anemia or hereditary spherocytosis, and chronic anemia in AIDS patients [2,3]. The risk of B19V infection in high-risk recipients of pooled plasma derivatives (e.g., B19V sero-negative pregnant women, patients with chronic anemias, AIDS patients) is currently attenuated by removal of high viral load B19V donations (detected by low-sensitivity PCR tests) from plasma pools [4,5]. Plasma units with low titer of B19V virus are tolerated with the assumption that infectivity is neutralized in large plasma pools by the anti-B19V antibodies present in approximately half of adult donors. The high sero-prevalence in the blood donor population results from childhood infections which cause common minor childhood rash erythema infectiosum or slapped cheek syndrome. B19V transmission through whole blood derived components, while rare[6], can cause symptoms in recipients [7], however screening for B19V is not generally performed due to the low risk of transmission and rarity of serious outcomes[4,7,8].

PARV4 was initially identified by viral metagenomic analysis of plasma from an injection drug user with symptoms related to those of primary HIV infection but who was found to be HIV RNA negative [9]. Related viruses have since been found in chimpanzees [10], baboons [10], bats [11], sheep [12], pigs/boars [13,14] and cows [14], with genetic relationships among them that parallel the phylogeny of their host species consistent with long term virus-host co-evolution (Sharp et al., 2010). These viruses can be classified into a distinct genus within the *Parvoviridae* family with a proposed name of *Partetravirus* [12]. Numerous studies have reported PARV4 DNA in human plasma for transfusion [15–18], plasma pools for the production of blood derivatives [19,20], and in purified coagulation factors [21–23]. Viral load, while typically low (often necessitating nested PCR for detection), but can also reach levels as high as 5×10^8 virions/ml during acute infection [24]. Beside its detection in plasma, PARV4 has also been reported in bone marrow[25–27], liver [28], skin[29], as well as other

organs[25]. PARV4 infections have been reported in the US [9], UK [15,16,21,27], Italy [25,26,29], Thailand [17], China [20,30], Ghana [31], Nigeria, and Congo [32].

Similar to B19, genetic analyses have revealed the presence of three PARV4 genotypes differing in their amino acids by 2.7–2.9% in the non-structural protein and 1.4–2% in their VP1 capsid proteins [31,32]. As for B19, where one genotype (B19-gt3) is mostly limited to Africa, the distribution of the PARV4 genotypes also varies geographically with PARV4-gt3 so far restricted to sub-Saharan Africa [31,32]. As for B19V [33], the DNA of the different genotypes of PARV4 can be amplified from human tissues even when undetectable in plasma[27,28]. PARV4, similar to B19V [34–37] can also be frequently detected at very low level in plasma of immuno-competent subjects indicating that tail-end viremia may be produced for extended periods of time following primary infection [15,29,38]. Such persistent detection of parvoviral DNA in tissues may reflect ongoing low-level replication or the formation of highly stable viral nucleic acids deposited in the skin and other tissues [33]. Sustained high titers of antibodies and high frequency of T cells responses to PARV4 are consistent with ongoing viral replication [39] as previously reported for B19V [37]. The genotypes of the B19V and PARV4 persisting in human tissues have been shown to differ by age, with, for example, B19-gt2 confined to people born before 1973 while B19-gt1 now predominates in younger subjects[27,33]. This phenomenon has been dubbed the “bioportfolio”, as it is thought to reflect a subject’s prior infectious history[33] and, at the population level, to result from epidemics of different parvovirus genotypes in temporal waves over large geographic regions, with virus becoming deposited for life in the tissues of the contemporaneously infected populations [33]. The limited genetic diversity within PARV4-gt1 which dominates in the younger European and US populations indicate that PARV4-gt1 may also have been only recently introduced into these populations [40]. It is well documented that highly infectious parvovirus can rapidly colonize new animal hosts worldwide, as happened with canine parvovirus 2 (CPV2) in the late 1970s and with subsequent CPV2 variants displacing earlier strains[41,42].

Serological assays for PARV4 have been developed and serosurveys have shown that infections in developed countries are strongly associated with HIV and HCV infections, the much higher prevalence observed specifically in injection drug users (IDU) indicates that blood-blood contact is the principal cause of PARV4 transmission [17,26,27,30,43–46]. Outside of Western countries, other parenteral transmission routes are suspected; for example, elderly Cameroonians are frequently seropositive for PARV4 but in this case was associated with injections for antimalarial drugs, streptomycin or contraceptives [47]. PARV4 was also shown to be transmitted through the placenta [48], and seropositivity was high in hemodialysis and HBV infected patients[30,49]. In contrast, seroprevalence of PARV4 infection was not higher in homosexuals who did not inject drugs than in heterosexuals in the same populations [40]. It is possible that the global distribution of PARV4 is a recent phenomenon associated with some of the same demographic factors that facilitated the spread of HIV and HCV[27,40,44].

Blood borne transmission is an unusual mode of transmission for parvoviruses, that are more typically transmitted by aerosol (eg B19V and HBoV1) or by the oral-fecal route for animal parvoviruses such as CPV2 (18, 44) and possibly for human HBoVs 2–4 which are detected almost exclusively in feces[50]. HBoV1 also has a short viremic phase associated with respiratory symptoms [51]. However, in contrast to the restriction of PARV4 infection to those exposed to parenteral routes of transmission in developed countries, PARV4 exposure was extremely high in the general population is several African countries (Cameroon, Burkina Faso and Democratic Republic of Congo, respectively showed PARV4 sero-prevalence of 25%, 37% and 35%), observations that strongly suggests a different mode of transmission [52]. Furthermore, infants from Ghana showed a PARV4 viremia frequency of

8% (all gt3), higher than in older then younger children and clearly indicative of a different mode of transmission. Respiratory or oral/fecal routes of PARV4 transmission may potentially be more efficient in very young children [31].

Although it is clear that PARV4 can be transmitted through exposure to blood and plasma-derived products whether PARV4 is a human pathogen that needs to be excluded from plasma pools or even non-pooled blood components remains uncertain. PARV4's original detection was in a homeless daily IDU with symptoms similar to other viral infections (fatigue, night sweats, pharyngitis, neck stiffness, vomiting, diarrhea, arthralgias, and confusion) [9]. Nested PCR testing of a larger set of such patients with related symptoms (suspected acute HIV infection but HIV RNA and antibody negative) showed a PARV4 DNA prevalence of 6%. Using the same nested PCR, 2% of healthy blood donors from California (a significantly lower prevalence) were also PARV4 DNA positive[15]. The higher prevalence of PARV4 DNA in symptomatic individuals may indicate that PARV4 infections can be pathogenic but may also simply reflect a higher rate of prior exposure to blood borne viruses resulting in more frequent chronic infections including PARV4. Two of nine hemophiliacs undergoing primary PARV4 infection showed exacerbation of their hepatitis [1]. PARV4 was also detected in Taiwanese newborns with hydrops, where 4/5 mothers were positive for anti-PARV4 IgM and PARV4 gt2 DNA was found in 5/6 patients [48]. More worrisome was the detection of PARV4 using viral metagenomics in the cerebral spinal fluid of 2 of 12 Indian children with encephalitis of unknown etiology where the one PARV4 DNA positive patient tested was also anti-PARV4 IgM positive and IgG negative indicating a recent infection[53].

Arguing against common and severe pathogenicity for PARV4 is the absence of severe symptoms in two HCV infected IDU undergoing PARV4 seroconversion [54], and the frequent detection of PARV4 in healthy blood donors and plasma pools (all collected from non-febrile, asymptomatic donors) [15–17,19–22,29]. The detection of PARV4 DNA in healthy children from Ghana also argues against severe disease, at least in a large fraction of recently infected subjects [31]. PARV4 is frequently detected in HCV and/or HIV infected donors (1–8) and its impact on the pathologies caused by these co-infections has begun to receive attention. HCV infection outcome was not affected by PARV4 seropositivity [55]. The emergence of early HIV related symptoms was significantly associated with anti-PARV4 antibodies detection [55] although the large fraction of PARV4-HIV-HCV co-infections and injection drug usage in that group complicates a definitive link of PARV4 to HIV disease acceleration[45].

It seems clear that blood product transfusions frequently expose recipients to highly prevalent viruses such as the ubiquitous and highly genetically diverse anelloviruses and the flavirus GBV-C resulting in chronic infections. Exposure during transfusion can even result in transmission of these viruses [56]. Such transfusion events are tolerated because of the lack of demonstrated pathogenicity of these viruses, very high viremia frequencies in donors, and for anelloviruses the recognition that nearly universal exposure occurs in infants and young children [57,58]. Although transfusion-transmitted B19V infections continue to occur from blood components, clear evidence of its pathogenicity led to the exclusion of high B19V titer donations from plasma pools derivatives. It took 6 years after its initial discovery in 1975 [59] to uncover B19's first association with disease when its role in causing hypoplastic crisis in sickle cell anemia was revealed [60,61]. Potential disease associations for PARV4 currently include encephalitis [53], fetal hydrops [48], and hepatitis [1]. Decisions on whether to initiate steps to reduce or exclude PARV4 from blood components and manufactured products are entirely dependent on future studies to investigate these links or reveal other ones. For example, ongoing epidemiological studies of encephalitis could re-test unexplained cases for PARV4 DNA and anti-PARV4 antibodies to determine if recent sero-

conversions occurred at higher frequencies in cases versus matched healthy controls. Similar studies could also be applied to individuals with unexplained fever or hepatitis and with chronic arthritis (a condition linked with B19V infection) [62]. Given its widespread distribution, it seems likely disease associations of PARV4 infection will be restricted to a small subset of highly susceptible individuals, perhaps those with overt immunological deficiencies or genetic polymorphisms in innate and intrinsic defense pathways that are increasingly recognized as underlying much of the variability in outcomes of infectious diseases [63]. Severe cases of PARV4-associated diseases may therefore benefit from in depth host genetic analyses, particularly of loci associated with innate immune responses to viruses.

There are no cell lines currently known to amplify PARV4. Quantitation of PARV4 infectivity in antibody positive and negative samples, following different virus inactivating treatments used for the manufacture of plasma products or to generically inactivate all viruses in blood products for transfusion[64–66], therefore remain unfeasible. The ability to culture PARV4 or to express infectious particles for infectivity measurements would greatly facilitate PARV4 inactivation studies and determine its susceptibility to cross-neutralization by antibodies to different genotypes or in plasma pools.

For the immediate future PARV4 is likely to remain under suspicion as a cause of different symptoms in subsets of infected individuals. Determining what disease association exists and for what susceptible populations, are some of the issues that will determine whether costly measures testing and excluding PARV4 positive donations from the blood supplies should be implemented.

Further progress in virus discovery will continue to yield previously un-recognized viral genomes whose risks to the safety of the blood supply will be initially unknown. The ability to rapidly test large numbers of banked blood samples or plasma pools for viral nucleic acids and antibodies in people of different age strata, geographic origins, and high levels of exposure to blood (IDU, hemophiliacs and thalassemia patients) will facilitate evaluation of the potential risks of these viruses to the safety of the blood supply. Coordination and collaborations between blood banks, clinical researchers, and laboratory scientists world-wide will be required for a rapid and balanced response to the detection of novel blood-borne viruses [67–72].

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