Review Article

Application of Biosensors in Diagnosis of Human Parvoviruses

Fatemeh Hosseini[1,2], Milad Zandi[3], Emad Behboudi[4], Shokrollah Salmanzadeh[5], Azadeh Rasooli[6], Aida Abbasi[3], Samaneh Abbasi[7*]

ABSTRACT

Human parvovirus B19 is a viral pathogen that causes acute and usually self-limiting disease. Because the B19 virus predicates erythroid progenitor cells, it can cause a transient aplastic crisis in immunocompromised individuals. This infection has been associated with nonimmunologic fetal hydrops during pregnancy; also, B19 can persist for months in immunocompromised individuals. In B19 infection, viremia with a high titer is observed for approximately one week. After that, a specific immune response is critical to control the infection. Although molecular and serologic tests commonly diagnose the B19 virus, laboratory diagnostic tests have limitations. For the detection of human parvovirus B19, an inexpensive, effective, and rapid biosensor may be considered as an alternative.

KEYWORDS: Human Parvovirus B19, Biosensor, Molecular and Serological Diagnosis.

INTRODUCTION

Human parvovirus B19 is an unenveloped and small virus with a linear ssDNA (5 to 6 kb) encoding two capsid proteins (VP2 & VP1) and a single non-structural protein (NS1) required for viral replication[1]. The virus belongs to the Parvoviridae family and is a common human pathogen that can cause asymptomatic infection and various clinical symptoms such as erythema infectiosum (EI), fetal hydrops, transient aplastic crises after infection, and arthropathy in patients[2,3]. Human parvovirus B19 can replicate in erythroid progenitor cells, resulting in B19 infection and viremia with a broad spectrum of human parvovirus B19 titers lasting from a few days to several months[4,5].

Some clinical manifestations, such as arthropathy, anemia, and rash, also occur with other infections; therefore, a differential diagnosis is required to detect the presence of the B19 virus[6]. Many studies have shown that viral DNA or viral proteins can detect B19. Viral DNA is found in many healthy and dysfunctional tissues, suggesting that B19 infection persists in tissues throughout life[1]. On the other hand, the prevalence and transmission of the B19 virus are common worldwide in people of all ages, from children to adults. Transmission occurs via the respiratory tract, blood products with symptoms such as fever, malaise, headache, and myalgia, and also from mother to fetus with severe fetal anemia and fetal death[7-9]. Because B19 infection can spread and break out relatively quickly, control and prevention of the disease is an important issue. However, there are several laboratory diagnoses for B19, and early detection techniques are needed to control the spread of the virus, especially in children, pregnant women, and immunocompromised individuals. A biosensor is a device that can be used for disease detection and diagnosis, as well as environmental, medical, water, and food applications. Viral biosensors enable inexpensive, sensitive, and rapid diagnostic testing[10-12]. Therefore, in this review, a simple and reliable method for the detection of the B19 virus using a biosensor is presented.

Human parvovirus B19 detection methods and limitation

Antibodies, antigens, nucleic acid tests, DNA detection, and B19V cultures are used in laboratories to detect B19 infection (**Table I**)[13]. The most reliable test for acute B19 infection is antibody detection in serum, measuring IgM, which occurs a few days after clinical symptoms, and IgG, a marker of past infection[14]. B19-specific IgA and IgE antibodies have also been detected in human serum and sera but

[1]*Department of Applied Cell Sciences, School of Advanced Technologies on Medicine, Tehran University of Medical Sciences, Tehran, Iran.*
[2]*Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Technologies on Medicine, Tehran University of Medical Sciences, Tehran, Iran.*
[3]*Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.*
[4]*Department of Microbiology, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran.*
[5]*Infectious and Tropical Diseases Research Center, Health Research Institute, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Tehran, Iran.*
[6]*Department of Biochemistry, Faculty of Sciences, Payame Noor University, Tehran, Iran.*
[7*]*Department of Microbiology, Faculty of Medicine, Abadan University of Medical Sciences, Abadan, Iran.*
***Correspondence:** s_abbasi80@yahoo.com*
doi: 10.22442/jlumhs.2023.01006
Received: 22-12-2022 Revised: 23-01-2023
Accepted: 26-01-2023 Published Online: 02-03-2023

cannot be used to diagnose acute infection[15]. Due to the lack of antibody production, DNA detection is routinely used. At a very early stage, DNA detection is performed in the respiratory tract and blood by PCR and in cells and tissues by in situ hybridization[16]. Following the epidemic spread of real-time PCR in clinical laboratories, the novel high-resolution melting (HRM) analysis is being finalized as a rapid, cost-effective, and efficient laboratory method[17]. Antigen detection methods include monoclonal antibodies in EIAs, radioimmunoassays, and immunoblot assays, but they are not sensitive or reliable for detecting acute infections[18].

On the other hand, immunohistology can be a helpful antigen detection method for localizing viral particles in individual host cells in tissues by electron microscopy. Antibodies are used in immunohistochemistry (IHC), immunocytochemistry (ICC), and immunofluorescence (IF) to obtain visual information about the abundance of viral proteins[19]. Apart from these methods, technical developments must be advanced in both directions. First, point-of-care lab-on-a-chip devices are being developed to perform amplification and detection in a single device. Then, a novel array-based assay for B19 detection will be created. As a result, next-generation sequencing methods are being developed to screen for all pathogens present in a sample[20]. It should be noted that most of these laboratory diagnostic tests do not have high sensitivity at low B19 viral loads, and there is no cell culture system in the routine diagnostic laboratory to grow the virus.

Biosensors

Detecting biomolecules is essential in medical fields such as diagnostics and developing new drug molecules. Since Leland C. Clark's first stimulating study on biosensors in 1962, numerous studies have been approved[21]. Biosensors, used in various critical applications such as genetic engineering, sequencing, and disease diagnosis, are machines that identify gas molecules when screening chemical signals in biological cells. In addition, biosensors are potent tools for biohazard screening and fundamental research[22].

Biosensors for pathogen diagnosis are rapidly evolving. The specificity of a biosensor for target analytes determines its success. For analyte detection, a biosensor for viral infection diagnosis requires the effective immobilization of antibodies, aptamers, nucleic acids, or peptides on the surface of a transducer (**Figure I**)[23]. The transducer can convert biological signals into electrical or optical signals. In electrochemical biosensors, the analyte interacts with a sensing layer, resulting in an electrical pulse proportional to the concentration of the analyte. Biosensors are classified into different categories based on signal transduction[24]. Today, voltammetric, conductometric, calorimetric, optical, enzymatic, immunological, piezoelectric, DNA sensors, impedimetric, amperometric, and potentiometric sensors convert sensor data into a measurable signal based on this principle[21]. Incorporating nanoparticles in biosensors improves parameters such as validity, reliability, lower detection limit, retention time, sensitivity, stability, etc. Gold nanoparticles (GNPs) have recently been used in platforms to improve diagnostic sensitivity. GNPs have unique diagnostic properties such as stability, high biocompatibility, unique electronic properties, and fascinating electron transfer potential[25]. Today, there are numerous studies on biosensors for bacterial pathogens but few on biosensors for viral pathogens. Biosensors have been developed for Zika virus[26], swine and avian influenza[27], Ebola virus[28], dengue virus[29], and coronavirus-19[30]. For example, a magnetic bead-mediated surface plasmon resonance (SPR) biosensor platform for HIV-1 protease or viral load in blood has been reported, and a fibre-optic localized surface plasmon coupled fluorescence (LSPCF) biosensor for detection of hemagglutinin protein in influenza virus. A field effect transistor (FET) has also been developed for Ebola virus detection. In addition to these platforms, plasmonic photothermal (PPT) and localized surface plasmon resonance (LSPR) biosensors, in which sensor transduction occurs on a single gold nanoisland (AuNI) chip, are also helpful. Finally, paper-based multiplexed colourimetric (MPBC) sensors are the most popular point-of-care devices[24].

Biosensors for parvoviruses diagnosis

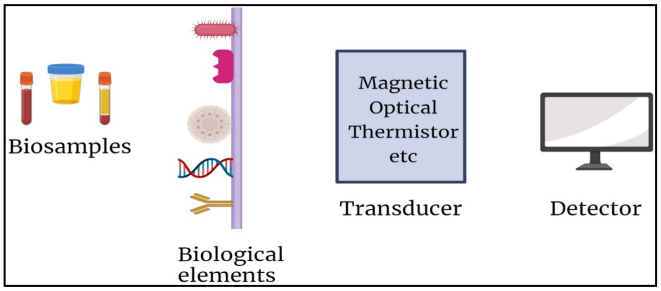
A biosensor is a portable analytical device detecting at least one biological or chemical substance[31]. Biosensors allow the detection of viral diseases in a sensitive, rapid, simple, and inexpensive manner[32]. Biosensors are distinguished according to the type of biological detection element or the type of physicochemical conversion. Depending on the type of transducer, biosensors are divided into optical, piezoelectric, electrochemical, and thermal biosensors[33].

The development of a B19 virus biosensor platform can be divided into three phases; 1) detection of various bioreceptors such as B19 DNA or proteins, human immunoglobulins, and human microRNA (miRNA); 2) hybridization detection methods such as electrochemical, piezoelectric, colourimetric, fluorescent, magnetic, and acoustic technologies, and 3) use of an immobilized bioreceptor such as a DNA probe, ligand, enzyme, antibody/antigen[34].

Table I: Human parvovirus B19 detection methods

		Technique	Time	Sample
Viral diagnosis	Antigen detection	* Counter immunoelectrophoresis * Immuno electronmicroscopy * Radioimmunoassay * Enzyme immunoassay * Blot immunoassay * Receptor-mediated hemagglutination	as soon as possible after the clinical presentation of the diseases	serum, bone marrow aspirates, cord blood samples, amniotic fluid samples and biopsy specimens of the placenta and fetal tissues
	Genome detection	* dot-blot hybridization assay * Microwell hybridization assay * in situ hybridization assay * amplification assays		
Serological diagnosis		* radioimmunoassay * enzyme immunoassay * Immunofluorescence	* IgM antibodies: the second week after viral infection to 4–6 months * IgG antibodies: persist for years	serum

Figure I: Various components of a biosensor for the B19 virus



DISCUSSION

Kim et al. used the quartz crystal microbalance (QCM) biosensor and ProLinkerTM B to rapidly diagnose parvovirus infection in dogs with 95.4% sensitivity and 98% specificity. They used ProLinkerTM B to bind antibodies to a quartz surface coated with gold in a regular pattern and in the correct orientation to attach to the antigen[35]. Mirasoli M et al.[36] developed a miniaturized multiplex biosensor for parvovirus B19 genotyping using a microfluidic oligonucleotide array and lensless chemiluminescence (CL). No cross-hybridizations between B19 genotypes were detected, and DNA-DNA hybridization reactions between sequences with different degrees of homology evaluated the assay's specificity. Another study developed a novel amperometric genosensor to rapidly detect parvovirus DNA from naturally infected dogs in faecal smears. Khatri R et al.[37] developed a biosensor that detects single-stranded genomic DNA (ss gDNA) isolated from a CPV vaccine strain in the 1.0-12.0 ng/l at 25°C for 10 min. Subsequently, the genobiosensor was used to detect CPV viral DNA in faecal swabs from naturally infected dogs. The detection limit of the sensor (LOD) was 1.0 ng/l of faecal viral DNA. In a study by Yamakawa AC 2023[38] AuNPs with antibody deposition were used to identify the presence of CPV-2 in stool samples. It has been demonstrated that AuNPs can be used with monoclonal and polyclonal antibodies, and combining both antibodies with LSPR can provide a reliable diagnosis compared to other molecular methods.

CONCLUSION

Biosensing technologies have been used as novel diagnostic tools for diagnosing viral pathogens. As susceptible instruments, biosensors provide results in a fraction of the time required by conventional methods. Because B19 diagnosis plays an essential role in infection control and public health interventions, developing a biosensor may be a crucial tool in detecting B19 infection; however, further research on parvoviruses is needed in this area.

Ethical Permission: Abadan University REC letter No. IR.ABADANUMS.REC.1400.108.

Conflict of Interest: No conflicts of interest, as stated by authors.

Financial Disclosure / Grant Approval: No funding agency was involved in this research.

Data Sharing Statement: The corresponding author can provide the data proving the findings of this study on request. Privacy or ethical restrictions bound us from sharing the data publically.

AUTHOR'S CONTRIBUTIONS

Hosseini F: Writing Original Draft
Zandi M: Conceptualization of the study
Behboudi E; Writing Original Draft
Salmanzadeh S; Writing Original Draft
Rasooli A: Investigation
Abbasi A: Investigation
Abbasi S: Writing original draft & Supervision
All authors reviewed and approved the final version of the manuscript.

REFERENCES

1. Qiu J, Soderlund-Venermo M, Young NS. Human parvoviruses. Clin Microbiol Rev. 2017; 30(1): 43-113. doi: 10.1128/CMR.00040-16.
2. Heegaard ED, Brown KE. Human parvovirus B19. Clin Microbiol Rev. 2002; 15(3): 485-505.
3. Broliden K, Tolfvenstam T, Norbeck O. Clinical aspects of parvovirus B19 infection. J Intern Med. 2006; 260(4): 285-304. doi: 10.1111/j.1365-2796. 2006.01697.x.
4. Luo Y, Qiu J. Human parvovirus B19: A mechanistic overview of infection and DNA replication. Future Virol. 2015; 10(2): 155-67. doi: 10.2217/fvl.14.103.
5. Musiani M, Zerbini M, Gentilomi G, M Plazzi, G Gallinella, S Venturoli. Parvovirus B19 clearance from peripheral blood after acute infection. J Infect Dis. 1995; 172(5): 1360-3. doi: 10.1093/infdis/ 172.5.1360.
6. Zerbini M, Gallinella G, Cricca M, Bonvicini F, Musiani. Diagnostic procedures in B19 infection. Pathol Biol(Paris). 2002; 50(5): 332-8. doi: 10.1016/s0369-8114(02)00308-5.
7. Hunter LA, Ayala NK. Parvovirus B19 in pregnancy: a case review. J Midwifery Womens Health. 2021; 66(3): 385-90. doi: 10.1111/jmwh. 13254. Epub 2021 Jun 8.
8. Mizumoto J. Parvovirus B19 Infection With Positive Rumpel-Leede Sign. Am J Med. 2020; 133(5): e195-e196.
9. Kostolansky S, Waymack JR. Erythema Infectiosum. In: StatPearls [Internet]. Treasure Island. (FL): StatPearls Publishing; 2022 Jan. Oct 30.
10. Nguyen HH, Lee SH, Lee UJ, Fermin CD, Kim M. Immobilized enzymes in biosensor applications. Materials (Basel). 2019; 12(1): 121. doi: 10.3390/ ma12010121.
11. Zandi M, Zandi S, Mohammadi R, Hosseini P, Teymouri S, Soltani S et al. Biosensor as an alternative diagnostic method for rabies virus detection: A literature review. Biotechnol Appl Biochem. 2022; 69(4): 1348-53. doi: 10.1002/bab. 2207. Epub 2021 Jun 9.
12. Zandi M, Fani M. Target genes used for biosensor development in COVID-19 diagnosis. Biosens Bioelectronic. 2022; 200: 113924. doi: 10.1016/ j.bios.2021.113924. Epub 2021 Dec 30.
13. Peterlana D, Puccetti A, Corrocher R, Lunardi C. Serologic and molecular detection of human Parvovirus B19 infection. Clin Chim Acta. 2006; 372(1-2): 14-23. doi: 10.1016/j.cca.2006.04.018. Epub 2006 Jun 9.
14. Kurtzman GJ, Cohen BJ, Field AM, Oseas R, Blaese RM, Young NS. Immune response to B19 parvovirus and an antibody defect in persistent viral infection. J Clin Invest. 1989; 84(4): 1114-23. doi: 10.1172/JCI114274.
15. Bluth MH, Norowitz KB, Chice S, Shah VN, Nowakowski M, Josephson AS et al. Detection of IgE anti-parvovirus B19 and increased CD23+ B cells in parvovirus B19 infection: relation to Th2 cytokines. Clin Immunol. 2003; 108(2): 152-8. doi: 10.1016/s1521-6616(03)00098-6.
16. Di Paola N, Mesquita FS, Oliveira DB, Villabona-Arenas CJ, Zaki Pour S, de Sousa-Capra C, et al. An outbreak of human parvovirus B19 hidden by dengue fever. Clin Infect Dis. 2019; 68(5): 810-7. doi: 10.1093/cid/ciy630.
17. Seetha D, Pillai HR, Nori SR, Kalpathodi SG, Thulasi VP, Nair RR. Molecular-genetic characterization of human parvovirus B19 prevalent in Kerala State, India. Virol J. 2021; 18 (1): 96. doi: 10.1186/s12985-021-01569-1.
18. Corcoran A, Kerr S, Elliott G, Koppelman M, Doyle S. Improved detection of acute parvovirus B19 infection by immunoglobulin M EIA in combination with a novel antigen EIA. Vox Sang. 2007; 93(3): 216-22. doi: 10.1111/j.1423-0410. 2007.00956.x.
19. Ramos-Vara JA, Kiupel M, Baszler T, Bliven L, Brodersen B, Chelack B et al. Suggested guidelines for immunohistochemical techniques in veterinary diagnostic laboratories. J Vet Diagn Invest. 2008; 20(4): 393-413. doi: 10.1177/10406 3870802000401.
20. Du J, Wang W, Chan JF, Wang G, Huang Y, Yi Y et al. Identification of a novel ichthyic parvovirus in marine species in Hainan island, China. Front Microbiol. 2019; 10: 2815. doi: 10.3389/fmicb. 2019.02815.
21. Singh S, Kumar V, Dhanjal DS, Datta S, Prasad R, Singh J (2020). Biological Biosensors for Monitoring and Diagnosis. In: Singh, J., Vyas, A., Wang, S., Prasad, R. (eds) Microbial Biotechnology: Basic Research and Applications. Environmental and Microbial Biotechnology. Springer, Singapore. https://doi.org/10.1007/978-981-15-2817-0_14Biological biosensors for monitoring and diagnosis.
22. Gergeroglu H, Yildirim S, Ebeoglugil MF. Nano-carbons in biosensor applications: an overview of carbon nanotubes (CNTs) and fullerenes (C 60). SN Applied Sciences. 2020; 2: 603.
23. Byrne B, Gilmartin N, Lakshmanan RS, O'Kennedy R. Antibodies, enzymes, and nucleic acid sensors for high throughput screening of microbes and toxins in food. In Book: High throughput screening for food safety assessment: Elsevier. 2015; 25-80.
24. Teklemariam AD, Samaddar M, Alharbi MG, Al-Hindi RR, Bhunia AK. Biosensor and molecular-based methods for the detection of human coronaviruses: A review. Mol Cell Probes. 2020; 54: 101662. doi: 10.1016/j.mcp.2020.101662.
25. Zhang D, Anderson MJ, Huarng MC, Alocilja EC. Nanoparticle-based bio-barcoded DNA sensor for the rapid detection of pagA gene of Bacillus anthracis. IEEE Transactions Nanotechnol. 2011;

10(6): 1433-8.
26. Afsahi S, Lerner MB, Goldstein JM, Lee J, Tang X, Bagarozzi DA et al. Novel graphene-based biosensor for early detection of Zika virus infection. Biosens Bioelectron. 2018; 100: 85-88. doi: 10.1016/j.bios.2017.08.051. Epub 2017 Aug 24.
27. Dong S, Zhao R, Zhu J, Lu X, Li Y, Qiu SH et al. Electrochemical DNA biosensor based on a tetrahedral nanostructure probe for the detection of avian influenza A (H7N9) virus. ACS Appl Mat Interface. 2015; 7(16): 8834-42.
28. Nguyen BTT, Peh AEK, Chee CYL, Fink K, Chow VTK, Ng MML et al. Electrochemical impedance spectroscopy characterization of nanoporous alumina dengue virus biosensor. Bioelectrochemistry. 2012; 88: 15-21.
29. Sharma PK, Kumar JS, Singh VV, Biswas U, Shyam SS, Alam S et al. Surface plasmon resonance sensing of Ebola virus: A biological threat. Anal Bioanal Chem. 2020; 412(17): 4101-12.
30. Seo G, Lee G, Kim MJ, Seung-Hwa Baek, Minsuk Choi, Keun Bon Ku, et al. Rapid detection of COVID-19 causative virus (SARS-CoV-2) in human nasopharyngeal swab specimens using field-effect transistor-based biosensor. ACS Nano. 2020; 14(4): 5135-42.
31. Church KH, Taylor RM. Inventors; Sciperio Inc, assignee. Biosensor. United States Patent US: 6,603,548. 2003.
32. Vidic J, Manzano M, Chang CM, Jaffrezic-Renault N. Advanced biosensors for detection of pathogens related to livestock and poultry. Vet Res. 2017; 48(1): 1-22.
33. Fu Z, Lu YC, Lai JJ. Recent Advances in Biosensors for Nucleic Acid and Exosome Detection. Chonnam Med J. 2019; 1; 55(2): 86-98.
34. Fani M, Zandi M, Soltani S, Abbasi S. Future developments in biosensors for field□ready SARS □CoV□2 virus diagnostics. Biotechnol Appl Biochem. 2021; 68(4): 695-99. doi: 10.1002/bab. 2033. Epub 2020 Oct 19.
35. Kim YK, Lim SI, Choi S, Cho IS, Park EH, An DN. A novel assay for detecting canine parvovirus using a quartz crystal microbalance biosensor. J Virol Methods. 2015; 219: 23-27. doi: 10.1016/ j.jviromet.2015.03.015. Epub 2015 Mar 23.
36. Mirasoli M, Bonvicini F, Dolci LS, Zangheri M, Gallinella G, Roda A. Portable chemiluminescence multiplex biosensor for quantitative detection of three B19 DNA genotypes. Anal Bioanal Chem. 2013; 405(2-3): 1139-43. doi: 10.1007/s00216-012-6573-7. Epub 2012 Nov 28.
37. Khatri R, Mohan H, Poonam, Brar B, Prasad M, Pundir CS. A Novel Amperometric Genosensor for Rapid Detection of Canine Parvovirus in Feces. J Nanosci Nanotechnol. 2021; 21(6): 3524-30.
38. Yamakawa AC, Basso CR, de Albuquerque Pedrosa V, Júnior JP. Canine parvovirus 2 detection using a LSPR biosensing method with gold nanoparticles. Sens Diagn. 2023; 2(1): 122-131.