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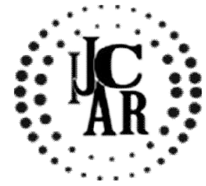

Research Article

ARE VIRUSES FOAMING AT THE MOUTH? FIGHT FIRE WITH FIRE

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A R T I C L E I N F O

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Transmission electron microscope (TEM), scanning electron microscope (SEM), Atomic force microscope (AFM), scanning near-field optical microscope (SNOM), HBeAg (Hepatitis virus e antigens), cytopathic effect (CPE), proximity ligation assay or PLA. Radioimmunoassay (RIA PCR (polymerase chain reaction)

A B S T R A C T

When we 'fight fire with fire' we are likely to employ more extreme methods than we would normally do. That was what Shakespeare was referring to in King John; 1595. Fire is a good servant but bad master. Large amounts of Measles virus is used to kill cancer cells. In a fighting fire with fire type approach to finding a cure for cancer, researches have successfully treated a little girl named Emma with the new radical treatment and are now in remission from her leukemia. Several modern diagnostic tests are useful to fight against viruses and thus saving lives of millions.

The diagnosis of viral infection remains a major challenge in developing therapeutics.

Mistakes and failures are integral part of any great effort worth the mention. Your best teacher is your last mistake. Developing new manifolds by revitalizing old ideas. The qualities of thinking action decide your strength.

Diagnostic error can be defined as a diagnosis that is missed, wrong or delayed, as detected by some subsequent definitive test or finding. The ensuing harm results from the delay or failure to treat a condition present when the working diagnosis was wrong or unknown or from treatment provided for a condition not actually present.

Incorrect laboratory tests account for significant harm. Researchers estimated that the number of patients suffering from missed diagnostic tests is annually in thousands. These are potentially preventable, subject to the condition if proper attention is paid.

Diagnosing diseases and disorders requires highly developed skill on the part of the physician or other medical professional. Usually the diagnosis calls for systematic use of instruments and diagnostic aids, various tests, and, often with sophisticated instruments and machines.

Quality systems are the mainstay of clinical laboratory management. The comprehensive laboratory testing process must be continually monitored and evaluated to ensure reliable test results and set the foundation for quality improvement. While such efforts have resulted in significant improvements in many of the processes, errors still occur. In order to implement corrections and improve the testing process, the laboratory technician must identify the various sources of errors

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INTRODUCTION

The diagnosis of viral infection remains a major challenge in developing therapeutics. The clinical diagnosis provides State of the art for developing diagnostics for treatment (I). In fact, as viruses are obligate intracellular parasites and exist like a dead nucleic acid particle it's very difficult to grow and cultivate then along. The prime requirement for viral growth and culture is finding a suitable host.

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The main hurdle in developing diagnostics for the virus is their genome nature and high-level genome plasticity (2). To develop diagnostic for viral infection, there have been tremendous efforts have been over a period of several decades. The microscopy remains a major tool for morphological identification and validation of viruses. The advancement of cutting edge microscopy including electron microscopy, confocal microscopy and scanning probe microscopy provide ease in identification and characterization of these intracellular pathogens (3). There have been continuous developments in Transmission electron microscope (TEM), scanning electron microscope (SEM), Atomic force microscope (AFM), scanning near-field optical microscope (SNOM), X-ray microscope. and ultrasonic microscope to enhance viral

diagnosis (4). These methods are good and offer ease in the study of viral morphology and their physical characteristics as well. The morphological and physical characterization of viral particles provides only a basic knowledge about these intracellular pathogens (5). Hence, these techniques largely fail in identifying a molecular signature for viruses. As mentioned above viral genome possesses a great level of plasticity, and hence molecular identifications are essential to developing diagnostics (6). The molecular diagnosis largely depends on nature of viral genome and antigen presenting on the surface of the viral capsid. The molecular diagnosis also depends on the biochemistry of viral genetic material. The DNA and RNA viruses are entirely different in their genome and flow of their genetic information (7). Hence, it's very difficult to develop a common diagnostic for both the category. The nature of viral capsid is also an important parameter in developing diagnostics as each class of viruses' possesses different pattern and nature of protein expressing on the surface of viruses (8). Addition to molecular diagnosis, genome itself is being used as a potential target for the development, of diagnostic devices. Now a day's genome sequencing and sequencing-based diagnostic devices are common not only in case of virus infection but also microbial infection as well. The genomic sequence-based diagnostics are accurate and effective and provide in-depth knowledge and information of pathogen (9). The genome-based diagnostics are also useful in studying molecular evolution and changes in the genome of viruses. There are several variants in genomic based diagnostics using PCP and Real-time PCP based technologies for the determination of viral load in the infected cell (10).

The viral diagnosis has a long history and several analytical tools and techniques have been used. The microscopic and antibodies based assays are key diagnostic methods under conventional approaches (11). These approaches are effective and reliable in preliminary identification of viral infections and also act base for molecular and other advanced diagnostics (12). The diagnosis of a viral infection can be established in several ways, like Detection Of virus particles in a specimen taken from the appropriate Site. Serological procedure to detect specific anti-viral antibodies (rise in antibody titer or presence of IgM antibody)/detection of the presence of a cell-mediated immune response. Detection of viral antigens (Ag) in blood or body fluids Detection of viral nucleic acids in the blood or body cells of patient The culture of infectious virus from the appropriate clinical specimen. Cytological or histological examination of cells from the site of the infection in those viral infections in which a characteristic viral cytopathic effect (CPE) is produced.

Throughout the history of clinical diagnosis, microscopy remains a major analytical tool in biology and medical applications. The use of microscopy is versatile and had a wide range spectrum in microscopic examination of the virus and other microscopic pathogens associated with human diseases (13). Viruses can be detected and identified by direct microscopic examination of clinical specimens such as biopsy materials or skin lesions. Three different microscopy techniques are currently in use-

The light microscopy is primitive and but effective tool for microscopic examination of a various organism including viruses. Since most of the viruses are much smaller than normal microbes in their size and hence light microscope are used for preliminary studies (14). It reveals characteristic inclusion bodies or multinucleated giant cells. V V Microscpy is used for fluorescent antibody staining of the virus in infected cells. The antibodies are raised against particular antigens. These raised antigens are conjugated with fluorescent tags and allow a reaction with virus-infected cells (15). The virus infected cells have viral protein which acts as an antigen and binds the fluorescently tagged antibodies. The magnitude of antigen present in the cell and reported fluorescent defines the extent of virus infection or in another word viral load in a cell. Electron microscopy is one of a most powerful microscopic tool for the microscopic organism and virus diagnosis. There is two major variants in electron microscopy one scanning electron microscopy (SEM) and second transmission electron microscopy (TEM). It detects virus particle which is further characterized by their size and morphology (16). Both TEM and SEM are used in virus diagnosis as each virus has a different host and varying pattern in its life cycle.

Serological procedure for the laboratory diagnosis of Viruses shows a rise in antibody titer to the virus can be used to diagnose viral infection. A serum sample is obtained in the acute phase (as soon as viral etiology is suspected), and a second sample is obtained in the convalescent phase (10-14 days later). If the antibody titer in the convalescent phase serum sample is at least four-fold higher than the titer in the acute phase serum sample. The patient is considered to be infected (17). In some viral disease for which cut- off titer is known a patient showing a rise in antibody titer than cut off value can be considered as infected and in another viral disease, the presence of 19M antibody is diagnostic. IgM governs primary antibody response (predominately produced).

Viral Antigens are detected by various tests such as ELISA. EFA, etc. can be done to detect the presence of viral antigens in the patient blood or biopsy materials. For the diagnosis of Hepatitis virus infection, HBsAg (Hepatitis viral surface antigen) or HBeAg (Hepatitis virus e antigens) can be detected (18). Similarly, detection of p24 viral antigen is the diagnostic method in case of HIV Infection. Detection of viral nucleic acids is one of the sensitive and rapid methods for the laboratory diagnosis of the virus (19). It requires the use of PCR (polymerase chain reaction) to amplify the viral genome present in the sample and the detection of the specific gene Sequence of that particular virus by the use of a specific primer (while performing PCR) and probe (while detecting the specific sequence) (20). RNA viral assay is currently in use to monitor the course of HIV infection and to evaluate the patient progress.

Viruses are obligate intracellular parasites so we cannot grow them in ordinary media (like we grow bacteria, fungi) and require living cells for the growth and} propagation. The growth of virus in the cell culture may produce characteristic cytopathic effect (CPE) which helps us for presumptive diagnosis (21). If that particular virus does not produce the cytopathic effect, it be detected by several other techniques such as Immunofluorescence assay (e.g., DFA, IFA), Radioimmunoassay (RIA decrease in acid production of infected cells, ELISA Complement fixation, Hemagglutination inhibition method. Neutralization, etc.(22).

PG-based techniques are the most commonly used methods in avian influenza diagnostics. The conventional reverse transcriptase PCR (RT-PCR) assay and the real time RT-PCR assay are used to identify influenza virus strains (31). The

diagnostic application of real-time PCR technology offers advantages over the conventional RT-PCR method.

Numerous real-time PCR-based diagnostic assays have been reported to data rapid real-time RT-PCR is one of the most sensitive methods which enable sensitive and specific detection of HPAIV virus H5N1 strain of the lineage which is combined with a cleavage site analysis without the need for sequencing (32). More recently reported the development of a TaqMan-based triplex real-time RT-PCR method that targets nucleoprotein gene of animal and human influenza viruses of all types: A, B, and C. This assay utilize a novel mismatch-tolerant molecular beacon that also serves as a TaqMan probe which allows for nucleotide variation within the probe-target region. When validated with various samples, the assay showed higher sensitivity than a PCR assay with the TaqMan probes (33). This new assay can detect one-tenth of the amount of viral RNA and cDNA compared to the TaqMan probe only assay. By and large, RT-PCR-based techniques currently are the major diagnostic tool due to Simplicity and reliability (34). Recently a novel PCR-based alternative assay for the detection of viral antigens in biological specimens has been reported. The proximity ligation assay or PLA is a new way to detect proteins by nucleic acid amplification. This method uses viral or bacterial surface protein antibodies coupled to DNA strands that get joined by ligation when several antibodies against surface proteins of pathogen come into proximity. This method enables the detection of target proteins by ligated DNA strands, which are then amplified in a real-time PCR (35). The assay with AE virus nucleoprotein-specific monoclonal antibodies were shown to be very specific and compares favorably to a commonly used reference real- time PCR assay because it removes the necessity of nucleic acids extraction.

Also, this method allows the use of inactivated samples that can be transported safely from a field to diagnostic laboratories. Despite the fact that it is a recently established technique, it holds a promise as an alternative assay for protein measurement in complex biological samples with a detection limit in the low femtomolar range (36).

The early virus detection achieved by reliable, rapid techniques and viral DNA sequencing plays an important role in the successful prevention of the disease. To achieve this, a very rapid PCR reaction combined with nucleotide sequencing analysis employing the principle of super convection was developed. The HA gene from a broad spectrum of influenza viruses is amplified in a one-step real-time PCR reaction, followed by rapid sequencing that covers the cleavage Site of HA gene The detection and evaluation of viral pathogenicity, including the (37) gene information of the HA gene. all are obtained in under two hrs. This novel approach is believed to be more cost-effective and useful when handling a high throughput of samples, which is required when monitoring field samples.

Addition to PCR based methods the Microarray technology proved to be a powerful tool for virus detection and subtyping. It allows simultaneous detection of a great diversity of genetic elements. For example a microarray with a clinical sensitivity of 95% and clinical specificity of 92% when validated against A/H5N1, A/H3N2, and A/HINI viral Strains has been published. Another type of microarray, a low-density microarray, also deserves mention (38). A low- density microarray is utilizing the NanoChip400 system (Nanogen Inc) which employs one probe for the M gene and 97 probes for the cleavage site region of HA gene, was shown to be a reliable tool for H5N1 virus detection. It is important to mention that the detection limits here were from ten to one hundred times lower than that of real-time RT-PCR concerning HA subtyping MD pathotyping. However, the presence of multiple steps involved in these assays, like several amplification Steps, probe labeling and incorporation of conjugated nucleotides into DNA makes them labor-intensive, time-consuming, and extremely costly (39). Additionally, the necessity of optimization of parameters and numerous primers design presents scientists with a challenge. Therefore microarray techniques come second to RT-PCR.

With the novel, cutting-edge technology in molecular and cell biology development of diagnostics gained a new momentum. The genome sequencing offers a complete information and data analysis to design new diagnostics for a candidate virus. There are several approaches for genome sequencing either L conventional means, i.e., using chain termination or Sanger method. Further, next-generation sequencing (NGS); metagenomics has been established for; complete genome sequencing and rapid methods for virus diagnosis as well (40), Efficient study design for accurate detection relies on the optimal amount of data representing a significant portion of a virus genome. The NGS has several advantages over conventional sequencing methods including ease in data analysis complete genome sequencing, sequencing of lost and fragmented genome part etc. The NGS database is also helpful in comparison of genome sequence study of phylogenetic analysis as well (41).

History and Mechanism

Patient safety agenda is gaining momentum in the health care systems of all developed countries. However, adverse event detection systems and initiatives to reduce error rates in medicine are in their infancy. Laboratory services play a crucial role in both individual and population-based healthcare, and clinical laboratories use many different methods to reduce errors, ensure patient safety, and improve quality including quality control procedures, quality assurance programs, accreditation of laboratories and certification of education programs. Considerable advances in analytical techniques, laboratory instrumentation, information technologies, automation and organization have granted an exceptional degree of analytical quality over the past 50 years. This, in turn, has resulted in a significant decrease in error rates, analytical error rates in particular. There is consolidated evidence that nowadays, most laboratory errors fall outside the analytical phase, and that pre- and post-analytical processes are more vulnerable to error than analytical processes (44,45)

Significant gap in research

These are the common misconceptions about adverse events, and the arguments and explanations against those misconceptions are noted in parentheses:

- "Bad apples" or incompetent health care providers are a common cause. (Although human error is commonly an initiating event, the faulty process of delivering care invariably permits or compounds the harm, and is the focus of improvement.(46)
- High risk procedures or medical specialties are responsible for most avoidable adverse events.

(Although some mistakes, such as in surgery, are harder to conceal, errors occur in all levels of care. Even though complex procedures entail more risk, adverse outcomes are not usually due to error, but to the severity of the condition being treated(46,) However, USP has reported that medication errors during the course of a surgical procedure are three times more likely to cause harm to a patient than those occurring in other types of hospital care(47)

- If a patient experiences an adverse event during the process of care, an error has occurred. (Most medical care entails some level of risk, and there can be complications or side effects, even unforeseen ones, from the underlying condition or from the treatment itself) (48)

Ideas Where Research Go Next

The prevention is always better than cure, and here in case of viral infection, the given fact is more important. The viral infection is highly regulated, and diseases caused by viral infection are comparatively difficult to cur. Here, clinical diagnosis is crucial not only in profiling and documenting infecting virus but also in making guidelines to minimize infections (42). As viruses are highly contagious and spread rapidly via different carrier including air and water hence prevention Of infection Stand and then treatment. Let's consider the example of human immune deficiency virus (HIV) infection that is widely distributed acquired immune deficiency syndrome (AIDS). It has been more than 30 of HIV discovery and associated diseases to human we stand nowhere in a complete cure for AIDS. Hence giving more emphasis to prevention is more economical and effective (43). Similarly, in case of flu including influenza and swine flu prevailing and spreading rapidly are having a major concern. There is several other contagious viruses' infection affecting a large number of human populations causing a threat to global health and increasing diseases burden as well. There are several parameters to minimize viral infection and associated diseases. First and most important factor in the control of viral infection is finding its host. Second, the spreading medium for viruses remains also crucial in minimizing viral-based diseases.

Current Debate

In the present scenario. Co-infections become another challenge not only for viruses and but also other infections. For example, HIV infections enhance change of other infections more precisely Mycobacterium tuberculosis (MTB). In case of co-infection, it becomes more difficult to study and understand nature of virulence genes and factors for prevention protocols. As HIV target immune cells and comprise an immune system that enables an ease of other infections as well. In such condition it becomes more difficult to study disease symptoms either caused by a virus as primary infectious agent and or secondary infections caused by microbes. The clinical diagnosis of viruses remains a major challenge and rigorous task and challenge in modern diagnostics. Over a period of decades several biological tools implemented in the diagnosis of viral load in a cell. The history Starts with the microscopic identification of viruses that offer only physical characteristics. Here, several levels of microscopy remain involved in virus identification including electron microscopy, confocal microscopy, atomic force microscopy and X-ray microscopy. The advancement of medical molecular biology and cutting-edge bioengineering techniques provide a base for molecular diagnosis. The genome sequencing and molecular markers of protein expressing on viral capsid are key targets in developing viral diagnostics. In recent time, polymerase chain reaction based techniques have shown tremendous promise in early diagnosis of viral load in an infected. The multiplex PCR and real-time PCR are most valuable and accurate tools in modern molecular biology not only viral load determination but also many other diseases as well. The nature of virus genome and its complex life cycle is a major challenge even in present time disable development of single and common diagnosis method. The virus life cycle possesses two major events after infection to host cell: one lytic and second lysogenic. There is a precise signal, and regulatory proteins guide viruses to opt one and or both events. Such complex genetic Structure and unique signal are a top priority for researcher worldwide in understanding virus biochemistry and developing diagnostics.

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