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COMMENTARY

False-Negative RT-PCR Findings and Double Mutant Variant as Factors of an Overwhelming Second Wave of COVID-19 in India: an Emerging Global Health Disaster

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Abstract

RT-PCR is considered to be the standard gold diagnostic test for detecting COVID-19 causing SARS-CoV-2. Recent reports and recent pieces of evidence from scientific literature, however, tell a different story. There have been speculations of SARS-CoV-2 escaping the RT-PCR because of the series of mutations it has gone through. It is possible that host-dependent RNA editing and high person-to-person transmission have equipped the virus with mutations enabling it to spread faster and even evade the RT-PCR. Added to this is burnout among healthcare workers and technicians handling the RT-PCR machines and sampling. All of these factors may be working in unison to result in the deluge of false-negative cases India is facing during the second COVID-19 wave. The mutant strains are spreading to other parts, posing challenges to the whole world. These circumstances warrant supplementary diagnostic tests such as serological and radiological findings to deal with cases of high clinical suspicion. Even one misdiagnosed COVID-19 patient poses a risk to hundreds of others in the vicinity. Healthcare workers' burnout also has to be dealt with. Erroneous staff should be re-trained.

Keywords COVID-19 · Double mutant · Second wave · SARS-CoV-2 · India

Abbreviations

COVID-19	Coronavirus disease 2019
WHO	World Health Organization
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
RT-PCR	Reverse transcription-polymerase chain reaction
CDC	Centers for Disease Control and Prevention
HIV	Human immunodeficiency virus

Introduction

Almost 6 months after the peak of the first wave of coronavirus disease 2019 (COVID-19) in India in September 2020, the surge in COVID-19 cases started again in the first week of March 2021. As of 28 August 2021, the COVID-19 positive cases summed up to 32,649,947 and are still counting with daily reported cases soaring to over 40,000 and death toll rising to 437,370 with over 500 deaths per day. Due to the second wave of COVID-19 in India, the test rate was significantly increased to meet the demand, and a total of 516,887,602 samples were tested as of 27 August 2021 [1]. In these unprecedented situations, India is combating the second wave of COVID-19 with an unusual ascent of daily cases.

This unexpected exponential surge of cases can be attributed to the rampant false-negative results of COVID-19 in the country and the newly identified B.1.617, a double

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mutant variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first detected in India. These, together with increased infection rate, have created a situation of patient overload and increased oxygen demand in hospitals in the country. The WHO has classified all the identified variants of SARS-CoV-2 into two definitive categories—variants of interest (VOI) and variants of concern (VOC). The list of VOCs designated by the WHO includes alpha, beta, gamma, and delta. Currently designated VOIs include eta, lota, kappa, and lambda. As per the WHO's weekly epidemiological update on COVID-19, as of 24 August 2021, the alpha variant has spread to 192 countries, beta to 141 countries, gamma to 86 countries, and delta to 163 countries. All the variants have shown increased transmissibility. In addition, the delta variant has been found to have similar transmissibility between vaccinated and unvaccinated individuals.

Discussion

Negative RT-PCR and the Second Wave of COVID-19

Owing to the expeditious transmission of COVID-19 and escalating number of cases, accurate and rapid detection of the virus or the disease is extremely essential for controlling the roots of infection, aiding the patients to prevent further progression, and reducing the severity of disease by creating a window for adequate treatment [2]. This faulty detection of real positive cases seems to be one of the potential causes for the rise in the COVID-19 cases at some places due to the indirect spread of infection from the false-negative persons.

The false-negative outcomes for SARS-CoV-2 from the respiratory samples of the patients are fluctuating between 1 and 30% [3]. These false-negative results can happen due to various reasons that may include too early or too late testing in the pathogenic process of the virus, suboptimal or poor specimen collection procedures, improper specimen types, scanty analytic sensitivity, negligible viral load, or changeability in the viral shedding. The consequences of these false-negative results could be serious, probably paving a way towards the positive case aggregations leading to negative outcomes and amplified transmission rates across the community [3]. The false-negative results also tend to prevent the person from taking the necessary precautions or treatment required; hence, he/she will be a potential carrier or transmitter of infection in the community, leading to the generation of infected case clusters and hotspots of COVID-19 [4].

Principle and Limitations of RT-PCR

Real-time reverse transcription-polymerase chain reaction (RT-PCR) is a nuclear-derived method that detects pathogens' genetic material, usually DNA. Since COVID-19 is an RNA virus, RNA is reversely transcripted into DNA using specific enzymes, and obtained DNA is amplified into multiple copies.

The samples from nasopharyngeal or oropharyngeal swabs collected from the patients are kept in specific solutions to eliminate unwanted substances like proteins and fats. The remaining genetic material mixture is placed in an RT-PCR machine. The machine amplifies the DNA into nearly 35 billion copies (from each strand of RNA) by undergoing 35 cycles (standard count). Then, marker labels that are attached to DNA strands release fluorescent dyes. The amount of dye is measured by a computer and displayed on the screen using real-time. The amount of dye in the sample is tracked after each cycle, and if the amount of fluorescent dye reaches a certain level, the presence of the virus can be confirmed. The number of cycles it takes to reach that certain level determines the severity of infection. A low number of cycles indicates severe infection [5, 6].

According to the Centers for Disease Control and Prevention (CDC), the negative results do not interdict COVID-19 infection, and collection of multiple specimens is recommended. Similarly, the presence of viral RNA may not be a confirmatory indication for clinical symptoms developed in a patient. False-positive and false-negative results highly depend on the prevalence of disease in the human body. The higher the prevalence of disease, the more chances of false-negative results, and vice-versa. Regarding the reliability of the test for detection of COVID-19, RT-PCR is considered the standard gold test due to its high specificity and significant sensitivity [2]. However, few authors have reported that the sensitivity of RT-PCR could be as low as 38%, almost like a chance. IgM and IgG serology tests have been reported across the globe and under being used, but the specificity and sensitivity of serology tests is also not high [7].

Mutations and Associated False-Negative Results

The release of the first SARS-CoV-2 genome sequence occurred on 10 January 2020, which paved the way for developing complementary RT-PCR assays [8]. However, due to high transmission cycles, the virus may have mutated, posing a threat to the sensitivity of RT-PCR as the reagents for the kits were also developed then.

The SARS-CoV-2 is an enveloped ssRNA virus, which generally tends to have very high mutation rates. However, human coronaviruses have an RNA polymerase with 3′ to 5′ proofreading activity that allows them to replicate

with "high-fidelity" and thus, its mutation rate is moderate [8–10]. The mutation rate of SARS-CoV-2 is ~ 2 nucleotides per month in contrast to that of influenza (4 nucleotides per month) or HIV (8 nucleotides per month) [11]. However, host-dependent RNA editing [9] and high rate of person-to-person transmissibility [8, 12] cannot be left out of the picture.

Physicians closely studying the second wave in India have claimed that bronchoalveolar lavage performed on RT-PCR negative patients presenting with definitive symptoms of COVID-19 yielded COVID-19 positive results. A doctor in the same report said that approximately 15 to 20% of COVID-19 patients are presenting with the above condition, and it is becoming a dilemma for the physicians [13]. In another report, a scientist argued that mutations in the SARS-CoV-2 may have made it capable of evading RT-PCR testing and that there is a need to re-configure the kits urgently [14]. There are reports where chest computed tomography (CT) findings are clearly indicative of COVID-19 (ground-glass opacity and grey patches), but repeated RT-PCR tests have yielded negative results. Although it is being speculated that since RT-PCR has a sensitivity of 70%, it is the remaining portion of patients that are getting false-negative results [13–17]. However, these reports have surfaced only recently, so the possibility of mutant(s) of SARS-CoV-2 causing this cannot be neglected completely. According to a news report, the data shared by the National Institute of Virology, India, almost 61% of the samples collected from the Indian state of Maharashtra were positive for the presence of the double mutant strain B.1.617 [18]. The Global Times reported that eleven Chinese crew members became positive with a mutant Indian strain of the SARS-CoV-2 [19].

Several studies have hinted out that the inevitable genetic evolution and mutation of SARS-CoV-2 can compromise the sensitivity of RT-PCR diagnostic kits [8, 10–12, 20–23]. The diagnostic assays used in RT-PCR have high specificity, due to which even a few mutations can lead to substantial loss of sensitivity [23]. Most of the mutations of SARS-CoV-2 occur on the Nucleocapsid (N) gene target, primers, and probes of which are extensively used around the world for the detection of this virus [21].

Various recent literature and scientific evidence support the rationale of mutations leading to increased false-negative RT-PCR results for SARS-CoV-2. A study found that an SNP (Single Nucleotide Polymorphism) in the N gene interfered with the detection through commercial diagnostic assays in a SARS-CoV-2 positive patient [23]. An analysis in a study also showed that there were mutations/mismatches in primer/probe binding regions of 7 out of 27 assays that were studied [10]. Another study detected the presence of a mutation in the N gene of SARS-CoV-2 in 3 patients, which affected its detection by commercial assays [12]. Reports claim that single mutation in forward N gene primer binding site, prevalent across the world, decreased the RT-PCR sensitivity for SARS-CoV-2 [22]. A study that had genotyped 31,421 SARS-CoV-2 genome isolates has also revealed that per se, "all of the current COVID-19 diagnostic targets have undergone mutations" [24]. Another study that investigated the impact of Intra-host Single Nucleotide Variants (iSNVs) and Single Nucleotide Polymorphisms (SNPs) on the probes and primers commonly used in RT-PCR found that most of the probes had iSNVs and SNPs [9]. Although this did not affect target hybridization in the study, our rationale is that mutations like these could increase the chances of false-negative results being obtained upon RT-PCR.

If the mutational profile and data could be integrated into developing PCR arrays, higher sensitivity for primer and probe hybridization could be achieved [9]. This also implies that having multiple gene targets in RT-PCR could vastly reduce the risk of loss of sensitivity due to the inevitable mutations in the virus [15, 16, 18, 20].

Collapsing Healthcare and Rampant False-Negative Results

The weakening of a country's healthcare system, its management, and the available medical infrastructure have been the most important contributing facets to the increasing morbidity and mortality due to COVID-19. The recent deterioration of the healthcare sector has further amplified false-negative RT-PCR results, and as a result has led to a rise in misdiagnoses, causing an increased risk of infection transmission. The fundamental cause for the false-negative test results among the COVID-19 patients during these times can be attributed much to the erroneous lab personnel who are having an acutely aggravated workload amidst the second wave. Collapsing healthcare and false-negative RT-PCR results are, therefore, now a part of a vicious cycle further fueling one another. False-negative RT-PCR results have been attributed to several pre-analytical, analytical, and post-analytical causes [25].

RT-PCR being extensively employed for mass testing has led to a scarcity of skilled personnel as well as snowballing rates of healthcare workforce burnout which include physicians and medical technicians among many others [26, 27]. As a result of the amalgamation of increased workload, risk of transmission, and shortage of necessary resources, the physical and mental health of healthcare workers has been severely affected [28]. Physicians' and healthcare workers' feeling of exhaustion may also be further accentuated in the future due to the growing backlog of healthcare services and procedures, which must also be given due consideration.

An immediate outcome of shortage of skilled personnel and burnout may include an improper collection of specimens giving rise to insufficient viral load required

for detection, improper transportation, improper handling of samples, inefficient extraction of RNA, and the inept removal of amplification inhibitors from the specimens [2, 29–31]. The above factors may also be influenced by the lack of equipment, material, bio-safety labeling, and instrumentation required for effective RT-PCR testing due to overburdened healthcare. The viral load in the specimen being fluctuant during the progression of the disease continues to perplex the timing of specimen collection, further contributing to false-negative results [31, 32].

As the SARS-CoV-2 RT-PCR is increasingly being applied to the asymptomatic population, avoidable repeat testing is becoming more prevalent. This consistently strains the supply chain network causing a delay in the turnaround time for the results, and more crucially leading to a paucity of tests for those who may need testing the most [33]. The multiplying demand has placed undue pressure on the principal manufacturing units causing disruption of overall logistics, leading to failure of delivery of the material required for diagnostic testing to the general population. [34].

Action Plan and Recommendations

RNA-based viruses change variants frequently and COVID-19 is no exception. To tackle this, genomic sequencing capacities should be ramped up so as to facilitate surveillance of emerging variants. Also, the limitations that exist in sampling strategies worldwide should be reduced. It is also possible that while the diagnostic kits do not change much over time, the virus is undergoing a myriad of mutations which may also give rise to variants/mutants that can evade the RT-PCR or at least substantially affect its sensitivity. There is a need to constantly watch out for such mutants/variants. Along with that, supplementary diagnostic tests like chest high-resolution CT scan and inflammatory markers (CRP, D-dimer, LDH, ferritin, IL-6) should be considered of great diagnostic value in a case of high clinical suspicion with a negative RT-PCR test report.

If the patient has clinical symptoms of COVID-19 and tests negative in RT-PCR, then multiple nasal and pharyngeal swabs at different times should be tested. Laboratory data, clinical symptoms, and CT images should be altogether considered to confirm the viral infection. The irrational results in RT-PCR can be minimized by following reasonable sampling procedures, standard laboratories, and premium quality RT-PCR kits [2]. Though RT-PCR is based on conserved sequences, primers in different genes can be affected by variations of viral RNA sequences.

Conclusion

The growing menace of increasing false-negative results in SARS-CoV-2 RT-PCR should be dealt with urgently. Even one falsely negative patient could put at risk the lives of hundreds of people in the vicinity. Additionally, the presence of double mutant B.1.617 variant is also a potential contributing factor to the exponential surge of COVID-19 cases in India as it has shown to be transmissible similarly in vaccinated and unvaccinated individuals. The B.1.617.2 (double mutant variant, delta variant) has been classified as a variant of concern. These factors are hampering the efforts of governments all over the world to contain the spread of COVID-19.

Changes in the viral nucleic acid and protein sequences put at risk the utility of certain in vitro diagnostic assays if the mutation occurs in an area critical for primer or antibody binding in RT-PCR and immunoassays. As the new variants of the SARS-CoV-2, including B.1.617, arise, it is the need of the hour that the PCR and diagnostic assays be re-configured and optimized. Multiple gene targets should be identified, and PCR assays should be reconfigured to use them. Extensive research/clinical trials should be sought in this direction. Data for the genome of the mutant variants of the virus should be readily available and infection prevention and control (IPC) measures as well as public health and social measures (PHSM) should change accordingly so as to accommodate additional preventive measures against the variants.

In addition, healthcare workers' burnout has to be looked at. Provisions should be made to recruit additional technical staff for handling various equipment and train them simultaneously. A possible reason for the high rate of false-negative RT-PCR results is improperly trained personnel who fail to take samples appropriately and lack basic training. Such staff should be re-trained.

Author Contribution Himanshu Jindal and Shubhika Jain conceived the idea and design, wrote the abstract, introduction, and discussion, organized the list of references, and edited the final draft; Tarun Kumar Suvvari and LV Simhachalam Kutikuppala wrote the introduction and discussion; Sudhan Rackimuthu and Radha wrote the discussion and conclusion; Samarth Goyal wrote the discussion and did the final revision; Ian Christopher Naungayan Rocha and Shubhika Jain made critical comments and revision. All authors revised and approved the final manuscript.

Declarations

Ethics Approval and Consent to Participate Not applicable.

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Conflict of Interest The authors declare no competing interests.

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REVIEW

Zika Virus Outbreaks: a Narrative Review

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Abstract

Purpose of Review This review aims to comprehensively analyse recent Zika outbreaks and their implications on public health. It discusses the evolving dynamics of the Zika virus transmission, factors contributing to outbreaks, health consequences, clinical manifestations, diagnosis, treatment, and challenges in controlling its spread. The goal is to provide a multidisciplinary understanding of Zika virus and guide public health strategies for effective outbreak prevention and management.

Recent Findings Recent findings reveal sporadic Zika cases with mild symptomatology. Major outbreaks occurred in the Yap Islands (2007), French Polynesia (2013–2014), and the Americas (2015–2016) with increased microcephaly cases. Recent research focuses on vaccine development, antiviral drugs, and point-of-care diagnostics. However, knowledge gaps remain in transmission dynamics, immune response, and long-term outcomes of Zika virus infection.

Summary Zika virus, which has sporadically prevailed in regions of Africa and Asia and causes mild febrile illness to asymptomatic cases, has expanded, leading to major outbreaks. Recent outbreaks include Yap Islands (2007), the first to occur outside Asia and Africa. In 2013, the Oceania outbreak showed neurological manifestations for the first time. The Americas outbreak (2015–2016) is considered the largest Zika epidemic with a spike in microcephaly cases, resulting in WHO declaring Zika-associated microcephaly a public health emergency of international concern. The burden of control of outbreaks falls primarily on public health interventions due to no effective vaccine or antivirals currently available, leaving major research lacunae.

Keywords Zika · Microcephaly · Zika virus outbreaks · *Aedes* mosquitoes · Public health response to Zika

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Introduction

The Zika virus (ZIKV) belongs to the genus *Flavivirus* of family Flaviviridae. ZIKV is enveloped and possesses a single-stranded, positive-sense RNA genome [1]. Phylogenetic studies have revealed two lineages of the ZIKV—the African and the Asian lineages, suggesting that the virus must have originated in East Africa and then spread to West Africa and Asia [2, 3].

The ZIKV was first isolated in 1947 from a febrile rhesus macaque monkey, known as 'Rhesus 766', in the Zika forest of Uganda near Lake Victoria [4]. Surveys show that 6.1% of the population were seropositive for ZIKV infection in Uganda at the time [5]. The date of emergence of the virus in East Africa is estimated to be around 1920 (C.I.: 1892–1947) [6]. The first human infection was reported in Nigeria in 1954 [4, 7]. Less than 20 cases had been recorded for the next five decades, most of which were reported as a part of yellow fever sero-surveys [3, 8]. Outside the African continent, ZIKV had been isolated from *Aedes aegypti* mosquitoes in Malaysia (1966), and human cases were reported in Central Java and Indonesia (1977) [9].

The purpose of this review is to provide a comprehensive overview of recent Zika outbreaks and their implications on public health. Based on current scientific research and extensive epidemiological data, this article aims to provide an understanding of the evolving dynamics of ZIKV transmission, the contributing factors behind its resurgence, and the subsequent health consequences. The review seeks to deepen understanding of Zika's epidemiology, clinical manifestations, and the challenges encountered in controlling its spread. The insights gained can guide public health strategies, influence policy decisions, and empower communities to effectively combat the threat of ZIKV outbreaks.

Epidemiology of Zika Virus

Transmission Cycle

ZIKV has been isolated from *Aedes* mosquitoes, suggesting their role in the transmission. *A. aegypti* is the most commonly involved species, although *A. albopictus*, *A. africanus*, *A. luteocephalus*, *A. furcifer*, and *A. taylori* also possess the potential to harbour the virus [10]. Out of these, *A. albopictus* poses an emerging threat due to its wide geographical distribution and vector capacity. Serological studies from Gabon (2007–2010) support this hypothesis [11].

The virus spreads in an enzootic cycle within the sylvatic habitat between non-human primates through mosquitoes. An epidemic cycle begins when an infected mosquito bites humans in this habitat or spills over from the sylvatic habitat to the human settlements [12].

Evidence of ZIKV disease transmission through all forms of sexual intercourse exists, and high viral loads have been detected in the semen of affected males (100,000 times higher viral load in the semen than the blood or urine) [13, 14]. Mother-to-foetus transmission of the virus can occur, thus causing intrauterine and intrapartum infections [15].

ZIKV RNA has been demonstrated in the blood, urine, cerebrospinal fluid, saliva, amniotic fluid, and breast milk of the infected individuals [16–18]. There lies a possibility of disease transmission through blood transfusion as well [16]. However, breastfeeding is not contraindicated in active maternal ZIKV disease due to the dearth of concrete evidence of transmission [10].

Studies have also suggested cases of laboratory-acquired Zika fever among researchers working on ZIKV, most probably associated with needle-stick injuries [19]. Remote evidences of aerosol-mediated and faeco-oral transmission have been postulated in controlled settings, highlighting the possibility of alternative routes of transmission of the virus in the future [20, 21

Clinical Features, Diagnosis, and Treatment

After a mosquito bites, ZIKV enters and replicates in human skin, lymph nodes, and dendritic cells (Fig. 1). It then disseminates through the bloodstream. ZIKV gains entry into target cells through interaction with specific receptors, particularly with TAM family receptors [22]. ZIKV has developed strategies to evade the immune system, by inhibiting interferon signalling pathways and suppressing immune cell activation [23••]. ZIKV's neurotropism allows it to cross the blood–brain barrier, infect neural progenitor cells, and induce neuroinflammation [24, 25, 25, 24].

ZIKV infection presents as a self-limiting illness with an incubation period of 4–10 days. Clinical symptoms are present only in 20–25% of the affected individuals [26]. Symptomatology of Zika fever is non-specific and resembles dengue and chikungunya infections. The common symptoms include transient low-grade fever, maculopapular rash, arthralgia, non-purulent conjunctivitis, and less commonly, retro-orbital pain, headache, myalgia, peripheral edema, and gastrointestinal disturbances [10]. Other clinical presentations include hematospermia, hearing difficulties, and thrombocytopenia [26].

Symptoms usually arise 2–12 days after the mosquito bite and resolve within 2–7 days, although arthralgia may persist up to a month. Infants and children with Zika fever present with irritability, limp on walking, and pain on active and passive joint movements. Individuals with clinical features

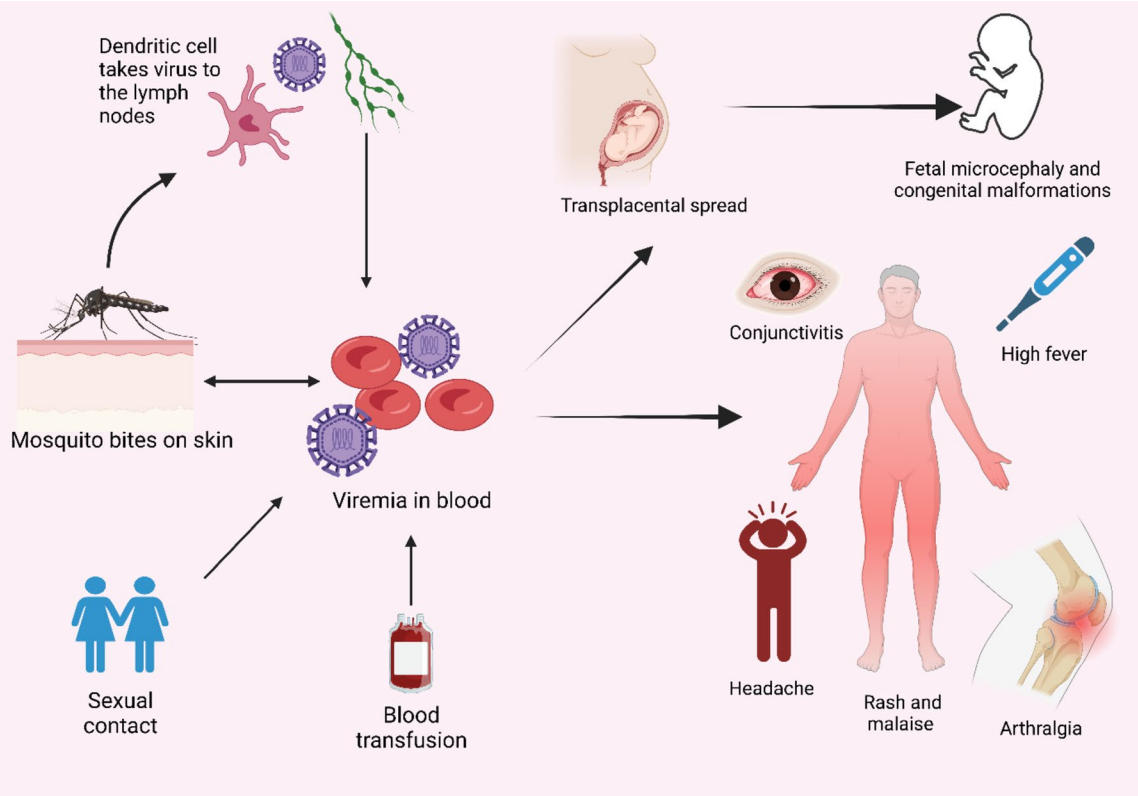

Fig. 1 Transmission and pathogenesis of Zika virus (created with BioRender.com)

and a history of recent travel to ZIKV-endemic areas should raise suspicion for infection [10].

Diagnosis of ZIKV disease can be cumbersome due to the significant overlap of clinical features with other arboviral infections. The differential diagnoses for Zika fever include dengue, chikungunya, parvovirus, malaria, leptospirosis, measles, rubella, and rickettsial infections [27].

The mainstay investigations for Zika fever are serum reverse transcription polymerase chain reaction (RT-PCR) for ZIKV RNA and ELISA or immunofluorescence for IgM antibodies against ZIKV. Serum RT-PCR is positive during the first 3–7 days of onset of symptoms (acute viremia), while specific IgM antibodies appear in the serum 4 days after the onset of symptoms [28]. Prenatal evaluation of pregnant women with suspected ZIKV infection through regular foetal ultrasound examination can detect signs of congenital ZIKV disease as early as 18–20 weeks of gestation [29].

No specific treatment modalities are available for Zika fever. Management is done on the lines of increased fluid intake for dehydration and administration of acetaminophen for fever and pain [27]. The course of the disease is self-limiting in most cases. Currently, there are no specific vaccines or antiviral therapies available for the treatment of ZIKV disease. However, active research is being undertaken in this field to explore the potential treatment options. Ribavirin and favipiravir are currently in the trial phase and have been shown to demonstrate effective anti-viral activity.

Recent Zika Virus Outbreaks

Initially, the distribution of ZIKV was confined to Africa and Asia. The outbreaks at Yap Islands of Federated States of Micronesia (2007) and French Polynesia (2013–2014) proved the expansion of the virus beyond the original confines [30]. It has been postulated that a combination of selective evolution and stochastic factors may have driven the rapid emergence and global spread of ZIKV [4]. Table 1 comprehensively summarizes the timeline of Zika virus from its discoveries to outbreaks.

Earliest Occurrences of Zika

The first evidence of Zika's existence was established through sero-agglutination studies on monkey serum in the Zika forest of Uganda (1947). In the subsequent years, Zika virus disease was by-and-large an endemic infection in Equatorial Africa, causing sporadic appearances on incidental testing for other flaviviruses. Though no major

Table 1 Zika virus timeline: discoveries and outbreaks (1947–2021)

Year	Event	Ref
1947	Discovery in rhesus macaque monkey in Zika forest of Uganda	**
1948	Isolation of ZIKV from *Aedes africanus* in Uganda	**
1954	First suspected human infection in Nigeria	**
1962–1963	First human ZIKV infection in Uganda	***
1950s–1980s	Prevalence of mild sporadic cases in Asia and Southeast Asia	*
1952	Uganda	*
1952	Tanzania	*
1954, 1977, 1983	Nigeria	*
1954	Egypt	*
1954	India	*
1954, 1963	Malaysia	*
1958	Philippines	*
1963	Thailand	*
1963	Vietnam	*
1970	Kenya	*
1975	Sierra Leone	*
1978, 1982	Gabon	*
1981	Central African Republic	*
1983	Indonesia	*
1993	Senegal	*
2007	First major outbreak at Yap Islands, Federated States of Micronesia	***
2013–2014	Outbreak at French Polynesia	***
2014	Minor outbreaks at New Caledonia, Cook Islands, and Easter Island	[8]
2015–2016	ZIKV outbreaks in South America (Brazil, Colombia, El Salvador, Mexico, Paraguay, Venezuela, Caribbean countries)	***
2015	Outbreak in Cape Verde, Africa	***
2016	Spread in North America (Florida, Texas)	[31]
	February: WHO declares ZIKV as Public Health Emergency of International Concern (PHEIC)	[31]
	August: Outbreak in Singapore	***
	October: Outbreak in Vietnam	***
	November: WHO declares that ZIKV disease is no longer a PHEIC	***
2016–17	Outbreak in Thailand	***
2017	First confirmed ZIKV cases in India (Gujarat, Tamil Nadu)	**
2018	First major outbreak in India (Rajasthan, Madhya Pradesh)	**
2019	Local transmission detected in France and Western Pacific	****
2021	Outbreaks in Uttar Pradesh, Kerala, Maharashtra (India)	[32••]

*[26], **[33], ***[4], ****[34]

outbreak was recorded in this period, the sero-prevalence of antibodies against ZIKV around that time in the general population was 10–20% [26] hinting the possibility of a silent infection over a long period. Similar sero-surveys in other areas showed the presence of similar antibodies in the population within the narrow equatorial belt of Africa (Senegal, Sierra Leone, Nigeria, Gabon, Central African Republic, Egypt, Uganda, Tanzania, Kenya) and Asia (India, Pakistan, Thailand, Malaysia, Vietnam, Indonesia, Philippines) (Fig. 2) suggesting a much wider geographical distribution [26].

Key Observations During the First 50 Years

- In the first 50 years of its discovery, fewer than 20 cases of ZIKV disease have been reported. The distribution of the cases was sporadic, and none of the infections had resulted in a full-blown outbreak.
- Most of the ZIKV-positive cases were asymptomatic or displayed mild febrile symptoms, with significant overlap of features with the other flavivirus infections. None of the cases had developed any neurological complications.

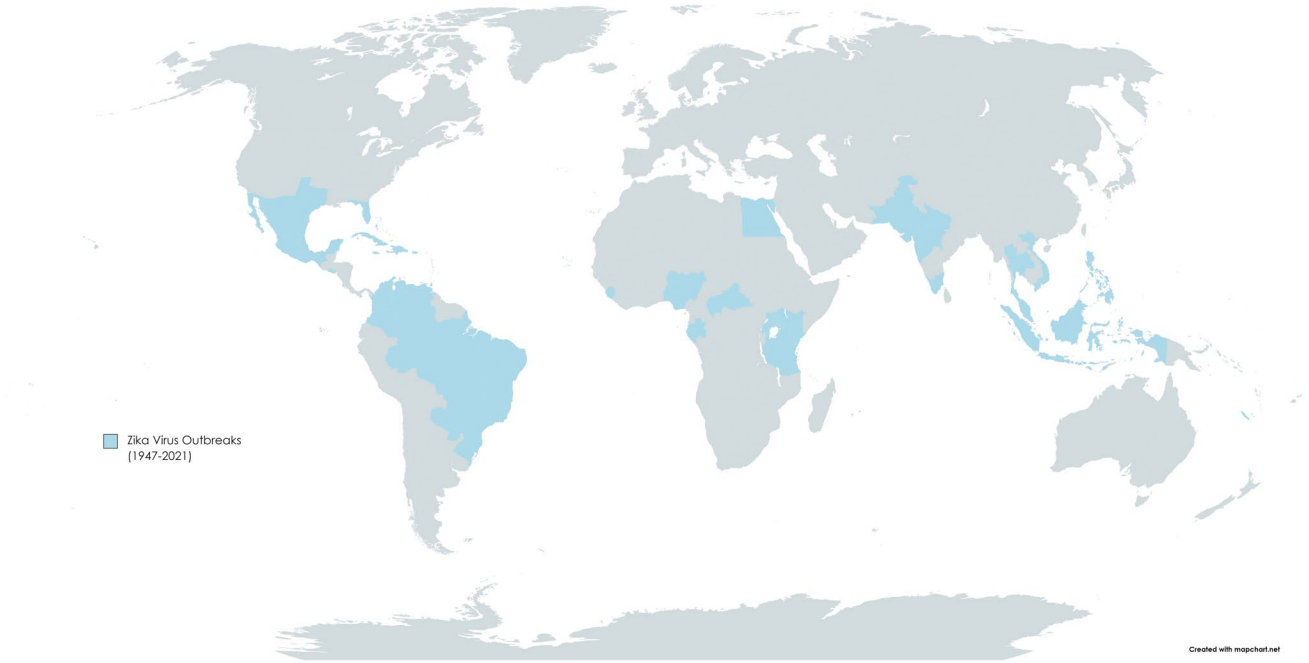

Fig. 2 Zika virus outbreaks (1947–2021)

- The distribution of cases and sero-positivity was confined to the tropical belt of Africa and Asia. This corresponds to the distribution of *Aedes aegypti* and other mosquitoes of *Stegomyia* subgenus. The dense forestation and adjoining pockets of urbanisation had set the perfect stage for the zoonotic transmission of ZIKV along the lines of Chikungunya [30].

Yap Islands Outbreak (2007)

In 2007, the Yap Islands experienced the first significant outbreak of Zika virus disease, infecting 5005 residents out of a population of around 7500, lasting for 3 months. The affected individuals displayed a mild 'dengue-like illness' characterized by fever, arthralgia, rash, and conjunctivitis [8]. No reports of microcephaly were noted during this outbreak. The *Aedes hensilli* mosquito was the predominant mosquito species identified [35].

The Yap Islands outbreak was a turning point in the natural history of ZIKV. It was the first time a major outbreak of Zika virus disease had occurred. From only 14 reported cases, the number of cases escalated to a few thousands during the outbreak [8]. It was also the first time ZIKV was noted outside Africa and Asia in the Pacific region [8]. Though the clinical features were mild, this outbreak marked the probably first major genetic mutation that enabled greater propensity and infectivity of the virus. It has been hypothesized that frequent travel between the Philippines and the Yap Islands led to the introduction of the virus into the region [8].

Outbreaks in Oceania (2013–2014)

A series of ZIKV outbreaks occurred in the South Pacific region during 2013–2014. Prior to this, the only arboviral infections detected in these areas were dengue and chikungunya, with minor evidence of Ross River virus in circulation [36]. Evidence of ZIKV outbreaks in the South Pacific has been noted in French Polynesia, New Caledonia, Cook Islands, and Easter Island.

In October 2013, health officials in the French Polynesia noted the spread of a 'dengue-like illness' amidst a concurrent dengue outbreak in the region, in which the patients tested negative for dengue, chikungunya, and West Nile virus by RT-PCR. The outbreak spanned for about 21 weeks, affecting an estimated 30,000 inhabitants (11.5% of the population) [8]. This outbreak saw the appearance of 42 cases of Guillain-Barré syndrome as a sequela of the arboviral infection [37].

In 2014, ZIKV outbreaks were seen in New Caledonia (1400 cases; 0.8% of population), Cook Islands (49 confirmed cases), and Easter Island (20 confirmed cases) [8]. These outbreaks were of a smaller magnitude and most probably due to the spill-over of cases from the previous Polynesian outbreak with travel exchanges.

Outbreaks in the Americas (2015–2016)

The Zika outbreak in the Americas is the largest ZIKV epidemic ever experienced. Estimates suggest that there were between 440,000 and 1,300,000 cases of suspected infection during this epidemic [33]. The distribution of the disease spanned from South and Central America northwards up to Florida and Texas.

The plausible origin for the outbreak in the Americas has been retrospectively hypothesized to be in the north-eastern parts of Brazil. Brazil is home to a wide range of arboviruses with an established transmission cycle. High population density, tropical climate, predominance of *A.aegypti* and *A.albopictus*, and lack of prior exposure contributed to the widespread distribution and magnitude of the epidemic.

A sharp increase in the number of cases of microcephaly was noted in the Zika-infected areas of Brazil, with more than 4300 cases of foetal abnormalities reported [33]. In February 2016, the WHO declared Zika virus disease a 'Public Health Emergency of International Concern' due to increasing evidence suggesting the occurrence of microcephaly and neurological complications [4]. In 2015–2016, travel-associated Zika outbreaks were seen in the USA, with widespread transmission in Puerto Rico and US Virgin Islands and limited local transmission in areas of Florida and Texas [31].

Recent Outbreaks in Asia and Africa

In the recent years, ZIKV has spread to parts of Asia, Africa, and Europe with favourable ecosystems, causing travel-associated sporadic outbreaks. Epidemic strains of ZIKV from Brazil have also re-emerged to its origins in Africa, where 17 cases tested positive of ZIKV in Cape Verde (2015–2016) [8]. In Asia, outbreaks have been recorded in Singapore (August 2016), Vietnam (October 2016) and Thailand (2016–2017). A sharp rise in cases occurred in Singapore after the 2016 Summer Olympics; however, genetic analysis showed that these strains were more related to the strains from Thailand than the ones in Brazil [38].

In India, the first Zika cases were seen in 2017 in the states of Gujarat (3 cases) and Tamil Nadu (1 case). In 2018, 159 confirmed cases were recorded in Rajasthan and Madhya Pradesh [33, 39]. A recent outbreak has also been reported in the state of Uttar Pradesh (2021) [32••].

Key Observations on Recent Outbreaks

- Outbreaks after the Brazil 2015–2016 epidemic are sporadic in distribution, characterized by an initial rapid surge in cases and a brief outbreak duration.
- Unlike the sporadic cases in the 2000s, the recent appearances are caused by epidemic strains probably cultivated from the outbreaks in French Polynesia and Brazil. Thus, these strains harbour the innate potential to cause a full-blown epidemic given the right circumstances.
- The areas with a high-risk of Zika infections are those that possess an uncontrolled population of *Aedes* mosquitoes (*A. aegypti*, in particular) and a high population density. These areas overlap with the sites of recent dengue and chikungunya outbreaks.
- Patients displaying a dengue-like clinical picture with a history of recent travel to areas of previous Zika outbreaks must raise suspicion for ZIKV infection. However, the possibility of a local transmission cycle should not be ignored.

In Table 2, we provide a comparative analysis of ZIKV outbreaks, contrasting recent occurrences with previous outbreaks. Recent outbreaks primarily affected the Americas between 2015 and 2016, transmitted mainly by infected *Aedes* mosquitoes. They showed a significant association with severe birth defects, particularly microcephaly. In contrast, previous outbreaks were localized in Africa, Southeast Asia, and the Pacific Islands. The public health response to recent outbreaks was extensive, focusing on mosquito control, public education, and research, while previous outbreaks received comparatively less attention.

Impact of Zika Virus on Public Health

In recent years, ZIKV has caused concern due to its rapid spread and potential for severe health consequences, especially in pregnant women and their unborn children [44]. ZIKV has exerted a substantial burden on healthcare systems and communities, causing economic, social, and psychological impacts. Treating infected individuals, supporting affected families, and implementing prevention measures have strained healthcare systems and budgets [45]. The fear of having a child with birth defects has caused significant stress and anxiety for many families, and the stigma associated with the virus has also led to discrimination and social isolation [46].

ZIKV has been associated with potential long-term health consequences, particularly in infants and children who were exposed to the virus during pregnancy. The virus can cause a range of developmental and neurological disorders, some of which may not become apparent until later in life. ZIKV has been associated with various neurological disorders, including Guillain-Barré syndrome, which is a rare but serious condition that can cause muscle weakness and paralysis [47]. ZIKV infection during pregnancy can lead to a condition known as congenital Zika syndrome, which can cause a range of congenital defects [48]. The most common developmental disorder associated with the virus is congenital microcephaly [49].

Table 2 Contrasting Zika virus outbreaks: recent vs. previous

	Recent outbreaks	Previous outbreaks
Transmission patterns	The most significant recent outbreaks of ZIKV occurred between 2015 and 2016 in the Americas, particularly in Brazil and other countries in South and Central America. The primary mode of transmission was through the bite of infected *Aedes* mosquitoes (*Aedes aegypti* and *Aedes albopictus*), which are also responsible for transmitting dengue and chikungunya viruses [33, 40]	Prior to the 2015–2016 outbreak, ZIKV outbreaks were relatively localized and sporadic, primarily occurring in Africa, Southeast Asia, and the Pacific Islands. The primary mode of transmission was also through *Aedes* mosquito bites [41, 42]
Clinical outcomes	One of the most significant differences in recent outbreaks was the association between ZIKV infection during pregnancy and severe birth defects, particularly microcephaly, a condition where babies are born with abnormally small heads and underdeveloped brains. Other neurological complications such as Guillain-Barré syndrome have also been linked to ZIKV infection [43]	While ZIKV infections were known prior to the recent outbreaks, the association with microcephaly and other severe birth defects was not as widely recognized. The majority of ZIKV infections were asymptomatic or caused mild flu-like symptoms, including fever, rash, joint pain, and conjunctivitis [43]
Public health response	The significant public health impact of the ZIKV outbreaks led to heightened global awareness and responses. Efforts focused on mosquito control measures, public education campaigns to prevent mosquito bites, travel advisories for pregnant women, and intensified research on developing vaccines and diagnostic tests	Due to the localized nature of previous outbreaks, the public health response was not as extensive. Limited attention was given to the potential long-term consequences, such as birth defects. ZIKV research and vaccine development efforts were relatively minimal compared to the recent outbreaks

Other developmental disorders associated with the virus include optic neuropathy, congenital glaucoma, ventriculomegaly, and lissencephaly [50]. The long-term health consequences of ZIKV are still being studied, and it is unclear whether individuals who were exposed to the virus during pregnancy will experience any long-term effects. However, some studies have suggested that children who were exposed to the virus in utero may experience developmental delays, learning disabilities, and other neurological disorders later in life [51].

Public health interventions and strategies have played a critical role in controlling ZIKV outbreaks. There is no vaccine or antivirals currently available for ZIKV, making public health prevention strategies imperative to control the disease [33]. Vector control, individual protection, household/residential protection, avoiding travel to endemic areas, surveillance and safe sexual practices are principle recommendations by CDC [40]. Vector control measures have been a crucial part of the response to ZIKV outbreaks. These measures include the use of insecticides to control mosquito populations [52], the elimination of standing water where mosquitoes breed, and the use of mosquito nets and other protective measures [53]. WHO does not impose any travel restrictions on countries affected by ZIKV, but advocates pregnant women to refrain from travelling, especially during outbreaks [54]. Governments around the world are advised to educate the people before travelling to Zika endemic areas; travellers should be equipped with appropriate resources and must comply with the guidelines, follow safe sexual practices, and should contact health care providers before returning home [55]. Public education has also been a critical part of the response to ZIKV outbreaks. Educational campaigns have focused on raising awareness of the risks associated with the virus and promoting behaviour change to reduce the risk of infection [56]. Surveillance has been another critical component of the response to ZIKV outbreaks. Surveillance mechanisms have been utilized to monitor the virus's transmission and assess the efficacy of interventions. These systems have included the use of diagnostic tests to identify cases of infection and the use of epidemiological investigations to identify clusters of cases [57].

Recent Developments

Research efforts in combating ZIKV infections have recently gained momentum, particularly in the development of vaccines and antiviral drugs. Currently, there is not any single vaccine approved for clinical usage but many potential vaccines are under trial. These include the Zika DNA vaccine, RNA vaccine, viral vector vaccine, virus like particle vaccine, purified inactivated,

live attenuated, peptide based and recombinant protein vaccines, and monoclonal antibody vaccine [58•]. Several vaccine candidates have undergone preclinical and clinical evaluations to assess their safety and efficacy. A promising vaccine candidate, GLS-5700, has shown encouraging results in early-phase clinical trials, eliciting strong immune responses against ZIKV [59]. Various compounds have been investigated in antiviral drug development to inhibit viral replication and reduce Zika-associated pathogenicity. Some antiviral drugs, such as nucleoside analogues [60] and NS2B-NS3 protease inhibitors [61], have shown inhibitory effects against ZIKV in vitro. Various compounds have been investigated in antiviral drug development to inhibit viral replication and reduce Zika-associated pathogenicity. The drug category includes entry inhibitors, protease inhibitors, rNDP inhibitors, assembly inhibitors, fusion inhibitors, and nucleoside biosynthesis inhibitors that are under extensive research. Several drugs have been experimented upon but only very few have shown promising results, which leaves a major lacuna for further research [62]. Ribavirin and favipiravir are two antiviral drugs that have been considered for the treatment of ZIKV disease. However, currently, there are no FDA-approved vaccines or therapies specifically for ZIKV [63]. This highlights the urgent need for effective treatments and preventive measures against ZIKV. The results from a study indicated that both favipiravir and ribavirin could effectively suppress ZIKV replication as well as reduce ZIKV-mediated hNPCs (human neuronal progenitor Cells) death [64]. Another study demonstrated that ribavirin-based nucleoside analogues could be potential candidates for ZIKV treatment [65]. Apart from these two drugs, sofosbuvir and niclosamide have been investigated for their off-label use against ZIKV. Sofosbuvir is a nucleotide polymerase inhibitor, whereas niclosamide is an anti-helminthic drug. A recent study concluded that treatment with sofosbuvir diminishes neurodevelopmental consequences in infant rhesus macaques [66]. The results from this study support the findings of a previous study in rhesus monkeys, which showed that sofosbuvir has a possible protective role against vertical transmission of ZIKV as well as the congenital syndrome caused by it [67]. Studies have also investigated the use of niclosamide and its derivatives as possible small molecule inhibitors against ZIKV and have shown positive results [68, 69].

Several investigational vaccines are under development and are being evaluated in early human clinical trials [63]. Multiple Zika virus vaccine candidates are under development by the National Institute of Allergy and Infectious Diseases (NIAID). These encompass a DNA-based vaccine, similar to one used for West Nile virus, which has shown safety and efficacy in phase 1 and phase 2 clinical trials [70]. Additionally, a purified inactivated Zika vaccine (ZPIV) has entered phase 1 trials and utilizes a proven approach from Japanese encephalitis and dengue vaccine development [71]. An investigational live, attenuated Zika vaccine, rZIKV/D4Δ30-713, engineered from a dengue virus backbone, is undergoing phase 1 clinical evaluation [72]. Another innovative approach involves AGS-v, a vaccine targeting mosquito salivary proteins to prevent various mosquito-borne diseases, including Zika [73]. Lastly, a genetically engineered vesicular stomatitis virus-based Zika vaccine is in early-stage development, building on the success of a similar approach in an Ebola vaccine [74]. These diverse strategies hold promise for preventing Zika virus infection and represent significant strides in vaccine research.

While RT-qPCR remains the gold standard for lab-based diagnosis of ZIKV from either patient samples or insect vectors, it exhibits significant limitations as a point-of-care (POC) tool. These limitations encompass high cost, extended diagnostic timeframes, and requirement for lab expertise. Such limitations, particularly in resource-constrained settings, have necessitated the exploration of alternative diagnostic methods- rapid diagnostic methods or POC devices. One such promising candidate is loop-mediated isothermal amplification (LAMP), which has been identified as a compelling alternative to RT-qPCR for the detection of ZIKV and other arboviruses [75]. LAMP is a low-cost molecular system that can be freeze-dried for distribution and exhibits high specificity, sensitivity, and efficiency [75]. This makes it particularly suitable for use in developing countries where ZIKV is now endemic. The method is advantageous as it does not require lab-based equipment or expertise, which is a major constraint of RT-qPCR. This makes LAMP a more accessible diagnostic tool for ZIKV infections, especially in resource-poor settings [75, 76]. Within the realm of rapid diagnostic platforms, lateral flow immunoassays (LFIA) and synthetic biology-based diagnostics, including CRISPR-based diagnostics, emerge as preeminent options for detecting ZIKV [77]. Furthermore, a highly-sensitive smartphone-based fluorescent LFIA platform for the POC detection of ZIKV's nonstructural protein-1 (ZIKV NS1) has also been developed [78]. Owing to its affordability, compact form, and impressive analytical capabilities, it exhibits significant promise for the swift and precise POC identification of ZIKV NS1. Kaushik et al. proposed an electrochemical biosensor for the detection of even picomolar/femtomolar concentrations of ZIKV in the early stages of infection at point of care [79]. Pardee et al. developed an engineered paper-based optical geno-biosensor coupled with CRISPR/cas9 to detect viral RNA genomes with high specificity [80]. Moreover, the recent outbreak of ZIKV in the Americas and its devastating developmental and neurological manifestations have underscored the urgent need for field-based diagnostics that are rapid, reliable, handheld, specific, sensitive, and inexpensive. Given the lack of antivirals or

approved vaccines for ZIKV infection, a POC diagnostic test is urgently needed for the early detection of new outbreaks and to adequately manage patients.

Despite progress, crucial gaps in our understanding of the ZIKV's transmission dynamics persist, especially regarding its vectors and mechanisms of spread among diverse populations [81]. More research is needed to identify additional modes of transmission and evaluate the effectiveness of preventive measures. The immune response to ZIKV infection is not fully elucidated [23••], necessitating further studies to comprehensively characterize the host immune response and identify potential biomarkers of infection and disease progression. Finally, long-term outcomes of ZIKV infection are still not well-defined, particularly concerning the potential neurological and developmental consequences [82]. Future research should focus on understanding the long-term effects on individuals infected with ZIKV, including infants born to mothers who were infected during pregnancy. Addressing these gaps will contribute to a more comprehensive understanding of ZIKV.

Conclusions

In light of its far-reaching consequences, a thorough understanding of recent Zika outbreaks holds paramount importance for multiple compelling reasons. Firstly, the virus poses substantial health risks, particularly for pregnant women and their unborn children, resulting in severe birth defects such as microcephaly. Secondly, the globalisation and changing climatic conditions have facilitated the spread of Zika to previously unaffected regions, potentially exposing vulnerable populations. Lastly, the coexistence of Zika with other mosquito-borne diseases, such as dengue and chikungunya, adds complexity to the public health landscape. By delving into recent outbreaks, a more comprehensive understanding can be achieved, thereby informing preventive measures and evidence-based interventions to mitigate the impact of ZIKV in the future.

The resemblance in clinical symptoms and serologic cross-reactivity with other co-circulating mosquito-borne diseases like dengue and chikungunya makes early diagnosis of ZIKV infection a challenge leading to cases of ZIKV being misdiagnosed and erroneously classified as dengue in regions where dengue virus (DENV) is prevalent [83]. A limited understanding of the pathophysiology of ZIKV disease and inadequate research funding can be attributed to the lack of specific anti-viral therapy and vaccine development. Recent Zika outbreaks in various regions across the globe demand prompt action from public health practitioners and policymakers to ramp up local and national surveillance.

Hospital-based sentinel surveillance of symptomatic acute febrile illness (AFI) cases and community surveillance of asymptomatic and non-hospitalisation-requiring AFI cases can prove to be effective in identifying Zika cases, anticipating outbreaks, estimating disease burden, and taking timely preventive measures [84].

Entomologic surveillance to estimate vector density in endemic regions should be carried out. ZIKA, a mobile app developed to provide real-time data on mosquito populations and coupled with neural networks and AI, could predict vector populations and provide an early warning for taking preventive measures [85]. Proper vector control strategies in the form of source reduction, repellents, space spraying, and biocontrol measures should be implemented to eliminate mosquito breeding sites and reduce the vector population.

Public health officers and policymakers should collaborate to formulate detailed preparedness plans and assign specific roles and responsibilities to members at different levels of administrative and health systems to prevent and control further outbreaks in the future. Governments should allocate more funds for Zika-related research and foster international collaborations for the development of novel strategies aimed at prompt diagnosis and prevention of ZIKV infection.

Author contributions HJ conceived the idea and design; created the manuscript outline, wrote the introduction section, prepared figure 2 and tables 1&2, made all final edits and revisions and supervised the writing. HS wrote epidemiology section, outbreaks section and helped create table 1. HM helped write the recent outbreaks section and table 2. AV wrote the recent developments section. ND wrote the impact on public health section. AW and VS helped create figure 1. AW made revisions to impact on public health and recent developments section. ND and AW worked equally. EK wrote the conclusions section. VS made critical comments and suggested final edits and revisions. All authors reviewed the final manuscript.

Data Availability Not applicable.

Declarations

Ethical Approval Not applicable.

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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The 2021 Zika outbreak in Uttar Pradesh state of India: Tackling the emerging public health threat

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Abstract

Zika virus is an RNA virus belonging to the Flavivirus family that is chiefly transmitted by the female Aedes mosquito. The Zika virus first infected humans in Uganda and Tanzania in 1952. Since, it has spread to several parts of the world causing outbreaks of variable extent. In India, these outbreaks have been reported from Gujarat, Tamil Nadu, Madhya Pradesh, Rajasthan, Kerala, and Maharashtra. The most recent outbreak is from the most populous state of India, Uttar Pradesh, where the climate is conducive to the breeding and transmission of other arboviral infections such as Dengue, Chikungunya, and Malaria. These infections also happen to share similar incubation periods and overlapping clinical manifestations with Zika virus (ZIKV) infection, leading to misdiagnoses or delayed diagnosis. We aim to provide an account of the outbreak, its repercussions, errors made in attempting to contain the spread of the disease, and, measures to be taken in the future.

Keywords

Aedes aegypti, *Aedes albopictus*, Guillain-Barre syndrome, Zika outbreak, arboviral diseases

Introduction

Zika virus (ZIKV) is a positive-sense single-stranded RNA virus belonging to the Flavivirus family. It is responsible for an arboviral disease transmitted by bites of the female *Aedes aegypti* (primary vector[1]) and *Aedes albopictus* (secondary vector) mosquitoes amongst other Aedes species, sexual contact, vertical transmission from mother to fetus, blood transfusion, and organ transplantation. The majority of urban transmission is thought to be mediated by the Aedes mosquitoes. ZIKV was discovered in Uganda in 1947.[1] Between 1969 to 1983, Zika spread had extended to Asia, as the virus was detected in mosquitoes in India, Malaysia, Indonesia, and Pakistan. According to the World Health Organization (WHO), the first recorded outbreak of Zika was reported from the Island of Yap in 2007. A large-scale outbreak was then reported from the French Polynesia in 2013. Subsequently, another outbreak was reported from Brazil in March 2015. On the 1st February 2016, the WHO designated ZIKV infection and its associated neurological disorders as a Public Health Emergency of International Concern (PHEIC). The African and the Asian are the two major lineages of ZIKV identified through ZIKV genetic analyses.[2] In India, the first case was reported from Gujarat in November 2016 when a 34-year-old female was found ZIKV positive at B.J. Medical college, a tertiary care hospital in Ahmedabad.[3] Next, a positive case was reported from the Krishnagiri district of Tamil Nadu in June 2017. Subsequently, two outbreaks occurred in the states of Rajasthan and Madhya Pradesh in 2018. Thereafter, cases were reported from Kerala and Maharashtra in July 2021. The latest outbreak is of 150 cases of ZIKV disease (as of 24th November 2021), reported from Uttar Pradesh (UP), of which 139 were from Kanpur district alone (Figures 1 and 2).

Most patients with acute ZIKV infection are either asymptomatic or have just mild symptoms. In symptomatic cases, the most common signs and symptoms include

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maculopapular rash, conjunctivitis, low-grade fever, headache, arthralgia, myalgia, and retro-orbital pain. In areas that are endemic to dengue and chikungunya, these symptoms are hard to differentiate. ZIKV infection is suspected to cause a number of neurologic diseases including Guillain-Barre syndrome (GBS), acute myelitis, meningoencephalitis, and congenital anomalies such as microcephaly in infants born to ZIKV positive mothers.[4]

Discussion

The index case was a 57-year-old Indian Air Force (IAF) officer who presented with a high fever, skin rashes, and muscle and joint pains. His blood sample was found positive by RT-PCR testing at the National Institute of Virology (Pune, India) on 23rd October 2021. Subsequently, Kanpur emerged as the epicenter of the state's very first Zika outbreak.

Following the detection of the first case, active surveillance was carried out in a 3 km radius of Chakeri area of Kanpur (where the patient lived); with a focus on close contacts, individuals exhibiting symptoms of ZIKV infection, and pregnant females.

Multiple batches of mosquito and larvae samples were collected from the localities with confirmed cases and sent for testing to the National Institute of Malaria Research (NIMR), New Delhi. Genetic sequencing confirmed the presence of ZIKV-RNA in one of the mosquito samples. *Aedes aegypti* and *Aedes albopictus* were found to be in the highest concentration among mosquito species circulating in Kanpur. Also, the findings suggested a marked increase in mosquito densities compared to the previous year – this is expressed as the number of mosquitoes per man-hour-catch. A surge in mosquito density, from 0.66 to 1.06 per 10 man-hours was noted; indicating the presence of *Aedes* mosquito in 2–3% of the houses of the studied area.[5]

Pregnant women living in this area were traced and screened regardless of their symptom status. Taking cognizance of the current situation and complications of Zika infection, the health authorities laid out a plan to monitor pregnant females. Any who presented with fever even once would be monitored till delivery. Second level ultrasound would be used to monitor the development of the fetus, in order to detect microcephaly as early as possible.[6]

A number of factors may be responsible for the outbreak in UP, namely: (a) the similarities of ZIKA with dengue and chikungunya, virtually endemic there, (b) the state-wide distribution of the vectors, *Aedes aegypti and Aedes albopictus,* (c) geographical conditions conducive for mosquito-borne diseases with a sudden increase in vector density, (d) immunologically ZIKV naive populations exposed to a global travel upsurge after lifting of COVID travel restrictions.

The co-circulation of DENV, CHIKV, and ZIKV should be considered a serious public health concern. All these arboviruses use *Aedes aegypti* and *Aedes albopictus* for completing their transmission cycle. They also share certain early clinical manifestations. A systematic review including 34 studies from ten countries reported significant co-infection of Zika with dengue and chikungunya (among arboviruses).[7]

A few studies describe that Indian mosquito strains have a lower susceptibility threshold for ZIKV.[8] It is also difficult to diagnose Zika infection early by serology because of its very high cross-reactivity with dengue virus.

The serious significance of ZIKV is its known sexual and vertical transmission that puts pregnant women and their fetuses at risk. ZIKV attacks the placental tissue inducing vascular damage and apoptosis of the barrier resulting in impaired placental function. Transplacental transmission is most common in the first trimester.[9] The syncytiotrophoblast cells, macrophages, and fetal endothelial cells allow entry and replication of the virus.[10] Altered perfusion and decreased oxygen permeability of the placenta leading to fetal hypoxia is the reason behind poor fetal development. The most important sign of congenital Zika infection is microcephaly which may be associated with decreased brain tissue and a specific pattern of brain damage. On neurological imaging, ventriculomegaly and cerebral calcification can be seen. Damage to the eye resulting in ocular abnormalities and increased muscle tone resulting in restricted body movements and joints with limited range of motion in the infant are other common findings.[11]

Pregnant women in an area with recent Zika virus transmission need to be tested for infection and serial fetal ultrasound scans are advised to look for signs of congenital infection. Obviously, advice to avoid traveling to Zika prevalent areas and to guard against mosquito bites is mandatory.

In the adult, neurological complications of ZIKV infection mainly include Guillain Barré syndrome, meningoencephalitis, transverse myelitis, seizures, and stroke.[10]

Prediction of an outbreak through vector surveillance and enhanced surveillance of people visiting ZIKV endemic areas, if properly implemented could have prevented an outbreak in the state of Uttar Pradesh. Lack of public health awareness about ZIKV and the inability to ramp up sample collection and testing resulted in delayed containment of the outbreak. Implementation of stringent control strategies is the need of the hour as the probability of future outbreaks cannot be dismissed owing to the conducive entomological and geographical conditions in the state.

Vector control strategies listed under the National Vector Borne Disease Control Program (NVBDCP) should be strictly implemented. These include source reduction, personal protective strategies (bed nets, repellents), space spraying with chemicals (e.g. malathion), and mechanical,

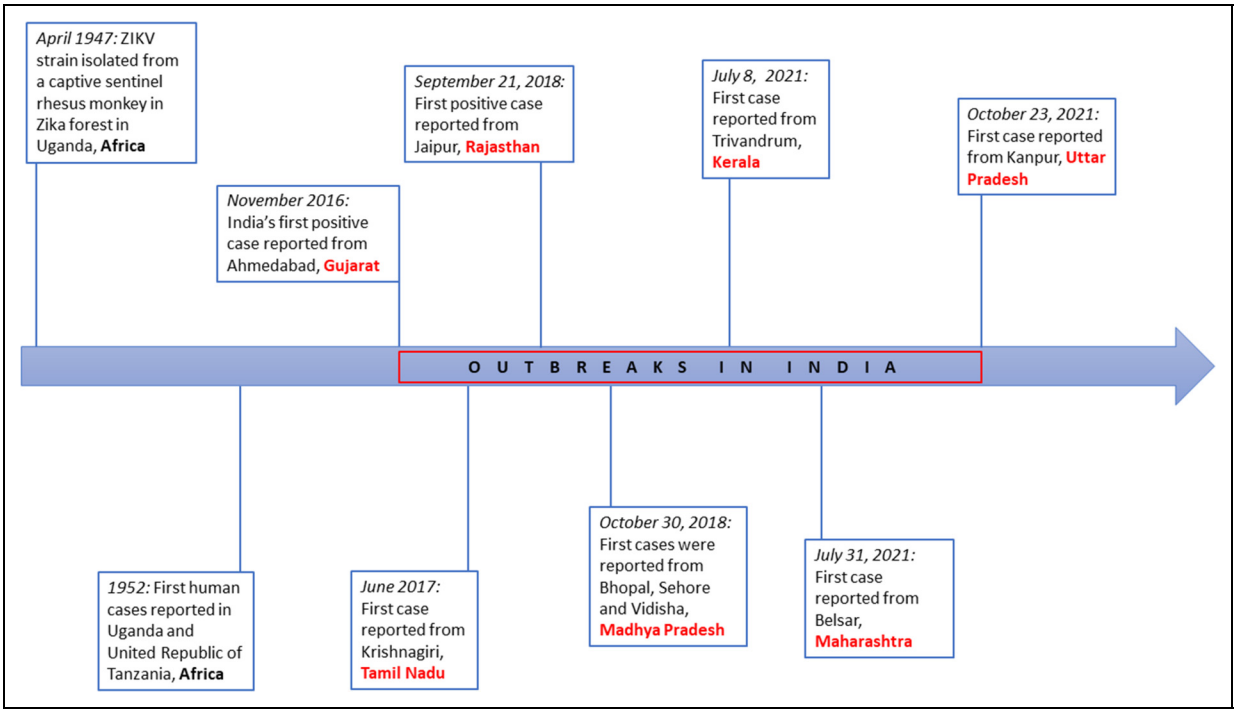

Figure 1. Timeline of Zika outbreaks in India.

chemical, and biological measures for mosquito and larva control. Some biocontrol measures which can be used in India to keep a check on mosquito population in areas with high vector density are:

1. Incompatible insect technique: Introduction of Wolbachia bacteria in mosquito populations reduces the lifespan of vectors. When an infected male mates with a normal female mosquito, no offspring is produced owing to the phenomenon of cytoplasmic instability. When an infected female mates with a normal male, Wolbachia infected offspring take birth.[12]
2. Mosquito species that can feed on larvae of other mosquitoes could also be used to reduce the vector population; one such species is *Toxorhynchites splendens*. Since it does not feed on blood, it is harmless to man.[13]
3. *Gambusia affinis*, a fish that feeds on mosquito larvae, is widely used in malaria control to reduce vector population. Such control strategies could be used in Zika vector control as well.

Techniques such as sterile insect technique (SIT) can be used to reduce vector population. Genetically modified mosquitoes have been used in dengue-endemic areas in the past, this approach could be implemented in ZIKV endemic areas also due to the same transmitting vector. Mosquitoes are genetically engineered to carry genes, which when passed on to the offspring, will not allow their survival.

Blood borne transmission can be prevented by performing screening tests and Zika virus testing should be made mandatory for blood donors in areas of outbreak. The surveillance of acute neurological illness should be strengthened and coordinated with more focus on adult surveillance in contrast to Polio where the pediatric population is focused.

Health workers providing antenatal services at ground level should be trained to recognize the symptoms early and notify the higher centers. All pregnant women should be tested in Zika endemic areas; they should be informed of the risks of congenital zika syndrome with infographics in local languages. Head circumference of the newborn should be measured by health care workers providing neonatal care and cases with microcephaly should be included under surveillance.

Directions for future

Setting up laboratories equipped with RT-PCR testing for surveillance of people in areas with high vector density should be made mandatory. Clustered regularly interspaced short palindromic repeats (CRISPR) based assays can be used for rapid detection of ZIKV in body fluid samples and for spotting the minutest mutations in the viral RNA. It can also be used for primary screening of pregnant females in endemic areas as it is quick, sensitive, and cost-effective.

The virus like particle (VLP) technology offers a promising immunization strategy against Zika for mass vaccination

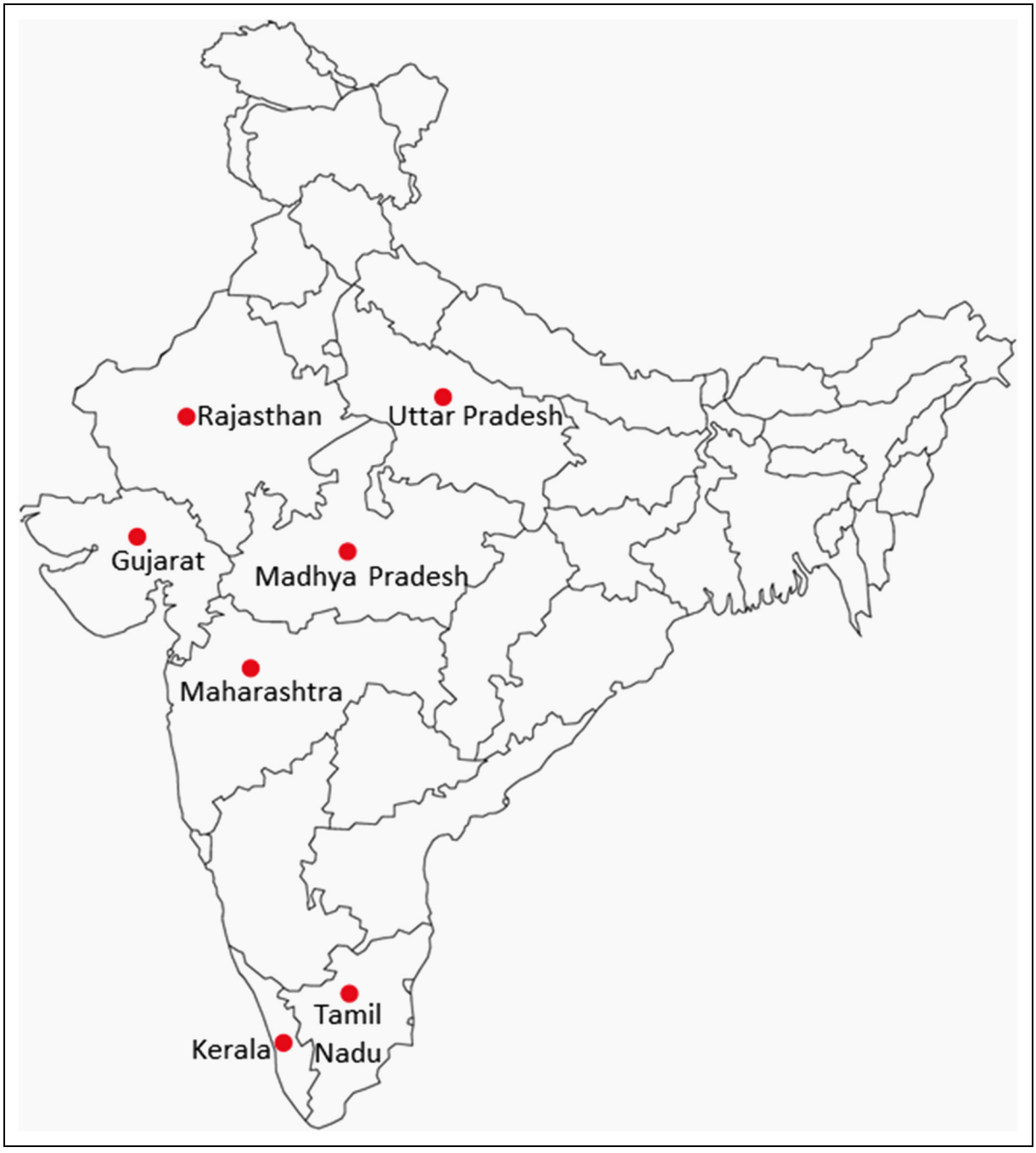

Figure 2. Locations of Zika outbreaks in India.

of the affected population, including childbearing women. Primary goal of immunization is to prevent Congenital Zika Syndrome so the vaccine should prevent intrauterine transmission in women of childbearing age; it should also prevent sexual transmission by providing mucosal protection. It should avoid the potential of antibody dependent enhancement (ADE) of disease among flavivirus infections. Recently, multiple VLP vaccine candidates have demonstrated excellent efficiency and do not cause ADE between ZIKV and flaviviruses.

Antivirals targeting specific genomic domains of ZIKV RNA like NS1 should be developed with the primary goal to prevent placental transmission of the virus. A study found increased Caspase-3 activity in ZIKV infected neural cells which induced cell apoptosis. Caspase inhibitor, Emricasan can be used as a neuroprotective agent as

it inhibits Caspase-3 in infected cells.[14] The virus has been found to target human neural progenitor cells (hNPCs) and attenuate their growth, resulting in a growth pattern similar to that of microcephalic brains.[15]

Entomological surveillance should be done on a regular basis to assess the geographical distribution of ZIKV in India. Improved approach aimed at fostering public health awareness and strict implementation of surveillance and control strategies is crucial to controlling the spread of ZIKV. These measures if properly followed can markedly reduce the risk of ZIKV outbreaks in the future.

Author contributions

Efa Khan and Himanshu Jindal conceived the idea and design, and wrote the introduction, and discussion. Himanshu Jindal organized the list of references, wrote the abstract and conclusion, and edited the final draft; Tarun Kumar Suvvari, Sadhana Joanna, Efa Khan, and Priya Mishra wrote the discussion; Efa Khan and Himanshu Jindal made critical comments and revisions. All authors revised and approved the final manuscript.

Declaration of conflicting interests

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Ethics approval and consent to participate

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Gracile Bone Dysplasia (GCLEB)

Himanshu Jindal

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Syndrome OMIM number: # 602361
Affected Gene/Chromosome: FAM111A gene
Gene OMIM number: *615292

Other Names

- Osteocraniosplenic syndrome
- Osteocraniostenosis
- Habrodysplasia
- Lethal skeletal dysplasia with gracile bones

Definition

Gracile Bone Dysplasia (GCLEB) is a perinatally fatal condition that primarily affects bone development and growth. The first cases of the disease were reported in 1988 by Maroteaux et al. as having brittle bones with narrowed diaphyses as well as slender ribs (Maroteaux et al. 1988). Other characteristics of the disease include narrowing of medullary cavities of long bones, gracile bones (bones are unusually more slender) with thin diaphyses, and premature closure of basal cranial sutures and microphthalmia (Unger et al. 2013). Since then, less than 30 cases of the disease have been reported so far. GCLEB is a rare disorder with an estimated prevalence of less than 1 in 1,000,000 (RESERVED IU-AR 2023). The age at onset of GCLEB is typically at birth or in infancy, although the severity of the disorder can vary widely among affected individuals.

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Etiology

It is currently believed that heterozygous mutations of the FAM111A gene, which codes for a protein of unknown function, is responsible for GCLEB. The majority of mutations have been found to arise de novo and inherited in an autosomal dominant fashion (Unger et al. 2013). The mechanism of causation and pathophysiology of the disease remain largely unknown.

Clinical Manifestations

Table (Maroteaux et al. 1988; Costa et al. 1998; Santos-Zabala 2012; Rosato et al. 2022; Verloes et al. 1994).

Systems	Major (signs/symptoms)	Minor (signs/symptoms)
Skeletal system	Extremely thin ("gracile") and brittle bones, long bones with diaphyseal stenosis and metaphyseal flaring, thin ribs and clavicle, cloverleaf shaped skull, flat facial profile, intrauterine bone fractures	Brachydactyly, hypomineralized skull, bone fractures at birth, platyspondyly, acromicria
Endocrine system	Low parathyroid hormone level (primary hypoparathyroidism) and hypocalcemia	–
Reticuloendothelial system	Splenic hypoplasia/aplasia	–
Nervous system	Ocular malformations including microphthalmia and aniridia	–
Genitourinary system	Micropenis in males	–
Others	Intrauterine growth restriction (IUGR), limb undergrowth	–

Diagnosis

Diagnosis is chiefly based on radiological and histopathological examination findings. Radiological findings can include hypomineralized skull, extremely thin long bones with dense metaphyses, fractures in long bones, brachydactyly, and hypoplasia or aplasia of the spleen. The diagnosis can be confirmed through genetic molecular testing for mutations in the FAM111A gene. The differential diagnoses include Kenny-Caffey syndrome, some variants of osteogenesis imperfecta, Hallermann-Streiff syndrome as well as other slender bone dysplasias (Rosato et al. 2022).

Management

Currently, there exists no treatment for this condition. The prognosis remains poor as most patients are either stillborn or die shortly after birth (Rosato et al. 2022) (Figs. 1 and 2).

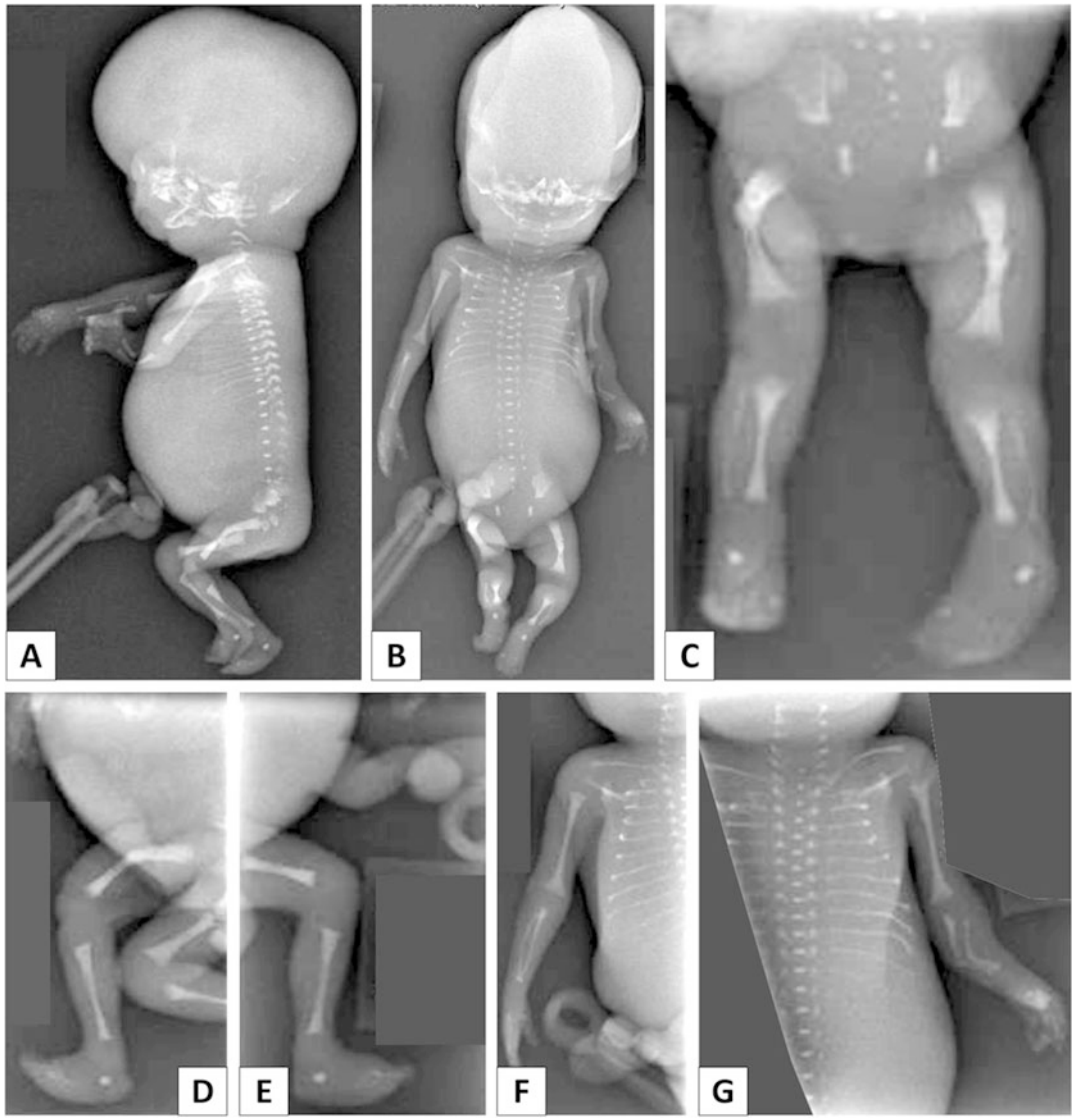

Fig. 1 Radiological findings in a case of Gracile Bone Dysplasia. (**a**–**e**) Reduced long bone length, thin long bones, bilateral femoral fractures with bowing. (**a**, **b**, **f**, **g**) Gracile and irregular ribs with fractures. (Adapted from Rosato et al. (2022). Copyright CC-BY 4.0 2022)

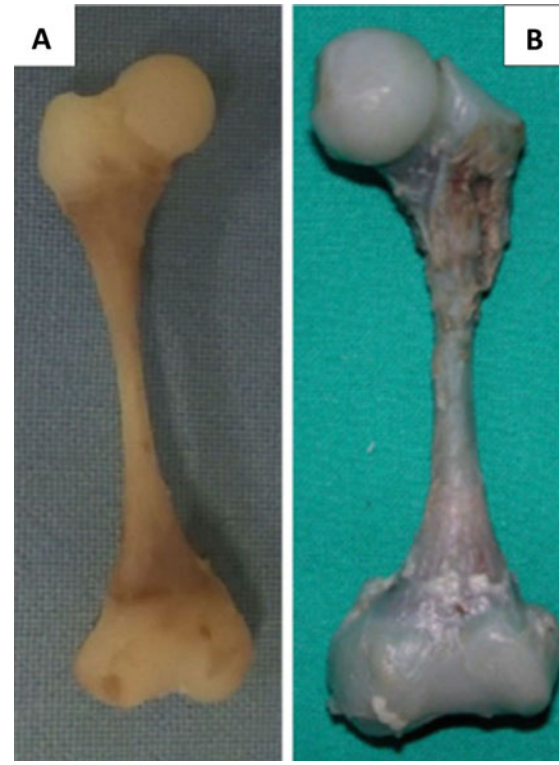

Fig. 2 Femur bones with thin diaphyses and wide metaphyses seen in Gracile Bone Dysplasia. (Adapted from Rosato et al. (2022). Copyright CC-BY 4.0 2022)

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Management of Postoperative Discitis with Debridement and Novel Technique of Local Antibiotic Instillation: Functional Outcomes from a Resource-Limited Setting

Vinay Suresh[1], Suresh H.S.[2], Bharath Raju[3], Himanshu Jindal[4], Ahmad Ozair[1,5]

■ BACKGROUND: **Patients in low- and middle-income countries (LMICs) have substantial treatment abandonment and non-adherence with outpatient oral medications. This work sought to investigate outcomes of postoperative discitis treated with debridement and a novel technique focused on reducing outpatient antibiotic requirement in an LMIC setting.**

■ METHODS: **This study, conducted and reported following STROBE guidelines, reviewed outcomes of all patients with postoperative discitis who had been debrided by 1 neurosurgeon in a resource-limited setting during 2008–2020. Patients had undergone single-level L4-L5 or L5-S1 discectomy elsewhere, later developing magnetic resonance imaging–confirmed discitis. After non-response or deterioration following intravenous antibiotics, patients underwent early debridement, followed by in-patient antibiotic instillation into disc space for 2 weeks via drain. Study outcomes were modified Kirkaldy-Willis Grade, Japan Orthopaedic Association (JOA) score, and visual analog scale (VAS) score, all assessed at 1 year.**

■ RESULTS: **Twelve patients were included, 10 male and 2 female, with median age of 46 (IQR 3.5) years. Debridement was done after median 82.5 (IQR 35) days and took median time of 105 (IQR 17.5) minutes. VAS scores (mean ± SD) decreased from 9.25 ± 0.75 preoperatively to 0.67 ± 0.89 1 year postoperatively (mean difference 8.58, 95% CI 8.01–9.15, $P < 0.001$). JOA scores (mean ± SD) improved from 4.5 ± 2.94 to 26.42 ± 1.31 1 year postoperatively (mean difference 21.92, 95% CI 20.57–23.26, $P < 0.001$). Kirkaldy-Willis grade was excellent in 6 (50%) patients, good in 5 (41.7%), and fair in 1 (8.3%). Patients became ambulatory within 2 weeks, with no major complications during 4.15 (IQR 3.45) years of median follow-up.**

■ CONCLUSIONS: **In LMICs, patients with medically refractory postoperative discitis potentially have good outcomes after debridement plus 2-week local antibiotic instillation.**

INTRODUCTION

Surgical site infections (SSIs) are a considerable challenge to the growing safety and efficacy of elective spine surgery, especially with regard to the expanding scope of less invasive approaches. Infection of the disc space, a type of deep SSI, is typically iatrogenic and may occur following both open and endoscopic spine procedures. The incidence of postoperative discitis varies between 1% and 25% in surgeries of the lumbosacral spine with a posterior approach.[1,2]

Key words
- Discectomy
- Global surgery
- Global health
- Spine surgery
- Spine infection
- Spondylodiscitis
- Spine endoscopy

Abbreviations and Acronyms
CRP: C-reactive protein
ESR: Erythrocyte sedimentation rate
HBO2: Hyperbaric oxygen
HIV: Human immunodeficiency virus
IQR: Interquartile range
IV: Intravenous
JOA: Japanese Orthopaedic Association
LMIC: Low- and middle-income country
MRI: Magnetic resonance imaging
SSI: Surgical site infection
VAS: Visual analog scale

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*Available online: **www.sciencedirect.com***

Postoperative discitis is usually treated with appropriate intravenous antibiotics for 4–8 weeks, with those not responding being taken up for surgical debridement and antibiotic wash.[3,4] Despite improvements in care systems worldwide, morbidity and mortality from postoperative discitis remain high, especially in low- and middle-income countries (LMICs), where antibiotic resistance levels may have extreme heterogeneity. This is accompanied by low levels of medication adherence for the entire recommended course of antibiotics coupled with high rates of abandonment of care.[5]

While considerable literature exists regarding discitis from high-income countries, little contemporary data exist on functional outcomes after surgical management of postoperative discitis from LMICs. This study sought to determine the outcomes of patients with postoperative discitis surgically managed in an LMIC setting and to demonstrate the utility of a novel method of 2-week disc space antibiotic instillation post-debridement.

METHODS

Study Design and Conduct

The present work was a single-arm, retrospective cohort study conducted and reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[6] The work was conducted following the ethics guidelines of the Declaration of Helsinki and after institutional ethics committee approval (approval no. BMCRI/PS/111/22–23). Informed consent for the use of de-identified data had been previously collected from the patients and/or their attendants at the time of presentation for future research activities. Patient data were collected through chart review and digitized, with confidentiality strictly maintained, through the use of an assigned record number.

Study Participants

All patients with clinically suspected and radiologically confirmed postoperative discitis who had failed conservative therapy and had undergone surgical management, by a single neurosurgeon, at a resource-limited setting in southern India from January 2008 to December 2020, were included. All patients had undergone single-level discectomy at other institutions, later developing discitis that had not responded to a minimum of 2 weeks of intravenous antibiotic therapy and had resulted in severe pain. We excluded those patients who had discitis without a history of discectomy or had undergone multi-level discectomies, or whose follow-up data on functional outcomes up until 1 year were not available.

Study Outcomes

The primary outcomes of the study were modified Kirkaldy-Willis criteria, modified Japanese Orthopaedic Association (JOA) score for low back pain, and visual analog scale (VAS) score for pain, all assessed at 1 year. The modified Kirkaldy-Willis criteria are a set of ordinal outcomes that have been well-validated in back pain.[7] These functional outcomes classify the patient into excellent, good, fair, and poor based on the patient's ability to return to work. The JOA scale, which awards a total of 29 points, has been extensively utilized in back pain-related research globally,[8] especially for evaluating functional outcomes of procedures.[9,10]

Care Pathway and Surgical Technique

All included patients had postoperative discitis diagnosed using clinical features, biochemical abnormalities, and imaging, with contrast-enhanced magnetic resonance imaging (MRI) performed in each for confirmation. All discitis patients had initially been admitted and started on intravenous (IV) linezolid and amikacin to ensure broad-spectrum coverage. The antibiotic dosage and frequency was customized to each patient based on body weight and associated comorbid status. Those who did not improve or worsened clinically even after 2 weeks of IV antibiotics, as determined through a holistic assessment based on clinical features and laboratory testing, were taken up for surgical intervention. Informed consent explaining the details of the procedure, risks involved, and the possible outcome was obtained from all patients.

The surgical procedure was done under general anesthesia, in prone positioning. The affected disc space was identified with the help of fluoroscopy and the surface was marked. The operative area was painted with betadine and draped under strict asepsis conditions. A linear incision measuring 5 cm was made over the previous surgical wound centered on the surface mark. The surgical site was dissected, carefully separating the layers of scar tissue until the lamina was exposed. The level of infected disc space was confirmed again using fluoroscopy. The lamina was minimally shaved leaving most of it intact, the posterolateral structures were then exposed and identified. The epidural scar tissue was resected, following which the dura and its nerve roots were exposed laterally on both sides. The nerve roots were carefully moved and retracted to look for any disc fragments. The infected disc material was removed from both sides and sent for culture. Thorough debridement was carried out removing all infected material from the disc space. The entire wound area and disc space were irrigated initially with normal saline followed by linezolid and metronidazole antibiotic solution. Subsequently, an infant feeding tube (number 8) was used as a drain. One end of this drain was left in the affected disc space while the other end was passed through layers of tissue away from the wound area, brought out to the skin surface, and subcutaneously fixed. The open end of the drain was closed with its cap. The surgical wound was then closed in layers using 2–0 Vicryl (Ethicon, Raritan, NJ).

Postoperatively, patients continued to receive intravenous linezolid, amikacin, and metronidazole along with a local bolus instillation of 10 mg linezolid and 25 mg metronidazole (total 5 mL each), into the disc space through the drain, twice daily for 2 weeks. Any collection in the disc space was removed before instilling antibiotics locally via the drain. Post-empiric therapy, microbial culture and sensitivity testing guided therapy. Patients were advised bed rest, with the drain being removed after 2 weeks. No postoperative oral or intravenous antibiotics were given after 2 weeks, and the patients were discharged home soon after.

Data Collection and Follow-up

Data for this study were collected via a retrospective chart review. All patients had been followed up at 2 weeks post discharge then monthly for the first 3 months and, thereafter, every 6 months. Data for primary outcomes had been recorded 1-year postoperatively and compared with preoperative values statistically. Follow-up was been conducted both in person and by telephone.

Statistical Analysis

Data analysis was performed in Stata Base Edition V17.0 (StataCorp LLC, College Station, TX). The Shapiro-Wilk test was utilized to ascertain the normality of JOA and VAS scores, which was non-significant, indicating parametric data. The preoperative and 1-year scores on JOA and VAS scales were compared using the paired *t* test. No missing data were present.

RESULTS

A total of 12 patients were included in our study, with their baseline details provided in Table 1. Median (interquartile range [IQR]) age was 46 (3.5) years, with 10 male and 2 female patients. Three patients had diabetes mellitus, 3 were obese, 2 individuals had a history of smoking, 1 had hepatitis B and 1 was human immunodeficiency virus (HIV)-seropositive, with the latter's CD4 counts >800 cell/mm^3 preoperatively and postoperatively. All patients had normal organ function. Discectomy had been performed previously in 10 cases at the L4-L5 level and in 2 cases at the L5-S1 level. All patients had constant and severe excruciating back pain (VAS score range 8–10) that got worse at night, exacerbated on movement, and showed positive straight leg raising test and pseudo-Gower sign. Six patients also had pain radiating toward the perineum, the thigh, and the legs.

Table 1. Baseline Characteristics of Included Patients in the Current Study (N = 12)

Variable	Value
Age, median (IQR; range)	46 (3.5; 28–65)
Sex, N (%)	
Male	10 (83%)
Female	2 (17%)
Prior spinal procedure, N	Single Level Discectomy (12)
Discectomy level	
L4-L5	10 (83%)
L5-S1	2 (17%)
Median ESR (IQR)	74.5 mm/hr (40.5)
Median CRP (IQR)	8.5 mg/dL (4)
Time since undergoing discectomy in days, median (IQR)	82.5 (35)
Comorbidities, N (%)	
Diabetes mellitus	3 (25%)
Obesity	3 (25%)
Smoking	2 (16.7%)
Chronic active hepatitis B	1 (8.3%)
HIV seropositivity	1 (8.3%)
Organism identified on culture	
Staphylococcus aureus	6 (50%)
Pseudomonas aeruginosa	2 (17%)
No growth	4 (33%)

IQR, interquartile range; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Debridement for postoperative discitis was performed after a median of 82.5 days (IQR 35, range 35–122 days) and had a median procedural time of 105 (IQR 17.5) minutes. None of the included patients required blood transfusion perioperatively, nor were any major intraoperative complications observed. Based on culture and sensitivity reports, *Staphylococcus aureus* was present in 6 (50%) cases, of which 4 were found sensitive to linezolid and vancomycin, and 2 others to ceftriaxone. Two cases had a positive culture for *Pseudomonas*, with sensitivity to piperacillin and amikacin. The remaining 4 cases did not show any growth in culture and hence these patients continued to receive linezolid and amikacin postoperatively in an empirical manner. The median length of stay was 32.5 (IQR 4.5) days, given the 2-week postoperative local antibiotic instillation.

Aggregate outcomes after debridement are described in Table 2 and Figure 1. VAS scores for pain (mean ± SD) decreased from 9.25 ± 0.75 preoperatively to 0.67 ± 0.89 1 year postoperatively (mean difference 8.58, 95% CI 8.01–9.15, $t = 33.02$, $P < 0.001$). JOA score scores (mean ± SD) improved from 4.5 ± 2.94 preoperatively to 26.42 ± 1.31 1 year postoperatively (mean difference 21.92, 95% CI 20.57–23.26, $t = 36.0$, $P < 0.001$). As per modified Kirkaldy-Willis Classification assessed at 1 year, outcomes were classified as excellent in 6 (50%), good in 5 (41.7%), and fair in 1 (8.3%). Representative cases of discitis treated with this technique are illustrated in Figure 2. No major complications were observed including postoperative neurologic deficits, dural tears, or cerebrospinal fluid leaks. All patients were ambulatory within 2 weeks. Patients did clinically well during median 4.15 (IQR = 3.45) years of follow-up. Relevant individual data of all 12 patients is described in Table 3.

DISCUSSION

Relevance to Global Clinical Practice

Postprocedural discitis remains a rare but inevitable challenge worldwide, which is further compounded by treatment abandonment and non-adherence to complete antibiotic therapy in LMICs. Our study finds that in resource-limited settings such as LMICs, patients with medically refractory postoperative discitis may have good functional outcomes with early debridement, followed by, in this case, subsequent use of novel 2-week local antibiotic instillation, concurrently with IV antibiotics. Given the unique challenges related to follow-up and return visits in LMICs, this work demonstrates the safety of reduction of the duration of antibiotic therapy post-debridement to 2 weeks, which eliminates the possibility of drug toxicity and also facilitates early discharge and lack of dependence on patient compliance with home antibiotics.

Postoperative spine SSI remains a challenging and inevitably encountered complication of spine surgery. Institutional protocols for the management of postoperative discitis are typically tailored based on local resource availability and clinician preferences. In this work, we utilized a novel protocol for managing such cases in a resource-constrained environment while optimizing for

feasibility and affordability. Early primary debridement of the infected disk space was combined with adjuvant local antibiotic instillation into the disc space along with parenteral antibiotics for 2 weeks. This procedure ensured that the infection site received appropriate antibiotics in adequate dosage.

Early diagnosis plays a vital role in initiating early treatment. Raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels along with characteristic MRI findings are suggestive of discitis. Similarly, all patients in the current work had raised levels of ESR and CRP along with positive signs on MRI. As the disc space is avascular in nature, various studies have revealed that direct intraoperative inoculation of the pathogen is the most likely etiology of postoperative discitis (postoperative discitis)[2,3,11] Surgical trauma, prolonged surgical time, dural tear, and intraoperative bleeding are some predisposing factors for postoperative discitis.[12]

In our study, we were able to isolate pathogens in 66.66% of the cases. The most common organism was found to be *S. aureus* (50%), which was comparable to prior studies. Ahsan et al., in 2021, reported *S. aureus* as the causative pathogen in 64% of their cases.[13]

While most cases of postoperative discitis typically respond well to conservative management, early surgical intervention plays a key role in managing refractory or potentially likely to be refractory cases. In the literature, the duration of conservative management widely ranges from 6–12 weeks and occasionally more.[4,14,15] Studies have also shown that less than 4 weeks of systemic antibiotics can result in high treatment failure.[4,16] In contrast, Rawlings et al.'s work[4] concluded that prolonged conservative management in postoperative discitis patients could lead to spinal deformities in 70% of cases even though most of them will be pain-free by the end of 2 years.[12] In the current work, surgical debridement was performed on all patients who had undergone 2 or more weeks of antibiotic therapy without major improvement and/or had debilitating symptoms despite medical therapy. Systemic antibiotics were started as per protocol, however, unlike other studies, the postoperative antibiotics were given locally and intravenously in a concurrent fashion for up to 2 weeks to eliminate the resources required and the risks involved with long-term antibiotic therapy.

Studies by Basu et al. and Ahsan et al. utilized a 3-week course of parenteral antibiotics and early intervention by performing debridement and internal fixation for achieving spinal stabilization.[13,14] In our study, we prioritized local instillation of antibiotics aided with surgical intervention with conservation of bony structures, thereby maintaining natural spine stability which allowed us to forego spinal fixation. All our patients showed remarkably rapid recovery from infection and maintained spinal stability without the need for instrumentation, which is prohibitively costly for most patients.

Outcomes of patients in our study correspond to the reasonably good outcomes reported prior, most of whom have focused on all postoperative discitis patients, not just the medically refractory ones per se. Anwar and colleagues retrospectively reviewed the outcomes of 75 patients of postoperative discitis in an LMIC setting (Pakistan) similar to the current study (India). Of these, 20 patients were operated upon after non-response to antibiotics alone.[17] They performed transforaminal lumbar interbody fusion in patients with medically refractory postoperative discitis. They reported significant improvement in pain scores as well as scores on the JOA scale in both conservatively and surgically managed patients.[17] While they hypothesized that instrumentation even during active infection does not cause re-infection, it is difficult to rule out the remote possibility of a re-infection leading to further complications. Meanwhile, Jain and colleagues reported on 12 cases of postoperative lumbar pyogenic spondylodiscitis, where a mix of management modalities was utilized, but the etiologic pathogen was not attempted to be identified in all but 2 cases. While their median antibiotic duration was 7.3 weeks, they also reported good clinical outcomes.[18] Further, Singh and colleagues had reported on outcomes of 31 cases of postoperative discitis from northern India, where they had 5 antibiotic-refractory cases. These were tackled with debridement and transpedicular fixation and had successful recovery.[19] A similar strategy was utilized in 5 medically refractory patients out of 18 postoperative discitis cases reported by Santhanam and Lakshmi from southern India.[20] Taken together, the body of literature indicates that postoperative discitis, despite the health care challenges of LMIC settings, may be managed successfully by surgeons, with outcomes similar to high-income country settings.[21,22]

Novel approaches to postoperative discitis continue to be reported, demonstrating the persisting challenge of this inevitable clinical condition. More than 15 years ago, a cross-sectional study conducted in Turkey reported a novel approach to reducing the duration of antibiotic treatment for postoperative discitis using hyperbaric oxygen (HBO2) therapy. Twenty-two patients were given HBO2 as an adjuvant for 4 weeks concurrent with IV vancomycin, and were disease-free with regard to pain and mobility after a month.[23] The same Turkish group also demonstrated

Table 2. Preoperative and Postoperative Scores of Included Patients on the Visual Analogue Scale (VAS) for Pain and the Japanese Orthopaedic Association (JOA) Score (N = 12)

Variable	Value (Mean±SD)	Mean Difference	95% CI	Paired *t* Test Value	*P* Value
Preoperative VAS score	9.25 ± 0.75	8.58	8.01 to 9.15	33.02	$P<0.001$
Postoperative VAS score at 1 year	0.67 ± 0.89				
Preoperative JOA score	4.5 ± 2.94	21.92	20.57 to 23.26	36.0	$P<0.001$
Postoperative JOA score at 1 year	26.42 ± 1.31				

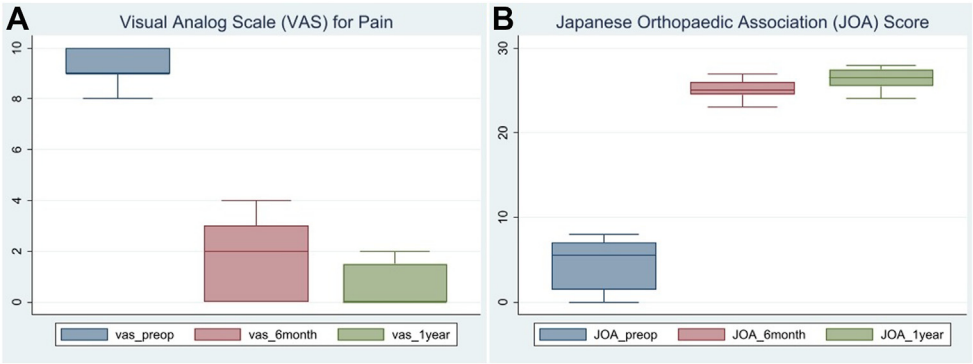

Figure 1. Box-and-Whisker plots of scores of included patients on (**A**) Visual Analogue Scale (VAS) for pain and, (**B**) Japanese Orthopaedic Association (JOA) scale. Pre, Preoperative; Post, postoperative.

efficacy of this approach with intracranial abscesses.[24] More recently, Tang and colleagues reported a novel technique of antibiotic-loaded calcium sulfate beads from China, where they used this strategy successfully on 32 patients with spondylodiscitis. They reported significant improvement in mean VAS score (7.5 to 1.6) and Oswestry disability index (65% to 10%), and found no recurrence of infection.[25]

Patients in India frequently do not adhere to the entire recommended course of antibiotics, including those recommended at our cente post-debridement. In addition, many have a tendency to self-discharge against medical advice if hospitalization is prolonged. Our novel antibiotic instillation technique allowed for both rapid resolution of symptoms during inpatient stay along with minimal/no dependence on oral antibiotics after discharge from hospital. Thus, this technique holds significant value for resource-limited settings with poor rates of medication adherence and follow-up.

Limitations

Our study had several limitations. First, we had a small sample size, which hindered the identification of predictors of superior functional outcomes post-debridement through multivariate

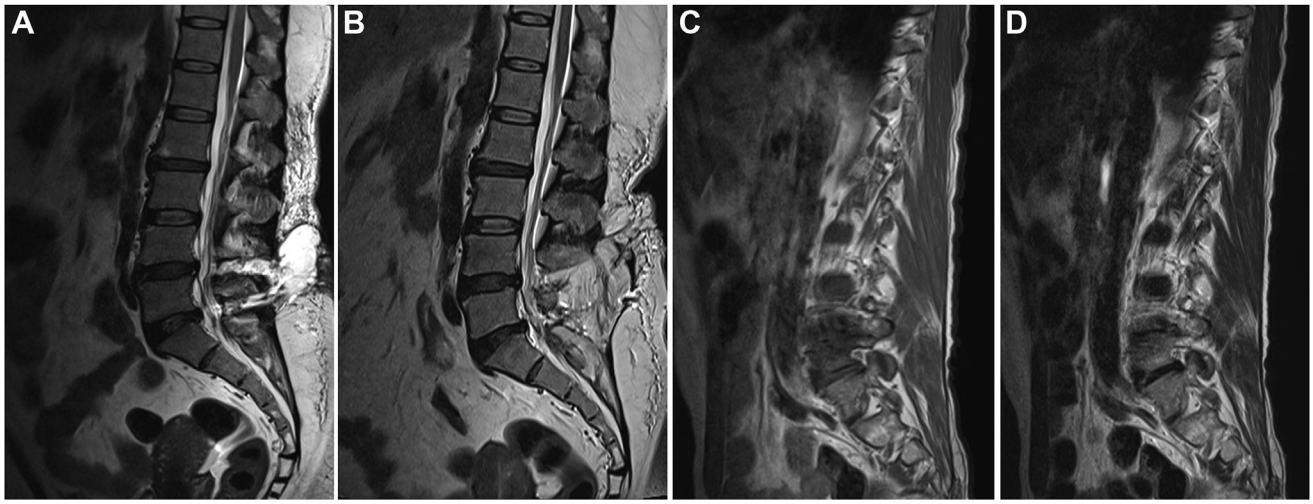

Figure 2. Representative cases treated with debridement combined with novel antibiotic instillation technique. (**A**) Case of a 47-year-old female included in the current series, who presented 8 weeks after L5-S1 discectomy with radiculopathy, ESR of 106 mm/hr and CRP of 14 mg/dL, with pre-procedure lumbosacral spine MRI shown in figure. Culture grew Staphylococcus aureus. (**B**) MRI lumbosacral spine of the same patient four years after the procedure, demonstrating healing with fibrosis, along with maintenance of disc space. (**C**) Case of a 48-year-old male with L4-5 level discectomy who presented with characteristic symptoms of discitis, with pre-operative MRI showing the involvement of the disc space along with the end plates. This patient was recently treated by the same neurosurgeon with the same technique but was not included in the current series due to not meeting minimum follow-up duration criterion. (**D**) Postoperative follow-up MRI of the 48-year-old patient after 3 months.

Table 3. Individual Data of the 12 Included Patients with Respect to Key Baseline Attributes, Clinical Profile, and Primary Study Outcomes

									VAS Score			JOA Score				
Patient Number	Age, years	Back Pain	Fever	Muscle Cramp	Radicular Pain	Time to Debridement, days	Surgical Time, days	Hospital Stay, days	Pre-op	6 months	1 year	Pre-op	6 months	1 year	Culture	Antibiotics Utilized
1	53	+	–	–	+	90	90	35	9	3	1	7	26	26	Staphylococcus aureus	Linezolid, amikacin, & metronidazole
2	65	+	+	+	–	80	110	39	10	0	0	3	26	26	Staphylococcus aureus	Linezolid, amikacin, & metronidazole
3	48	+	+	+	–	105	100	30	10	3	2	2	25	27	Staphylococcus aureus	Linezolid, amikacin, & metronidazole
4	46	+	+	+	+	120	120	35	10	2	0	6	25	26	Staphylococcus aureus	Linezolid, amikacin, & metronidazole
5	44	+	+	–	+	85	100	32	9	0	0	6	25	27	Staphylococcus aureus	Linezolid, amikacin, & metronidazole
6	28	+	–	+	+	85	95	30	8	3	1	1	24	25	Pseudomonas aeruginosa	Linezolid, amikacin, & metronidazole
7	36	+	+	+	–	65	130	37	9	2	0	8	25	28	No growth	Linezolid, amikacin, & metronidazole
8	45	+	+	+	+	35	110	35	10	3	2	1	24	25	No growth	Linezolid, amikacin, & metronidazole
9	46	+	–	+	–	55	90	33	9	0	0	5	26	28	Pseudomonas aeruginosa	Gentamicin, Levofloxacin, & metronidazole
10	44	+	+	+	+	122	120	31	10	4	2	0	23	24	Staphylococcus aureus	Linezolid, vancomycin, & metronidazole
11	47	+	–	–	+	73	110	32	9	0	0	8	27	28	Staphylococcus aureus	Linezolid, vancomycin, & metronidazole
12	47	+	–	–	+	60	100	30	8	2	0	7	27	27	No Growth	Linezolid & metronidazole

regression analyses. Second, we did not have available data from any quality-of-life scale, such as the 36-Item Short Form Survey. Third, we did not have enough data available on other predictors of postoperative discitis, due to the lack of records possessed by patients and the retrospective nature of the present study. Finally, the logistics of the present study hindered the use of an adequate comparator arm, and we plan to conduct further studies evaluating comparative effectiveness of this new intervention.

CONCLUSIONS

In resource-limited settings such as LMICs, patients with postoperative discitis not responding to conservative management have good functional outcomes following early surgical debridement, and in this case, a subsequent 2-week use of a continuous disc space antibiotic instillation concurrently with intravenous antibiotics. This protocol demonstrated the safety of reduction in the duration of post-debridement antibiotic therapy to 2 weeks, reducing dependence on patient compliance with home antibiotics. Prospectively registered and propensity score-matched cohort studies are needed to investigate whether the latter practice may further improve outcomes compared to an antibiotic wash.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Vinay Suresh: Conceptualization, Investigation, Methodology, Data curation, Writing - original draft, Writing - review & editing. **Suresh H.S.:** Conceptualization, Investigation, Methodology, Data curation, Writing — original draft. **Bharath Raju:** Writing — original draft. **Himanshu Jindal:** Writing — original draft. **Ahmad Ozair:** Supervision, Methodology, Visualization, Writing - original draft, Writing - review & editing.

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Perspective

The current status of hand transplantation in India: Challenges and opportunities*

Losing a hand can have devastating impacts on the functionality and mental health of the amputee. Hand transplantation is a procedure of modern surgery that has been known to uplift the quality of life for many patients. The first-hand transplant in India was performed in 2015 by Amrita Institute in Kerala [1]. Later that year, an Afghan soldier underwent this procedure that costed approximately 23,500 US dollars [2]. In 2017, Asia's first bilateral above-elbow hand transplant was performed in India. In the same year, a female patient received hand transplants from a male donor. It was the first such surgery in Asia. It turned out to be a milestone because, with time, the grafts started matching the muscle tone, hair growth, and skin color of the patient [3]. In 2018, an Indian soldier received bilateral hand transplantation at Armed Forces Medical College but suffered hyperacute graft rejection. It is the only reported case of hand transplant failure in India to date. A total of thirteen patients have undergone hand transplantation, and hitherto, eight institutions have performed this procedure in India (Table 1). Twelve Indian institutions have received the permission for hand transplantation [4].

However, there are multiple challenges. One of the challenges is avoiding graft rejection with lifelong immunosuppressants. Although drugs like Tacrolimus, Mycophenolate mofetil, and steroids are available in India, biological drugs like Alemtuzumab and Basiliximab are difficult to obtain. These drugs are very expensive and require special authorization from various government authorities for every individual patient. Follow-up of the patients at regular intervals can continue for years, which can be difficult in a country like India. Several legal, ethical, and social barriers are associated with this procedure. The organ transplantation act of India (1994, later amended in 2014) included hand as an 'other organ' requiring special permissions from the state-level authorities [1]. Getting informed consent from the patient is an ethical dilemma as the outcomes' data is sparse. Explaining the risks associated with hand transplantation can be difficult, especially for an Indian patient with limited education. Because of the possibility of getting a limb back, the patient may underestimate the risks associated with the procedure and immunosuppressant therapy. Moreover, there is a lack of availability of patient advocates to deal with this issue. Hence, appropriate patient selection is the most critical challenge.

There is a palpable concern regarding the acceptance of hand transplantation by society as obtaining the graft from the donor might be

Table 1
Timeline of hand transplantation performed in India.

Year of procedure	Centre where procedure was performed	Gender	Age	Unilateral/ Bilateral	Type of allotransplantation	Complications/Notable Events
2015	Amrita Institute of Medical Sciences, Kochi	Male	30	Bilateral	Below elbow	N/A
2015	Amrita Institute of Medical Sciences, Kochi	Male	30	Bilateral	Below elbow	N/A
2017	Amrita Institute of Medical Sciences, Kochi	Female	19	Bilateral	Above elbow	N/A
2017	Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry	Male	16	Bilateral	Below elbow	N/A
2018	Armed Forces Medical College, Pune	Male	33	Bilateral	Below elbow	Hyper-acute graft rejection
2018	Stanley Medical College and Hospital, Chennai	Male	29	Bilateral	Below elbow	N/A
2018	Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry	Male	31	Bilateral	Left – Above elbow; Right – Below elbow	N/A
2020	Global Hospitals, Parel, Mumbai	Female	24	Bilateral	Below elbow	N/A
2021	Amrita Institute of Medical Sciences, Kochi	Male	34	Bilateral	Below elbow	N/A
2021	Global Hospitals, Parel, Mumbai	Male	22	Bilateral	Left – Above elbow; Right – below elbow	N/A
2021	Global Hospitals, Parel, Mumbai	Male	32	Bilateral	Above elbow	N/A
2021	King Edward Memorial Hospital, Mumbai	Male	21	Unilateral	Right – Below Elbow	N/A
2022	Global Hospitals, Parel, Mumbai	Male	22	Bilateral	Left – Below elbow; Right – partial hand (2^{nd}, 3^{rd} and 4^{th} lumbricals allotransplanted)	N/A

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considered a 'mutilating procedure.' [1] Hence, there remains a dearth of donors. There is a waiting list of 108 patients, and the demand continues to grow [5].

In recent years, there has been immense research in the field of prosthetics. Ground-breaking advances in biomechanics have led to the development of prostheses with an excellent range of motion, lesser rehabilitation time, and satisfactory sensory inputs. However, these prostheses are subject to research, approval, cost, availability, and acceptance. These prostheses are therefore beyond the scope of the majority of the patients in India and other developing countries.

Recommendations to effectively deal with these challenges include formulating a national registry to keep records of all the hand transplant procedures performed across the country and help match prospective recipients with suitable donors. The highest priority should be given to optimizing patient education and rigorous follow-up. Interdisciplinary training should be provided by authorized bodies to prospective institutions. An increase in the number of authorized hand transplantation centres can help in meeting the increasing demand for the procedure. Collaboration with charitable institutions and non-governmental organizations can substantially help in procuring the necessary funding for the patients in need and in increasing awareness about the procedure in the community. India has become a renowned hub for solid organ transplantations around the world. Patients from the developing countries prefer India due to substantially lower procedural and hospital expenses as compared to developed countries. Similar potential can be mirrored for hand transplantation by streamlining the regulations.

As all the hand transplants in India have been performed within the past six years, the long-term outcomes of these procedures are yet to be studied. However, with international collaboration and intensive research, the best possible outcomes can be achieved in future patients. In the coming years, the awareness and acceptance of hand transplantation are expected to rise in India, along with the increase in government support and institutional capabilities. Although significant obstacles still remain, the future of hand transplantation in India seems promising.

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Author contribution

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Himanshu Jindal: Data curation: Writing- original draft

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Commentary

ANNALS OF MEDICINE & SURGERY

OPEN

Emergence of Japanese encephalitis in nonendemic regions of India: a public health concern?

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The case in Pune, India

The eve of 3 November 2022 witnessed the first case in about 3 years of the viral-borne disease Japanese encephalitis (JE) in the city of Pune, a nonendemic A region for the virus. A 4-year-old boy from the Wadgaonsheri area was admitted to the Pediatric ICU at Sassoon General Hospital with complaints of fever, convulsions, spastic paralysis, and altered sensorium. The child received treatment with little effect and was kept on ventilator support for 9 days. Blood and cerebrospinal fluid samples were sent for scrutinization to the National Institute of Virology (NIV), Pune. Considering suspicions of an infectious pathology, the sera of seven household members, 16 nearby residents, 18 dogs, and pigs were also sampled and reported. The samples tested positive for JE on 29 November 2022[1]. This raises concerns for a potential outbreak when considering the geographical, climatic, and sociocultural conditions of the population in the area.

The disease

JE is a viral infection caused by the Japanese encephalitis virus (JEV), a member of the family *Flaviviridae*. This neurotropic virus has five genotypes (GI–GV), with the GIII variant seen in the India–Sri Lanka–Nepal region[2]. It transmits via the bite of *Culex* mosquito species and is amplified in hosts that include pigs and ardeid birds. Humans and cattle are dead-end hosts.

JE mostly causes an asymptomatic infection, and rarely presents with clinical features that progress to a fulminant condition which include fever, altered sensorium, headache, excessive reflexes, seizures, and coma. Neuroimaging such as cranial computed tomography and MRI show bilateral thalamic changes suggestive of JE[3]. IgM capture ELISA on serum/cerebrospinal fluid is the preferred investigation of choice.

Currently, three vaccines against JE are available in India. The SA 14-14-2 is a live-attenuated cell culture–derived vaccine with a high seroconversion rate and minimal side effects. JEEV by Biological Evans India Ltd is recommended for travelers to JE endemic areas. JENVAC by Bharat Biotech is an inactivated Vero cell culture vaccine with very good seroprotection postexposure.

Treatment options for JE are quite limited, and only the complications are treatable. The administration of steroids or mannitol to manage elevated ICP is known to improve the prognosis in cases of sequelae such as seizures or status epilepticus. Good nursing and optimal electrolyte monitoring can take care of pressure sores, paralysis, and contractures[4].

Similar outbreaks in the past

In Assam, there were numerous outbreaks which resulted in 773 patients with clinically suspected viral encephalitis being admitted to various hospitals during June and August of 2000–2002[5].

A similar outbreak occurred in Gorakhpur, from July to November 2005. It was the longest and deadliest pandemic in three decades, killing 1344 people and affecting 5737 people across seven districts of eastern Uttar Pradesh[6].

Twenty-four fatalities were recorded in the Malkangiri district of Odisha between September and November of 2012 which marked the advent of the disease in the state after nearly two decades[7].

Another large outbreak broke out in the northern districts of the state of West Bengal in July 2014, infecting as many as 398 while claiming the lives of 115 citizens[8].

A large number of affected districts and a higher caseload suggest that the Northeast has been the most severely impacted region over the past decade. The figure represents a choropleth map of India and the North-Eastern States that details acute encephalitis syndrome outbreaks caused by JEV (Fig. 1).

The timeline in the figure shows similar outbreaks that have spread to various Indian states (Fig. 2).

Concerns to be raised

As JE is a vector-borne disease, open drainage in urban areas and stagnant irrigation in waterlogged fields are major concerns as

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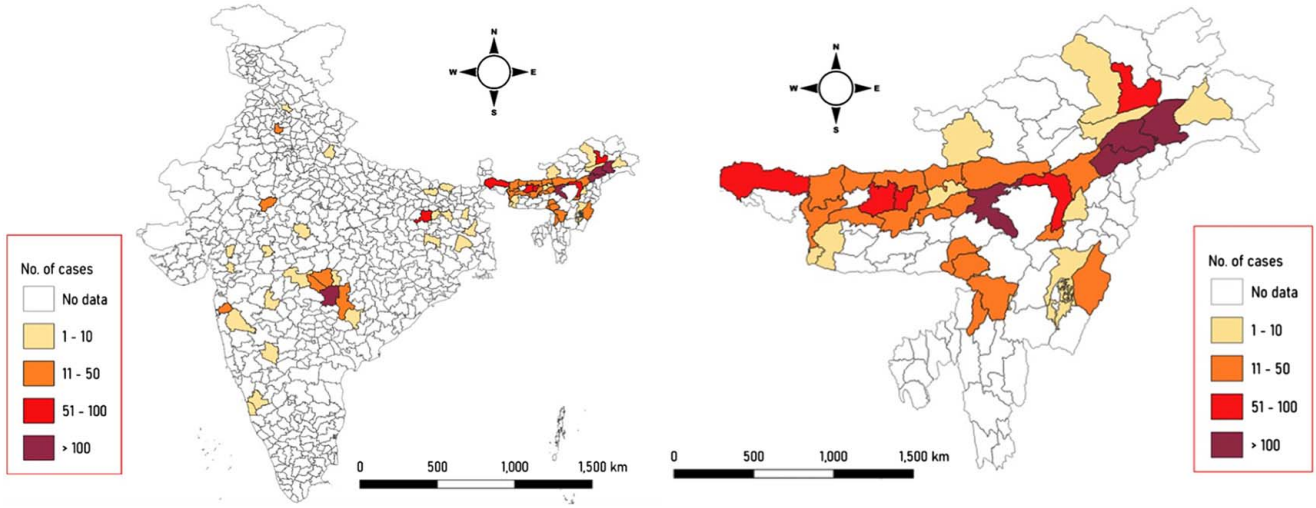

Figure 1. Choropleth maps of acute encephalitis syndrome – Japanese encephalitis outbreaks across India (left) and specifically the North-Eastern states (right).

they provide excellent mosquito breeding grounds. Pigs near these mosquito breeding hotspots raise serious epidemiological concerns. The huge population of pigs in Pune is attributed to their commercial breeding, lack of slaughterhouses, and community opposition to slaughter.

Since no anti-JEV treatments exist, prevention against JE is of utmost importance. It is mostly based on three strategies: vector control, pig immunization, and human immunization. In India, prevention is mainly based on vector control, however, vaccination is the method of choice for obtaining long-term, effective protection against JE.

There exists no effective treatment for this disease, and therefore prophylaxis in the form of vaccination is recommended. Future research prospects should include developing a vaccine that is safe, economical, and able to provide life-long immunity with a single dose.

The way forward

Following the reporting of sporadic JE and Zika cases, Pune saw the implementation of many surveillance measures, including a fever survey programme covering 480 households and an

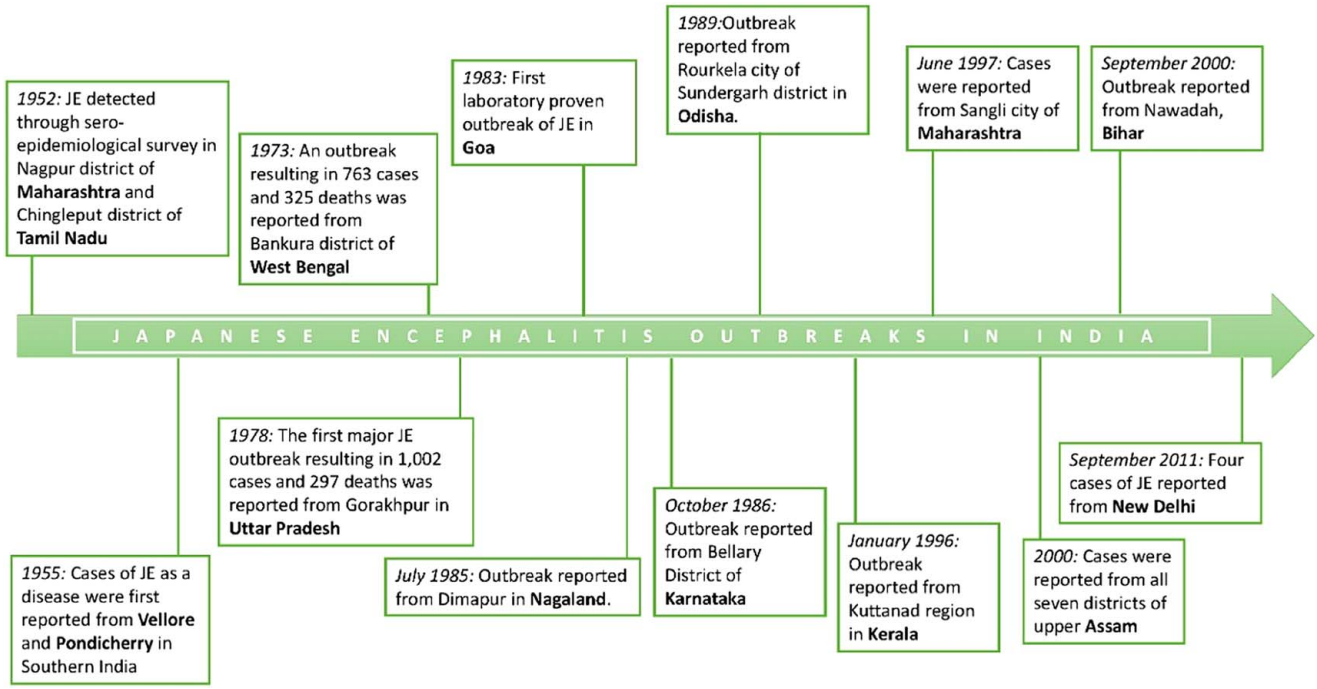

Figure 2. Japanese encephalitis (JE) outbreaks in India (timeline).

entomological survey to check for *Culex* (primarily *Culex tritaeniorhynchus*) mosquito breeding sites in commercial complexes and housing societies[9]. To curtail the spread of the disease, many Indian states have implemented public health measures like community education campaigns, vector control measures, as well as efficient surveillance under the aegis of the National Vector Borne Disease Control Program (NVBDCP).

Following the sporadic JE and Zika cases, Pune is set to immunize over 11 lakh children in the age group 1–15 years due to the district's continued *Culex* infiltration through a first-of-its-kind immunization drive in the state of Maharashtra. The Pune Municipal Corporation (PMC) is one of three municipal corporations in the state to participate in the immunization program, the others being Parbhani, and Raigad[10].

Keeping in mind the nature of recent events, clinicians and biologists should collaborate to develop tests that can invariably identify cases, to begin treatment protocols as soon as possible, while also participating in active research and trials to develop new drugs and vaccines with potential anti-JEV activity.

Conclusions

JE is the most important cause of viral encephalitis in Asia which has resulted in multiple deadly outbreaks in the Indian subcontinent. One positive case of JE, such as the one reported in Pune could lead to an upsurge in the number of cases and subsequently an outbreak. It is imperative to take measures that preclude the development of an outbreak, such as vector control and vaccination drives. The management mostly comprises supportive treatment, as no potential cure exists.

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Systemic Lupus Erythematosus With Multi-Organ Involvement in a Young Female: Lymphadenopathy, Lupus Cerebritis, Lupus Nephritis, and Cardiac Manifestations

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Abstract

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease that can affect almost every organ in the body. Its complications can often be fatal. The fatal complications include lupus cerebritis, lupus nephritis, and cardiac manifestations such as pericardial effusion. In this report, we discuss the case of a 23-year-old female who presented with complaints of high-grade fever, seizures, and altered mental state (AMS) and was found to have generalized lymphadenopathy (LAP). Various blood and urine analyses and radiological findings (chest X-ray, MRI of the head) were suggestive of lupus nephritis, lupus cerebritis, massive pericardial effusion, and thrombocytopenia. Her anti-double stranded DNA (anti-dsDNA) antibody was positive, and her pericardial fluid was positive for anti-nuclear antibodies (ANAs). She was administered IV glucocorticoids and phenytoin. She reported improvements in her symptoms gradually for a few days but eventually succumbed to the disease. Although generalized LAP is a rare initial presentation of SLE, it should be included in the differential diagnosis of the disease.

Categories: Internal Medicine, Allergy/Immunology, Rheumatology
Keywords: systemic lupus erythematosus, anti-ds dna, ana, lupus nephritis, lupus cerebritis, lymphadenopathy

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Introduction

Systemic lupus erythematosus (SLE) is a major multisystemic autoimmune disease. It has many clinical manifestations, the severity of which ranges from mild (skin involvement) to fatal complications such as lupus cerebritis [central nervous system (CNS) involvement], lupus nephritis, and pericardial effusion. The incidence and prevalence of SLE vary among different countries. The global prevalence of SLE ranges from 20 to 150 cases per 100,000 persons [1]. SLE is more prevalent in females than males due to the hormone estrogen [2]. The etiology of SLE is multifactorial, including genetic, hormonal, and environmental factors [1]. In most patients, SLE ramifies itself chiefly through hematologic, renal, and cerebral manifestations. During the early course of the disease, the symptoms generally include fever, fatigue, weight loss, joint involvement, mucocutaneous symptoms, as well as pulmonary and ophthalmic involvement. The conventional treatment of SLE includes non-steroidal anti-inflammatory drugs (NSAIDs), antimalarials, glucocorticoids, and immunosuppressive agents [1]. In this report, we present the case of a 23-year-old female who was diagnosed with SLE with multi-organ involvement. The case was complicated by lupus cerebritis, lupus nephritis, and pericarditis with massive pericardial effusion. The case posed a diagnostic challenge as it initially presented with generalized lymphadenopathy (LAP), which is not frequently seen as an initial presentation of SLE.

Case Presentation

A 23-year-old female was brought to the emergency department with complaints of recurrent high-grade fever, seizures and, altered mental state (AMS). She had been seeking treatment from a local practitioner for a previously diagnosed tuberculous pericardial effusion, which had not yet resolved. Her past medical history included iron deficiency anemia, stomatitis, right mastitis, and she had been on anti-tubercular treatment (ATT) for the past 45 days. She had a family history of tuberculosis but denied having diabetes, hypertension, or asthma. She had suffered five to six episodes of abnormal body movements and altered sensorium before being admitted to the hospital. On admission, she had a fever of 101 ℉, tachycardia with 180 beats/minute, respiratory rate of 24 breaths/minute, blood pressure of 110/70 mmHg, and low oxygen saturation of 85% on ambient air. The patient's hematological and biochemical parameters are shown in Table *1* and Table *2* respectively.

On physical examination, her lymph nodes were found to be tender and painful, and she had generalized LAP, involving the right-sided cervical, axillary, bilateral inguinal, and inter-trochanteric lymph nodes. The LAP had started as a swelling below the medial aspect of the right chin; the swelling had then progressed to

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the medial aspect of the right elbow and finally evolved to be generalized LAP. She also presented alopecia and malar rash. Her respiratory examination revealed the presence of bilateral crepitus. Her deep tendon reflexes were present but were depressed. Her CNS examination revealed a Glasgow Coma Scale (GCS) score of 8 (eye: 2, verbal: 2, motor: 4). Neck rigidity was also present. She was administered IV methylprednisolone. However, the LAP did not resolve. Later on, she was started on IV glucocorticoids and phenytoin, along with the continuation of ATT.

Parameter	Reference range	Day 1	Day 5
Erythrocyte sedimentation rate, mm/hr	0.00-20.00	53	-
Hemoglobin, g/dL	12-16.5	6.6	6.5
Total leucocyte count, cells/mm^3	4,000-10,000	18,200	12,700
Platelet count, cells/mm^3	150,000-450,000	104,000	53,000
Red blood cell count, x 10^6 cells/mm^3	3.8-4.8	2.46	2.55
Mean corpuscular volume, fL	80-100	64.2	65
Mean corpuscular hemoglobin, pg	27-32	26.9	25.5
Mean corpuscular hemoglobin concentration, g/dL	32-35	42	39.1
Packed cell volume, %	36-46	15.8	16.6

TABLE 1: Hematological parameters of the patient at the time of admission

Parameter	Reference range	Day 1	Day 5
Anti-ds DNA antibody, IU/mL	<30.00	533.77 (positive)	-
C-reactive protein, mg/dL	<0.50	16.00	-
Serum protein, g/dL	6.0-8.3	5.6	6.5
Serum albumin, g/dL	3.8-5.5	2.6	3.3
Serum urea, mg/dL	13-43	42	-
Serum creatinine, mg/dL	0.6-1.2	1.1	1.6
Serum bilirubin (total), mg/dL	0-1.2	0.6	0.6
Serum bilirubin (direct), mg/dL	0-0.2	0.2	0.2
Serum bilirubin (indirect), mg/dL	0.2-0.7	0.4	0.4
Serum sodium, meq/L	137-150	141.8	152
Serum potassium, meq/L	3.5-5.3	4.33	4.1
Serum calcium, meq/L	4.5-5.5	4.88	5.20

TABLE 2: Biochemical parameters of the patient at the time of admission

The patient's urine examination revealed proteinuria (total protein: 226.90 mg/dL; creatinine: 86.96 mg/dL; protein-creatinine ratio: 2.61), macroscopic hematuria with 15-20 red blood cells/high power field, and was indicative of lupus nephritis. Her cerebrospinal fluid (CSF) examination was suggestive of meningitis (total protein: 270.40 mg/dL; cell count: 10/mm^3; all mononuclear and glucose: 56.21 mg/dL). Her MRI scan of the head revealed enhancements in the brain parenchyma, signifying inflammation and indicating lupus cerebritis (Figure *1*).

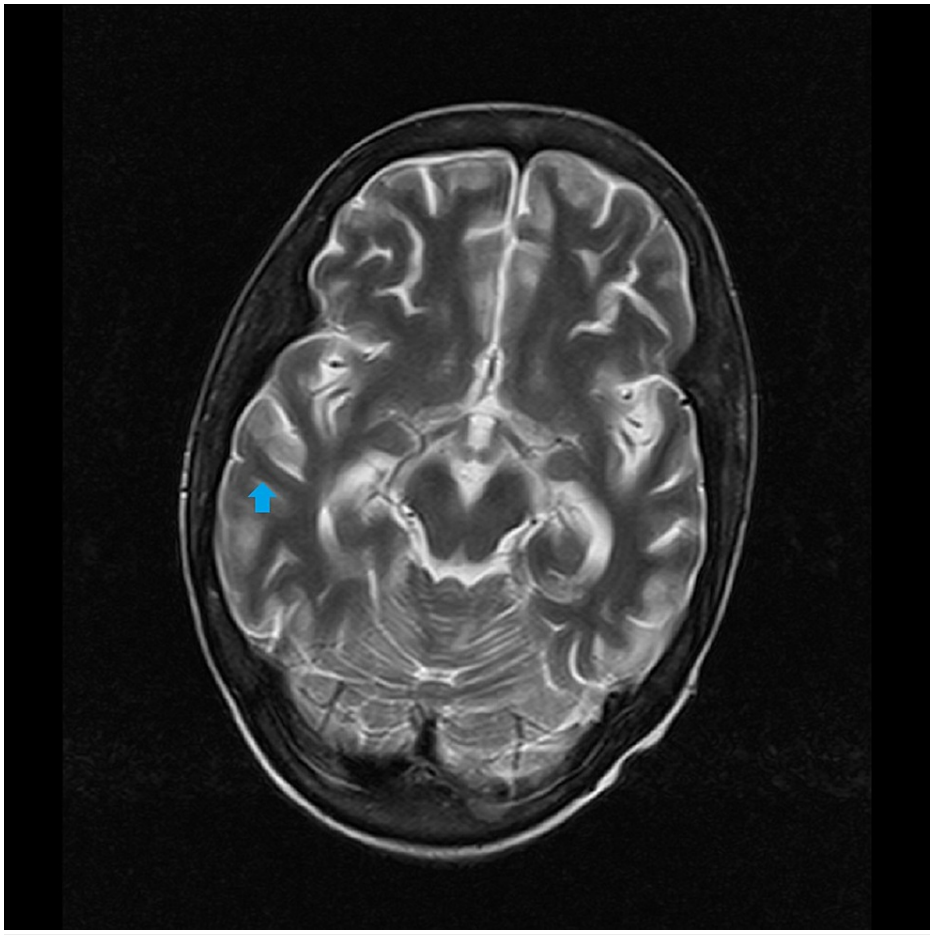

FIGURE 1: T2-weighted MRI of the transverse section of the brain showing enhanced brain parenchyma (arrow)

MRI: magnetic resonance imaging

Her chest X-ray revealed a bilaterally enlarged cardiac silhouette (Figure *2*), which raised suspicion for pericardial effusion. Her subsequent echocardiography confirmed our suspicion. Her anti-double stranded DNA (anti-dsDNA) was positive, and the anti-smooth muscle antibody (ASMA) was negative. Her immunofluorescence assay of pericardial fluid was positive for anti-nuclear antibodies (ANAs) with cytoplasmic dense fine-speckled pattern and intensity of 2+ (mildly positive) with a dilution of 1:80. In light of these findings, we concluded that her pericardial effusion was a complication of SLE rather than one caused by tuberculosis as diagnosed earlier by her local practitioner. According to the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) 2019 diagnostic criteria for SLE, a score of 10 or more must be considered as indicative of SLE. In our case, the score was 37, which is much more than what is needed to satisfy the criteria.

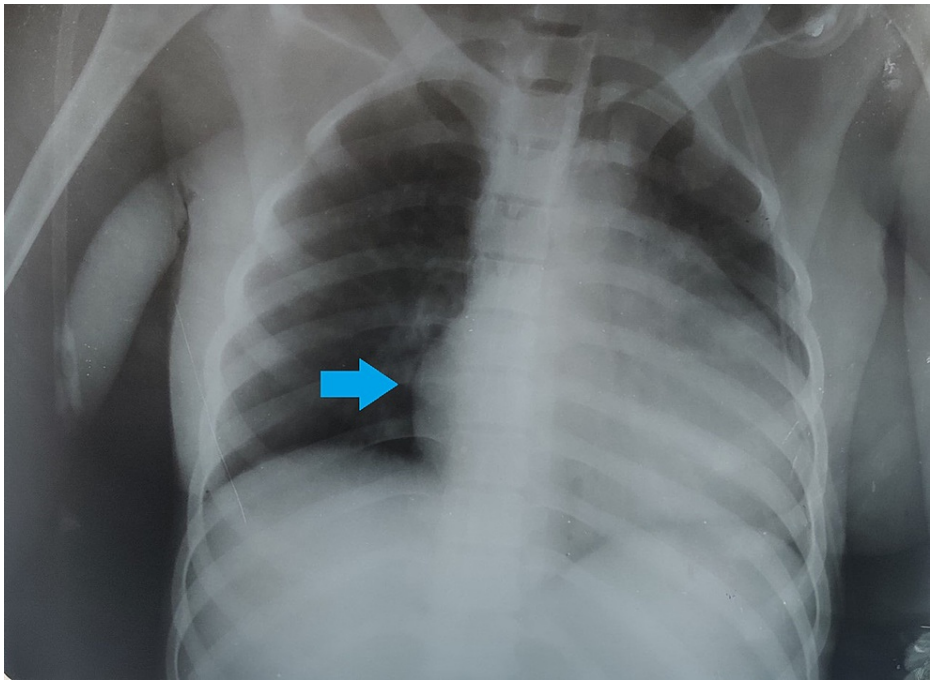

FIGURE 2: Plain chest X-ray of the patient showing bilaterally enlarged cardiac silhouette (arrow)

Even though the patient responded well to the treatment initially, she succumbed to the disease after one week of treatment.

Discussion

SLE is a multisystemic autoimmune disorder that can affect any organ in the body; it is more prevalent among females than males, one of the possible causes being the hormone estrogen. The female-to-male ratio for adults is 7-15:1 [3,4]. Many infectious and non-infectious diseases can cause LAP. Generalized/peripheral LAP is not considered to be a specific symptom of SLE. According to the EULAR/ACR 2019 diagnostic criteria for SLE, LAP is not listed as a diagnostic criterion for SLE [5]. Though the exact prevalence of LAP in SLE is unknown, there have been a few case reports where LAP has been reported as the first presenting feature in SLE. Thus, generalized LAP as the presenting feature in SLE patients is relatively uncommon [6]. Hence, when LAP presents as the first clinical feature, the diagnosis becomes quite problematic, as in our case.

Thrombocytopenia is reported in 20-40% of patients with SLE. The possible pathophysiology for thrombocytopenia is the clearance of platelets by anti-platelet antibodies [4]. Lupus nephritis is among the most severe complications of SLE; it may lead to kidney failure and is associated with a high risk of mortality. Proteinuria is reported in all patients with lupus nephritis and can be the only clinical finding besides normal or elevated serum creatinine levels. However, lupus nephritis can be classified into six types based on renal biopsy results [7]. The renal biopsy also helps determine the severity of lupus nephritis. In our case, the patient presented with marked proteinuria and elevated serum creatinine levels (Table *2*).

Cardiac complications affect 15-50% of all SLE patients, the most common one being pericarditis. A massive pericardial effusion as a presenting feature in SLE is not generally common. However, it is usually associated with kidney complications [8]. The psychiatric and neurological symptoms associated with SLE are termed lupus cerebritis and include depression, seizures, AMS, psychosis, and delirium. The clinical features that our patient presented with (seizures and AMS) and the subsequent MRI findings confirmed that she had cerebritis.

Cases with such diverse presenting complications are extremely rare. In our case, three fatal complications - nephritis, cerebritis, and pericarditis - were involved, along with various other specific and non-specific clinical features that complicated the case. Managing cases like these on an individualized basis is complex and needs a multidisciplinary approach. The details of the standard treatment for SLE are presented in Table *3*. Besides the standard treatment and phenytoin, the patient's ATT was also continued.

	Mild/constitutional symptoms of SLE and no vital organ is affected	Severe symptoms of SLE and no vital organ is affected	Multi-organ damage and thrombocytopenia are present
Basic therapy	Hydroxychloroquine (HC); addition of methotrexate or azathioprine in case the patient does not respond to hydroxychloroquine		
Induction therapy	Low-dose oral glucocorticoids (GC)	Medium-dose oral glucocorticoids	High-dose IV glucocorticoids
		Immunosuppressants, monoclonal antibodies (e.g., belimumab*, rituximab**)	

TABLE 3: Systemic therapy for SLE***

*In patients who do not respond adequately to HC and GC, with residual disease activity. **In patients with intolerance/contraindications to immunosuppressants. ***[9]

SLE: systemic lupus erythematosus

Conclusions

LAP can be associated with several etiologies. Although generalized LAP as the initial presentation of SLE is rare, it should be included in the differential diagnosis of the condition. In our case, the patient presented with generalized LAP, which made the diagnosis hard to narrow down to SLE. SLE can affect almost every organ in the body. In our case, SLE was complicated by nephritis, cerebritis, and pericarditis, along with the involvement of other tissues. We treated the patient with IV glucocorticoids (methylprednisolone) and phenytoin for seizures besides ATT for tuberculosis. Initially, the patient responded well to the treatment, but she succumbed to the disease after one week of treatment.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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A Clinical Case of Polymyositis Complicated by Antisynthetase Syndrome

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Abstract

Antisynthetase syndrome is an autoimmune condition that manifests clinically through signs and symptoms, such as interstitial lung disease, myositis, Raynaud's phenomenon, fever, hyperkeratotic fingertips (mechanic's hands), and arthritis. It is associated with antibodies against aminoacyl tRNA synthetase enzyme, the most common autoantibody being the anti-Jo-1. An 18-year-old girl presented with weakness of both the upper and lower limb, swelling and generalized body pain, difficulty in swallowing. MRI of the thigh was highly suggestive of myositis with symmetrical bilateral involvement. Based on proximal muscle weakness, elevated creatine phosphokinase (CPK), and lactate dehydrogenase (LDH), strongly positive anti-nuclear antibodies human epithelial cell type-2 (ANA-HEp2), and a normal nerve conduction velocity test with precise MRI findings, a diagnosis of polymyositis was made. She was given bolus intravenous methylprednisolone for five days, followed by oral methylprednisolone with subcutaneous methotrexate weekly. She reported a 50% improvement in muscle weakness; however, partial bulbar weakness persisted at the time of discharge. On her next follow-up, her blood investigations for auto-antibodies were done. The autoantibodies anti-Jo-1 (3+), Ro-52 (2+), and Mi-2β (2+) were found to be positive. These investigations, coupled with the clinical features she was presenting, finally led us to conclude that it was a case of polymyositis complicated by the antisynthetase syndrome.

Categories: Internal Medicine, Allergy/Immunology, Rheumatology
Keywords: antisynthetase syndrome, interstitial lung disease, myositis, aminoacyl trna synthetase, anti-jo-1 antibodies

Introduction

Antisynthetase syndrome and polymyositis are included in a broad group of heterogeneous diseases known as idiopathic inflammatory myopathies [1]. Polymyositis is an autoimmune disorder that presents with myalgia, swelling, tenderness, and proximal muscle weakness in the flexor muscles of the neck, pelvic region, thigh, and shoulders in the symmetric distribution. The estimated prevalence of polymyositis and dermatomyositis is five to 22 per 100,000 persons. The incidence of these diseases happens to be somewhere around 1.2 to 1.9 per million people per year. Though there is no official data for the epidemiology of antisynthetase syndrome, about a quarter of polymyositis/dermatomyositis cases may involve antisynthetase syndrome [2]. Dissecting the antisynthetase syndrome diagnosis, which complicates the presenting issue of polymyositis/dermatomyositis, is generally a herculean task for clinicians. The overall female-to-male incidence ratio is 2 to 3:1. In the United States, the African American to white ratio of incidence is 3 to 4:1. Antisynthetase syndrome includes the involvement of antibodies against aminoacyl transfer ribonucleic acid (tRNA) synthetase enzyme. Polymyositis patients experience difficulties performing repetitive movements, walking upstairs, working with their arms above their shoulders, or rising from a chair. Some patients may also have trouble swallowing due to throat muscles' weakness, leading to aspiration pneumonia. In rare cases, there is the involvement of respiratory muscles requiring mechanical ventilation. We present a case of polymyositis with generalized muscle weakness acute in onset and associated with significant bulbar and respiratory muscle involvement.

Case Presentation

We present the case of an 18-year-old lady who came to the outpatient department (OPD) of a public tertiary care hospital with myalgia along with proximal muscle weakness associated with the pelvic and pectoral girdle symmetrically for the last two and a half months. The weakness was preceded by febrile illness one week prior and was sudden in onset and progressed further. She was given a short course of oral steroids elsewhere, with which she had partial relief, but weakness reappeared after stopping the steroids. On admission, she was afebrile. In addition to having proximal myopathy, she admitted to having dysphagia upon deglutition of solid and liquid foods, dysphonia, and dyspnea (single breath count of only 14. There were no cutaneous rashes, fasciculations, tingling/ numbness, with no family history of autoimmune disorders. General physical examination revealed anasarca, while the neurological and sensory studies were normal. At a later stage, she had significant muscle weakness with no muscle wasting. Neurological examination showed intact higher mental function, and gag reflex was absent while the rest of the cranial

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nerves were normal. The sensory review was within the normal limits with no wasting of muscles. However, there was significant muscle weakness with grade 2/5 power at both the shoulder joints, 3/5 at elbows, wrists, hip joints, knee joints, and 4/5 at the ankle joints. All deep tendon reflexes were present, and there was bilateral plantar flexion.

There was no added sound on chest auscultation, and other systems findings were unremarkable. Her biochemical and hematological parameters are shown in Tables *1*, *2*. Viral screening for hepatitis B, C, and human immunodeficiency virus (HIV) was negative. Urine analysis revealed mild albuminuria without hematuria and pyuria. Indirect immunofluorescence assay was positive for antinuclear antibodies- human epithelial cells type-2 (ANA HEp2) with nuclear subtle speckled pattern and intensity 4+ (strongly positive) primary titer 1:100 and endpoint titer of 1:3200. Chest x-ray, echocardiogram (ECG), ultrasound abdomen, and pelvis were normal. The nerve conduction study was also normal.

Parameter	Value	Reference range
Alanine transaminase	434 IU/L	<40
Aspartate transaminase	402 IU/L	<34
RF	5.9 IU/mL	0-20
CPK-NAC	10,215 IU/L	<145
Serum LDH	1,776 IU/L	<247
Serum urea	29 mg/dL	15-40
Serum creatinine	0.9 mg/dL	0.4-1.1
Serum bilirubin-total	0.8 mg/dL	0.2-1.2
Serum bilirubin-direct	0.4 mg/dL	0.1-0.4
Serum bilirubin-indirect	0.4 mg/dL	0.2-0.8
Serum Na^{+}	147 mEq/L	135-147
Serum K^{+}	4.7 mEq/L	3.5-5.5
Serum Ca^{+2}	4.96 mEq/L	4.4-5.2
Total protein	5.7 g/dL	6.4-8.3
Serum albumin	3.3 g/dL	3.5-5

TABLE 1: Biochemical parameters of the patient at the time of hospitalization.

RF: rheumatoid factor; LDH: lactate dehydrogenase; CPK-NAC: N-acetyl cysteine activated creatine phosphokinase

Parameter	Value	Reference range
Hemoglobin	10.4 g/dlL	12-16.5 g/dlL
Total leucocyte count	11,000/mm^3	4000-10000/mm^3
Neutrophils	80%	40-60%
Lymphocytes	15%	20-40%
Red blood cell count	3.51 x10^6/mm^3	3.5-5.5 x10^6/mm^3
Platelets	270,000/mm^3	150,000-450,000/mm^3
ESR (Westergren)	45 mm/hour	Up to 20 mm/hour
HBsAg	Negative	
HCV	Negative	
HIV	Negative	
ANA-HEp2	Strongly Positive	

TABLE 2: Hematological parameters of the patient at the time of hospitalization.

ESR: erythrocyte sedimentation rate; HBsAg: hepatitis B surface immunoglobulin; HCV: hepatitis C virus; ANA-Hep2: antinuclear antibodies-human epithelial cells type-2

Magnetic resonance imaging (MRI) of the thigh was highly suggestive of myositis with symmetrical bilateral involvement (Figure *1*). A pulmonary function test revealed a possible severe restriction, but the patient had inadequate respiratory efforts. Hence, we did high resolution computed tomography (HRCT) thorax, which showed no interstitial lung disease evidence. Based on proximal muscle weakness, elevated creatine phosphokinase (CPK), and lactate dehydrogenase (LDH), strongly positive ANA HEp2, and a normal nerve conduction velocity (NCV) with precise MRI findings, a polymyositis diagnosis was made. She was given bolus intravenous methylprednisolone 750 mg/day for five days followed by oral methylprednisolone 16 mg twice a day (0.8 mg/kg) with subcutaneous methotrexate 7.5 mg weekly.

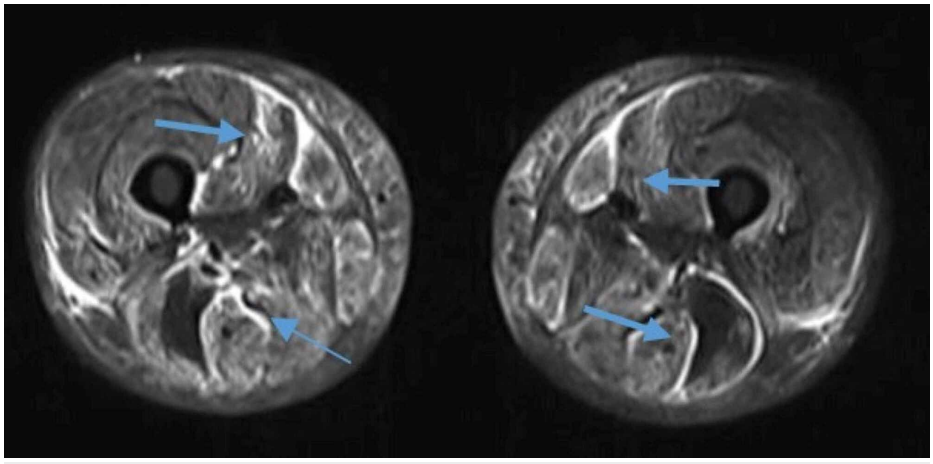

FIGURE 1: T2-weighted MRI thighs showing altered signals in thigh muscles (predominantly in adductors and extensors) symmetrically with circumferential involvement.

Following this, she had a 50% improvement in muscle weakness; however, partial bulbar weakness persisted at the time of discharge. To that, she was asked to follow-up. When she showed up on the follow-up, her blood investigations for auto-antibodies were done. The autoantibodies anti-Jo-1 (3+), Ro-52 (2+), and Mi-2β (2+) were found to be positive. Based on these investigations conjugated with the presenting clinical features, the diagnostic criteria for polymyositis complicated by antisynthetase syndrome was fulfilled. She

was then started on the following drug regimen (Table 3).

Serial number	Dosage form	Drug	Titration
1.	Injection (subcutaneous)	Methotrexate	7.5 mg once a week
2.	Tablet	Folic Acid	5 mg once a day except on the day when methotrexate was administered
3.	Tablet	Methylprednisolone	32 mg once a day
4.	Tablet	Vit. D3	60,000 IU once a month
5.	Tablet	Pantoprazole	40 mg once a week
6.	Tablet	Paracetamol	500 mg SOS

TABLE 3: The drug regimen administered to the patient.

Note: SOS, if necessary.

Discussion

Antisynthetase syndrome is an autoimmune condition that manifests clinically through signs and symptoms, such as interstitial lung disease, myositis, Raynaud's phenomenon, fever, hyperkeratotic fingertips (mechanic's hands), and arthritis (Table 4) [3]. It is associated with antibodies against aminoacyl tRNA synthetase enzyme, the most common antibody being the anti-Jo-1 [4]. Other antibodies that are commonly associated with the antisynthetase syndrome include anti-PL-7 and anti-PL-12. It is rarely diagnosed in general clinical practice, which adds to the dubiousness involved in its treatment. It has a typical constellation of symptoms in up to 30% of patients with polymyositis [5]. Polymyositis is an autoimmune inflammatory myopathy that presents as proximal myopathy and multisystem involvement, including respiratory, cardiac, and gastrointestinal systems. Some cases may have significant respiratory and bulbar participation, leading to aspiration pneumonia and respiratory failure. Evaluation of other systems is also necessary to correctly monitor the disease course. Polymyositis, complicated by antisynthetase syndrome, usually involves lung manifestations that affect the prognosis. In this case report, we present the case of a lady who got diagnosed with polymyositis complicated by the antisynthetase syndrome.

Proposed diagnostic criteria for antisynthetase syndrome by Connors et al. (2010)[2]
Required: Presence of autoantibodies against amino-acyl tRNA synthetase enzyme
Plus one or more of the following clinical features: Raynaud's phenomenon, arthritis, interstitial lung disease, fever (unattributable to other causes), mechanic's hands (hyperkeratotic fingertips)

TABLE 4: Proposed diagnostic criteria for the antisynthetase syndrome.

Polymyositis complicated with the antisynthetase syndrome is associated with multisystem dysfunction. Inflammation of the lung tissue leads to interstitial lung disease development in a vast population of individuals with polymyositis complicated by the antisynthetase syndrome. Respiratory muscle weakness results in restrictive lung disease, rarely pharyngeal, and upper esophageal muscles weakness, leading to dysphagia, which further aggravates because of the weakness of neck region muscles, resulting in an increased risk of aspiration pneumonia. Previous studies show that it is present in up to 70% of patients when investigated with sensitive techniques, such as HRCT, pulmonary function tests, and diffusion capacity.

Cardiovascular involvement is a risk factor for death among patients with polymyositis. Cardiac conduction abnormality, myocarditis can be associated with polymyositis. However, clinically evident heart involvement is rare; therefore, cardiac evaluation with ECG, echocardiography, Troponin-I is required. Constipation, diarrhea, stomach pain, gastric reflux is due to disturbed motility of the gut tract inflammation. Polymyositis can be associated with malignancies, including hematologic malignancies, such as lymphoma, solid tumors such as lung, ovarian, breast, and colon cancer. The screening for malignancies should include, at a

minimum, a careful clinical examination, routine blood tests, and a chest radiograph. For women, mammography and a gynecologic study should be conducted as well. Our patient did not show any evidence of malignancy, cardiac involvement. The patient has severe weakness in respiratory muscles, pharyngeal muscles, and upper esophageal muscles leading to dysphagia for solid and liquid foods.

Indeed, the addition of autoantibody profiles, characteristic histopathological and immunohistochemical features, and imaging techniques such as MRI would significantly strengthen the diagnosis and better define this disorder. However, our patient's diagnosis of the antisynthetase syndrome was made purely based on antisynthetase autoantibodies, certain clinical features, and MRI findings. Although these autoantibodies are present in approximately 20% of patients with polymyositis or dermatomyositis [6], a combination of MRI and P-31 magnetic resonance spectroscopy examination produces the most comprehensive and accurate evaluation of patient and outcome tool in the longitudinal analysis of response to therapy [7,8].

There is enough evidence from the literature and personal experience to leave no doubt that immunosuppressive drugs can be useful. There is currently inadequate data to suggest that anyone drug is superior to another, and the choice is primarily determined by personal experience, often from using the medicine to treat other diseases. Thus, rheumatologists tend to use methotrexate (up to 30 mg weekly), as they experience its use in arthritis and psoriasis, respectively. In contrast, many neurologists favor azathioprine (2.5 mg/kg body weight per day). Methotrexate can cause pneumonitis, and possibly this could be confused with the interstitial lung disease associated with myositis. Cyclosporin (up to 5 mg/kg body weight per day) has been advocated for use in childhood DM but is also used in the adult form of the disease. Mycophenolate mofetil (2 g daily) is currently in vogue. Cyclophosphamide has been given as intravenous pulses (up to 1 g/m2 body surface area) and oral treatment (up to 2 mg/kg body weight per day). There is some evidence suggesting that it is conducive to treating associated interstitial lung disease [9]. Immunosuppressive agents treat the pulmonary or muscle manifestations of the antisynthetase syndrome.

Our patient responded well upon administration of the drug regimen mentioned in Table *3*, leading to improved weakness and dysphagia; however, she still has mild girdle weakness, and she is still recovering from the disease.

Conclusions

Polymyositis may or may not be complicated by the antisynthetase syndrome. Treating patients under this dilemma is often a tough choice on part of the treating physician. We identified antisynthetase syndrome complicating an earlier diagnosed case of polymyositis in our patient. Corticosteroids and cytotoxic drugs are common therapies. The patient has responded well to the treatment and is now recovering from the disease.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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A Case of Sheehan Syndrome Six Years Postpartum Presented With Adrenal Crisis and Complicated by Hypothyroidism and Massive Pericardial Effusion

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Abstract

Sheehan syndrome is often a sequela of massive postpartum hemorrhage in resource-poor healthcare settings where blood loss during delivery is often neglected. The diagnosis of this rare but fatal disease is often delayed because the symptoms are vague and the pituitary dysfunction is insidious in nature. We report the case of a 35-year-old multiparous female with anhedonia and raised serum transaminases. She presented with constitutional symptoms. Her last vaginal delivery, six years back, was the last obstetric event that yielded a stillbirth child. She had had amenorrhea since then. Upon further evaluation, she was found to have a massive pericardial effusion, hypopituitarism, and a partially empty sella. This case report highlights the uncharacteristic symptoms that a patient presents with which ultimately lead to delayed diagnosis. Early diagnosis can go miles in improving the quality of life of the patient besides saving the patient from an adrenal crisis.

Categories: Endocrinology/Diabetes/Metabolism, Internal Medicine, Obstetrics/Gynecology
Keywords: sheehan syndrome, postpartum hypopituitarism, pituitary apoplexy, hypopituitarism, empty sella syndrome, adenohypophyseal hyposecretion

Introduction

First described by HL Sheehan in 1937, Sheehan syndrome refers to ischemic necrosis of the adenohypophysis due to severe hypotension usually resulting from a massive postpartum hemorrhage (PPH) [1]. It can present acutely or months to years after a delivery complicated by PPH, with symptoms of partial or panhypopituitarism. The majority of Sheehan syndrome cases occur in underdeveloped or developing countries where the risk of obstetric complications is high and skilled obstetric care is scarce, particularly in rural areas.

Certain factors have been linked with the pathogenesis of Sheehan syndrome - pituitary enlargement in pregnancy via estrogen-mediated hyperplasia of lactotrophs. An enlarged pituitary may compress the superior hypophyseal artery, a predisposition to severe ischemia in the case of massive blood loss [1,2].

Clinical presentations vary depending on the deficient pituitary hormones, ranging from selective hormonal insufficiency to classic panhypopituitarism. Magnetic resonance imaging (MRI) of the brain is the diagnostic test of choice, an empty or partially empty sella being the characteristic finding except in acute cases. Some remarkable findings include sparse pubic and axillary hair, dry skin, fine wrinkling around the mouth, and involution of breast and vaginal atrophy. Adrenocortical insufficiency due to corticotroph failure is an important consequence of Sheehan syndrome that can result in hypotension, asthenia, hypopigmentation, hyponatremia, and hypoglycemia [3].

The mean interval between a complicated delivery and diagnosis of Sheehan syndrome is reported to be around 13 years. Delayed diagnosis can be explained by non-specific presentations such as fatigue, anemia, and asthenia during the postpartum period which may be misdiagnosed as having baby blues [4]. Most patients remain asymptomatic for a prolonged duration, their condition may worsen during acute stressors resulting in adrenal crisis, myxoedema, coma, or death. This article was previously posted to the Research Square preprint server on March 23, 2022.

Case Presentation

A 35-year-old female, gravida three para three (G3P3), presented to the emergency medicine department with generalized body weakness for two months, fever for three days, and loss of appetite for 15 days. On admission, the patient was found to be hypotensive (BP: 64/30 mm of Hg) with a pulse rate of 112/min, Glasgow Coma Scale (GCS) of 11 ($E_3V_3M_5$), and oxygen saturation of 95% on room air. She had menarche at 15 years of age with normal subsequent sexual development. She admitted to having recurrent episodes of jaundice that resolved upon the local practitioner's intervention. Her history did not reveal hospitalization

for any medical condition in the past except for her deliveries. She was on anti-tubercular therapy (ATT) for the past three months. In her obstetrical history, she mentioned two vaginal deliveries that were uneventful. However, her last vaginal delivery (six years back) at a primary health care (PHC) center yielded a stillbirth child and she was kept under observation for two days for unknown reasons. The delivery took place with the help of drugs to augment labor for a vaginal delivery. This was her last delivery. She began losing weight, her health deteriorated and, she had had amenorrhea since then. She gradually had progressive body weakness and anhedonia to the extent that she could not perform day-to-day activities and was essentially bedridden.

Her physical examination revealed anasarca, generalized pallor, and asthenia. She had thinning limbs, facial edema, hair fall, and dryness of skin (Figure *1*).

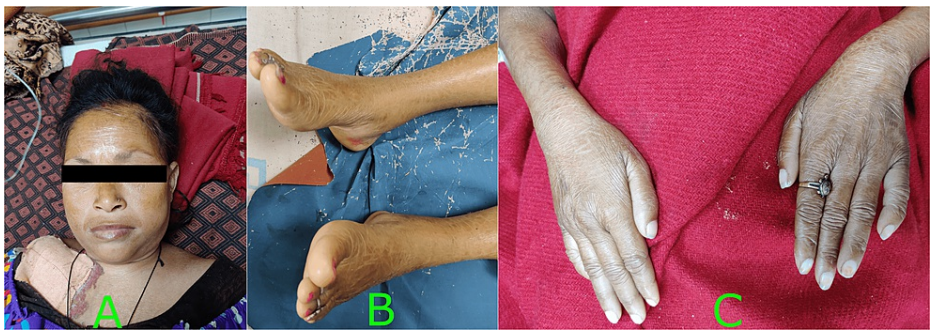

FIGURE 1: Photographs of the patient showing: (A) Coarse facial features with facial edema, wrinkles, scanty scalp hair on the forehead, and partial loss of both eyebrows; (B) Dry, scaly, and pale skin of legs; (C) Dry and scaly skin of hands

The CBC (complete blood count) revealed thrombocytopenia (135,000 cells/mm^3) and erythropenia (3.51 x 106/mm^3) (Table *1*). She was thus transfused with two units of blood on the third day of admission.

Parameter	Day 1 (On admission)	Day 4	Day 7	Day 14	Reference Range
Hemoglobin, g/dL	6.3	10.5	9.9	10.0	12-16.5
Total leukocyte count, cells/mm^3	8,700	7,500	6,600	12,100	4,000-10,000
Platelet count, cells/mm^3	135,000	79,000	61,000	38,000	150,000-450,000
Red blood cells, x 10^6 cells/mm^3	2.91	4.11	4.1	4.22	3.8-4.8
MCV, fL	62.8	62.2	72.1	72.5	80-100
MCH, pg	21.7	25.6	24.1	23.8	27-32
MCHC, g/dL	34.5	41.1	33.5	32.9	32-35
Hematocrit, %	18.2	25.6	29.5	30.6	36-46
Serum urea, mg/dL	44	-	-	46	13-43
Serum creatinine, mg/dL	1.6	-	-	1.2	0.6-1.2
Serum bilirubin (total), mg/dL	3.8	2.7	-	-	0-1.2
Serum bilirubin (direct), mg/dL	1.0	1.5	-	-	0-0.2
Serum bilirubin (indirect), mg/dL	2.8	1.2	-	-	0.2-0.7
Serum protein, g/dL	6.2	6.4	-	5.8	6.0-8.3
Serum albumin, g/dL	3.4	4.2	-	4.0	3.8-5.5
SGOT, IU/L	71	74	-	33	<40
SGPT, IU/L	14	12	-	63	<34
Serum ALP, IU/L	398	406	-	220	<240

TABLE 1: Results of complete blood count (CBC), kidney panel, and liver panel enzymes of the patient

MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, SGOT: serum glutamic oxaloacetic transaminase, SGPT: serum glutamic pyruvic transaminase, ALP: alkaline phosphatase

Her chest X-ray (CXR) revealed an enlarged cardiac silhouette that raised the suspicion of either a massive pericardial effusion or a massive cardiomegaly (Figure *2*). A 2D echocardiography confirmed that it was a massive pericardial effusion. Her pericardial fluid was sent for examination. The following test results were insignificant or inconclusive: Ziehl-Neelsen staining, adenosine deaminase (ADA), and gram staining. The cytopathology of the pericardial fluid indicated moderate cellularity with few polymorphs and macrophages in the background of an eosinophilic proteinaceous material and red blood cells. Her electrocardiography (ECG) findings revealed the presence of short-wave complexes.

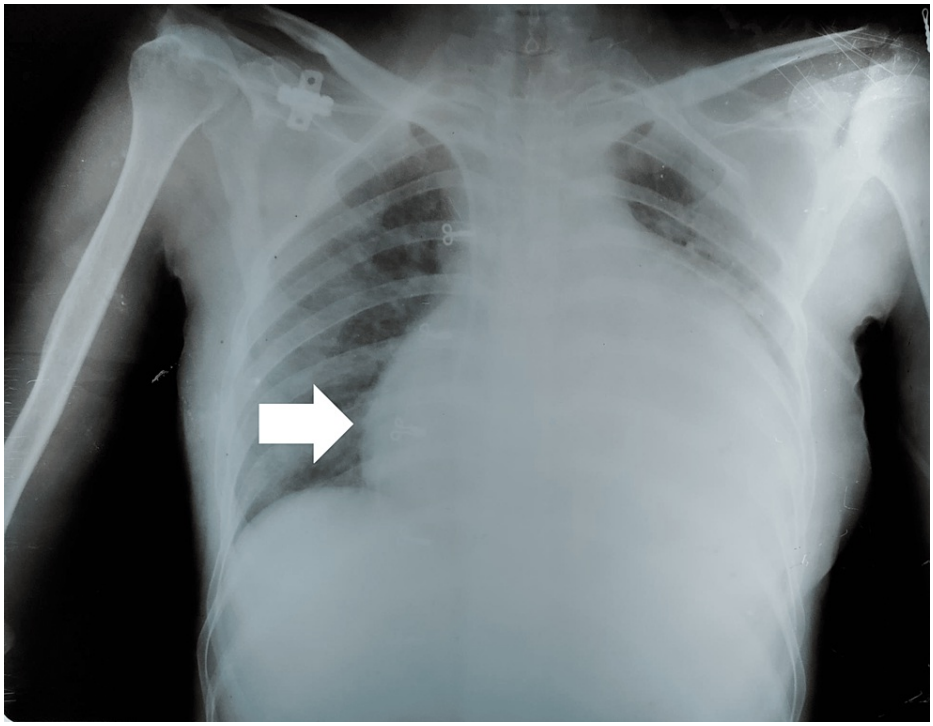

FIGURE 2: Plain chest X-ray of the patient showing enlarged cardiac silhouette (arrow)

For further evaluation, a battery of endocrinological tests was ordered (Table *2*). The hormone levels pointed towards adrenal insufficiency and hypopituitarism. A gadolinium-enhanced MRI of the brain was thus advised to the patient which revealed thinning of the pituitary gland (atrophic pituitary gland) with partially empty sella (Figure *3*). Following the initial symptomatic management and after the diagnosis was made, she was started on appropriate hormone replacement to which she responded well.

Parameter	Value	Reference Range
Serum TSH, µIU/mL	0.63	0.35-5.5
Serum free T3, pg/mL	1.28	2.30-5.0
Serum free T4, pmol/mL	0.82	12-32
ACTH, pg/mL	<5	0-46
Prolactin, ng/mL	0.689	4.79-23.3
Serum Cortisol (morning), µg/dL	1.50	3.70-19.40
Serum FSH (post-menopausal), mIU/mL	4.82	23.00-116.30
Serum LH (post-menopausal), mIU/mL	1.89	5.16-61.99

TABLE 2: Results of hormonal investigations of the patient

TSH: thyroid stimulating hormone, ACTH: adrenocorticotropic hormone, FSH: follicle stimulating hormone, LH: luteinizing hormone

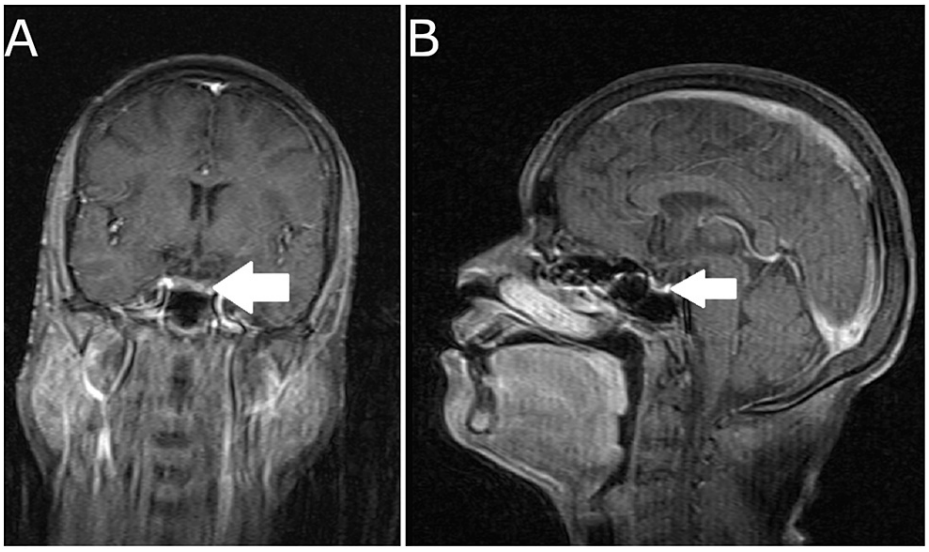

FIGURE 3: (A) T1 weighted MRI of the coronal section of the brain; (B) T1 weighted MRI of the sagittal section of the brain

The scans reveal thinning of the pituitary gland with partially empty sella (arrows). However, the pituitary stalk is normal in length and width.

MRI: magnetic resonance imaging

Discussion

The blood supply of the posterior pituitary comes from the inferior hypophyseal artery while the anterior pituitary is supplied indirectly by portal vessels coming from the hypothalamus and posterior pituitary. This low-pressure system feeding the anterior pituitary makes it more susceptible to ischemia after any vascular insult [5]. During pregnancy, this gland undergoes hyperplasia, increasing the nutritional and metabolic demands of the gland. In the case of a massive PPH, this gland undergoes ischemic necrosis in 1-2% of women who lose 1-2 L of blood with associated hypotension [3].

The clinical manifestations associated with this condition can result from selective loss of pituitary function or even panhypopituitarism. There is often a delay of months to years in the diagnosis of the condition due to the late presentation of vague and non-specific symptoms including fatigue, weakness, and anemia after the initial vascular insult [6]. Our patient presented six years after her last obstetric event because the signs of adenohypophyseal insufficiency are often delayed and subtle [7]. She gave birth to a stillborn and thus could not provide a history of failure to lactate. Owing to pituitary dysfunction and hypoprolactinemia, failure to lactate can occur along with a low serum level of prolactin as seen in this patient. Her amenorrhea and gradual deterioration after the delivery were, to the most extent, neglected until she was hospitalized.

In our patient, the history was also notable for six years of amenorrhea and low serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) compared to the post-menopausal levels, indicating pituitary dysfunction as the cause of early menopause. Another less frequent cause of panhypopituitarism is lymphocytic hypophysitis, an autoimmune condition that needs to be ruled out in the diagnosis of Sheehan syndrome [8]. The low serum prolactin level in our patient along with a history of PPH makes Sheehan syndrome a more likely diagnosis.

Hypothyroidism from the deficiency of thyroid-stimulating hormone (TSH) secreted by the anterior pituitary is responsible for a majority of clinical manifestations in our patient. Fatigue, loss of appetite, edema, hair loss, and dry wrinkling skin seen here can be explained by the deranged thyroid profile. A major cause of pericardial effusion is hypothyroidism, which usually gets corrected upon achieving a euthyroid state [9]. Pituitary dysfunction leads to disruption of normal adrenocorticotropic hormone (ACTH)-cortisol axis seen as adrenocortical insufficiency. Common features of adrenal insufficiency like weight loss, anorexia, nausea, vomiting, lethargy, and fatigue along with skin pigmentation and loss of axillary and pubic hair have been observed in people with primary adrenal failure [10]. Hypotension and tachycardia accompanied by impaired consciousness at the time of admission of our patient indicate that she was in a state of adrenal crisis secondary to ACTH deficiency which was confirmed by low serum levels of ACTH and cortisol on analysis (Table *2*).

According to a cohort study in Costa Rica, approximately 50% of patients with Sheehan syndrome develop

panhypopituitarism, whereas only adrenal insufficiency is seen in around 33% of patients, and the remaining present with just hypothyroidism [11]. Confirmation of diagnosis of Sheehan syndrome is done by imaging of the pituitary gland and sella turcica where an empty sella is present in about 70% of patients, and a partially empty sella is present in about 30% of patients on MRI [12]. After the establishment of diagnosis, the aim of the treatment is to correct the endocrine imbalances such as hypoglycemia and adrenal insufficiency that warrant urgent care. The normal function of the thyroid, adrenals, and ovaries can be maintained by hormone substitution for life. It is important to have regular follow-ups for response assessment and dose regulation of the medications.

Conclusions

Though the occurrence of Sheehan syndrome has slowly declined over time with better management of labor and delivery, in the resource-poor healthcare settings of developing countries, its cases are still witnessed owing to neglected blood loss during delivery and poor management. The late presentation of this condition can result in a delay in diagnosis. The condition can be fatal and warrants an early diagnosis through recognition of symptoms as well as a blood workup in a female with massive PPH.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Priya Mishra and Himanshu Jindal contributed equally to the work and should be considered co-first authors.

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Anesthetic Management of a Patient With Common Carotid Artery Stenosis Undergoing Laryngeal Carcinoma Surgery: A Case Report

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Abstract

Laryngectomy is a common surgery for an oncosurgeon, but underlying carotid compromise is a serious concern for anesthesiologists, making this routine procedure a high-risk one. The utmost vigilance of the anesthesiologist is demanded by the surgery to prevent morbidities such as hemiplegia, hemiparesis, or speech abnormalities that may occur due to perfusion insufficiency secondary to the mechanical blockage of the carotid arteries. Hence, an undiagnosed case of carotid artery block may result in disastrous consequences for the patient, surgeon, and anesthesiologist. Hence, it is imperative to perform all the pre-operative investigations with due diligence. We present the case of a 74-year-old male who was admitted to our set-up for laryngeal carcinoma surgery. The patient had received chemoradiotherapy (CRT) six months earlier. He complained of hoarseness in his voice and a painless neck mass. He was a known case of hypertension for 14 years, controlled by oral medication, and had a history of stroke five years ago, when he was also diagnosed with a completely blocked right common carotid artery (CCA) and a partially blocked left common carotid artery.

Categories: Anesthesiology, Otolaryngology, Oncology
Keywords: carotid artery block, laryngeal carcinoma, general anesthesia, laryngeal neoplasm, carotid artery stenosis

Introduction

Carotid artery stenosis is found in 10-20% of all patients suffering from an ischemic stroke [1]. Studies show that, out of all the co-morbidities, arterial stenosis is the one that is most directly related to a higher risk of stroke. Hence, the primary objective of all diagnostic tests and strategies must be to ascertain the degree of stenosis [2]. The North American symptomatic carotid endarterectomy trial (NASCET) states that in patients who are treated conservatively for carotid artery stenosis, the ipsilateral recurrence of stroke is 4.4% and 13% for stenosis occluding 50-69% and 70% of the arterial lumen, respectively. In asymptomatic patients, the risk of getting a stroke is 1-2% for 60% stenosis. However, the risk increases with age, occlusion of the contralateral artery, poor collateral circulation, evidence of silent embolization, coronary artery disease, longstanding inflammatory state, or peripheral artery disease [3].

Administering general anesthesia in a patient with carotid artery stenosis, on one hand, allows us to control the ventilation and airway of the patient, while on the other hand, anesthetic agents reduce the sympathetic and baroreceptor activity, resulting in an alleviation in cardiac output and blood pressure. In addition to this, the anesthetic depth may mask intraoperative neurological complications [4,5]. Some studies proposed the ability of hypercapnia to cause cerebral vasodilation and increase cerebral blood flow; however, it may lead to cerebral vascular steal phenomenon causing adverse effects [6-8]. Propofol is the most widely used induction agent; however, it causes hypotension by reducing sympathetic outflow and producing a negative inotropic effect, among other mechanisms. Thiopental causes a milder reduction in cardiac output and blood pressure, due to which it is preferred over propofol in cases where severe hypotension is to be prevented [9,10]. In addition to this, thiopental shows neuroprotective effects against hypoxia, inflammation, degeneration, and energy failure. Ketamine and nitrous oxide (N_2O) increase brain metabolism and, consequently, oxygen consumption, while the former also interacts with neurological monitoring. Hence, both of these anesthetic agents must be avoided in patients with already compromised cerebral blood flow [11]. Studies have revealed that a combination of sevoflurane, propofol, and N_2O perturbs cerebral homeostasis and vascular reactivity [12].

Case Presentation

A 74-year-old married male with a body mass index of 20.11 kg/m ^{2}, was admitted to our set-up on June 29, 2019, for surgery in a case of carcinoma of the larynx post chemoradiotherapy (CRT) six months back at another set-up. The patient complained of hoarseness of voice for the past nine months and of a painless neck mass for eight months, which was gradually increasing in size without redness or restriction in neck

movement. The patient was a known case of hypertension for the past 14 years, which was moderately controlled by amlodipine (5 mg BD). He had an episode of ischemic stroke five years ago, and he had been taking clopidogrel (75 mg OD), aspirin (81 mg OD), and atorvastatin (80 mg OD) since then. The patient admitted to having no history of smoking or alcohol intake. The patient's family history was insignificant.

On admission, the patient's vitals were stable, and the pre-anesthetic workup ordered by the anesthesiologist revealed low hemoglobin (10.3 g/dL), low red blood cell count (4.1 × 106/mm^3), low packed cell volume (30%), high creatinine (1.36 mg/dL), and high potassium (5.2 mEq/L; reference range: 3.5-5.1 mEq/L). Other investigations were within the normal range. An electrocardiogram (ECG) and echocardiography showed sinus bradycardia with no other abnormalities. The general physical examination revealed pallor, an enlarged right supraclavicular lymph node, and a non-palpable right carotid artery. Other peripheral pulses were palpable. The patient's American Society of Anesthesiologists Physical Status (ASA-PS) was grade III.

The patient had undergone bilateral carotid doppler study and multi-detector computed tomography (MDCT) carotid angiogram five years back when he had suffered a stroke. The studies revealed that the right common carotid artery (CCA) was totally occluded at the bulb and there was no flow in the right internal carotid artery (ICA). The left CCA showed a 57% diameter reduction. Repeat bilateral carotid doppler study in April 2019 (Table *1*) showed a complete thrombus in right CCA from origin to the bifurcation causing 80% luminal compromise and two calcified plaques in the left CCA causing 55% luminal compromise. There was increased anterograde flow in both vertebral arteries due to distal narrowing.

Date	Important events
2005	Diagnosed with hypertension
2014	Suffered from a stroke, was diagnosed with common carotid artery block
October 2018	Developed complaint of hoarseness in voice
November 2018	Noticed a painless neck mass
January 2019	Underwent chemoradiotherapy for Ca Larynx
April 12, 2019	Repeat MDCT carotid angiography, bilateral carotid doppler study
April 19, 2019	DLscopy (direct laryngoscopy) biopsy
June 20, 2019	PET-CT
June 24, 2019	Stopped clopidogrel and started LMWH
June 29, 2019	Admitted at our set-up for surgery
July 1, 2019	Underwent surgery for carcinoma of the larynx
July 4, 2019	Patient discharged
September 4, 2019	Follow-up

TABLE 1: Chronology of the patient's illness and his management

LMWH: low molecular weight heparin, MDCT: multi-detector computed tomography, PET-CT: positron emission tomography and computed tomography.

After the routine investigations, a direct laryngoscopic biopsy was performed and the histopathological report confirmed the presence of well-differentiated squamous cell carcinoma of the keratinizing type. Positron emission tomography and computed tomography (PET-CT) revealed increased fluorodeoxyglucose (FDG) uptake in the anterior half of the right vocal cord with a maximum standardized uptake value (SUVmax) of 6.3. A diffuse increase in FDG uptake was seen in the left vocal cord with a SUVmax of 4.1, which appeared physiological in nature. FDG uptake was also seen in the metabolically active right supraclavicular node measuring 0.5 × 0.8 cm^2 with a SUVmax of 3.7 and the prominent right upper paratracheal node measuring 0.1 × 0.6 cm^2 with a SUVmax of 7.2 (Figure *1*). Hence, total laryngectomy with partial pharyngectomy, bilateral modified neck dissection, central compartment clearance, and permanent tracheostomy was scheduled for July 1, 2019 (Table *1*). According to the intraoperative frozen section histopathological report, out of the 13 lymph nodes examined, none showed neoplastic involvement.

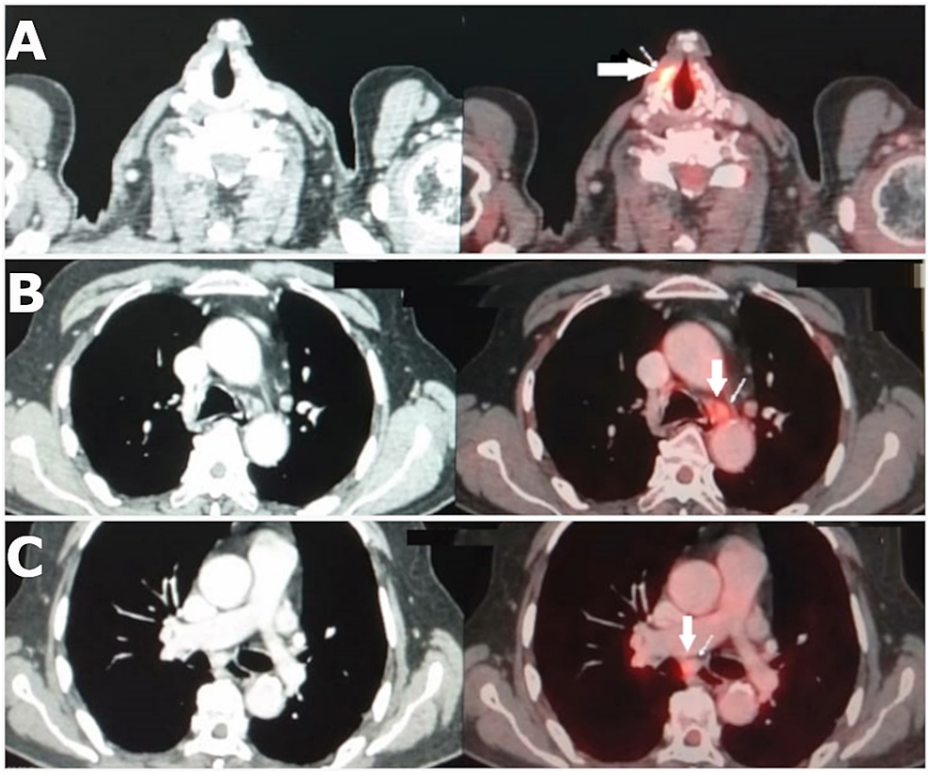

FIGURE 1: PET-CT for the spread of the carcinoma of the larynx

(A) Transaxial CT and fused PET-CT images showing focal FDG avidity along anterior half of right vocal cord (arrow); (B) transaxial CT and fused PET-CT images showing mild degree FDG avid left lower paratracheal node (arrow), which appeared nonspecific reactive in nature; (C) transaxial CT and fused PET-CT images showing mild degree FDG avid subcarinal node (arrow), which appeared nonspecific reactive in nature. FDG: fluorodeoxyglucose, PET-CT: positron emission tomography and computed tomography.

We stopped clopidogrel seven days before surgery and started low molecular weight heparin (LMWH) on a prophylactic dose as advised by the physician and neurologist (4000 units of injection Dalteparin given subcutaneously once a day). On the day before surgery, the patient was kept nil-by-mouth overnight for eight hours with an ongoing maintenance intravenous (IV) infusion of 0.45% saline at 2 mL/kg/hour. On the day of the surgery, after shifting the patient to the operating theatre in the morning, we secured an 18-gauge IV line and attached a monitor to the patient to record his blood pressure (non-invasive), SpO_2, respiratory rate, heart rate, end-tidal CO_2 ($etCO_2$), agent gas monitor (AGM), ECG, temperature (oropharyngeal), and peripheral nerve stimulator (PNS). Foley's catheter was inserted to monitor urine output.

Induction of anesthesia

The patient was pre-oxygenated for five minutes with 100% oxygen. Premedication was done with fentanyl (2 mg/kg/hr), midazolam (1 mg), glycopyrrolate (0.2 mg), and ondansetron (8 mg). The patient was induced at 9:00 am with thiopental (200 mg IV slowly) followed by succinylcholine (100 mg). Nasal intubation with a north nasal Ring-Adair-Elwyn (RAE) tube (no. seven) under the guidance of video laryngoscopy (no. 3 non-channel blades, Ambu India Pvt. Ltd., New Delhi, India) was uneventful.

Maintenance of anesthesia

Anesthesia was maintained with a 40:60 mixture of oxygen and air along with sevoflurane, and relaxation was maintained with atracurium (a 50 mg loading dose followed by a maintenance dose of 0.2 mg/kg/hr throughout surgery by continuous infusion). Intra-operatively, the patient was hemodynamically stable. Hypotension was prevented by keeping the mean arterial pressure (MAP) at more than 90 mmHg. Fluid (0.45% saline) was given at the rate of 6 mL/kg/hr, and urine output was well-maintained at 50 mL/hr. Total blood loss during the surgery was 210 ml, and crystalloids given to the patient amounted to two liters. We kept the dobutamine and norepinephrine drips ready in case hypotension occurred; however, its need did not arise. Ventilation was maintained with a tidal volume of 300 ml, respiratory rate of 14 breaths/minute, inspiration/expiration ratio of 1:2, (fiO_2) = 40 with closed-circuit ventilation and low flow anesthesia.

During the operation, at the time of permanent tracheostomy, the nasal RAE tube was changed to the tracheostomy tube.

Reversal of anesthesia

The reversal was achieved at 2:00 pm with neostigmine (0.05 mg/kg) and glycopyrrolate (0.004 mg/kg) administered very slowly, and the complete reversal was confirmed with peripheral nerve stimulation (PNS). The patient was fully awake, conscious, cooperative, well oriented to time, place, and person without any CNS abnormalities or signs of any neurological damage, and was shifted to the intensive care unit (ICU).

The patient was discharged on the fourth postoperative day (POD) without any complications. Injection Dalteparin (4000 IU OD subcutaneous), atorvastatin (80 mg), and thrice-daily nebulization were started from the first POD onwards. On the second POD, the patient was started on a liquid diet, and physiotherapy was started as the patient complained of difficulty in the neck and upper arm movement. On the third POD, the patient was shifted to the ward from the ICU. Post-operative neurology consultation was not needed as there were no neurological deficits. The patient was called for follow-up one week later to check for surgical wound discharge, and a review of the medication was done by the consulting physician on the date of restarting Aspirin and Clopidogrel. On follow-up after two months, the patient was assessed for alleviation of his presenting complaints (Table *1*).

Discussion

Any surgery requiring the administration of general anesthesia in a patient who has a known case of carotid stenosis falls under high risk and must be performed under caution. Risk factors in our patient comprised carotid artery stenosis, the patient being on clopidogrel, a history of stroke, high creatinine and potassium levels, a medical history of hypertension, and a history of radiation to the head and neck region. Before planning the surgery, we advised the patient to go for carotid endarterectomy, which is a moderate-risk procedure with a MACE (major adverse cardiac events) risk of 1-5%. However, the patient did not consent to the procedure. To maintain cerebral perfusion during surgery, hypotension was avoided in the patient by using thiopental sodium (200 mg IV slowly) instead of propofol for induction, and a 0.45% saline drip was maintained throughout the surgery to keep the MAP at more than 90 mmHg. We stopped clopidogrel seven days before surgery and started LMWH on a prophylactic dose as advised by the physician and neurologist (4000 units given subcutaneously once a day). Due to the patient's high creatinine levels, we avoided using nephrotoxic drugs. As a consequence of high potassium levels, we refrained from using IV fluids containing potassium; hence, we used 0.45% saline rather than ringer lactate (Hartmann's solution), which we normally use at our set-up. Since we anticipated difficult intubation as a result of past radiation to the neck, we used succinylcholine during intubation as its benefits outweighed the risk of further increasing serum potassium in this situation [13]. Anti-hypertensives were given on the day of the surgery, and the patient was kept under strict hemodynamic control throughout the duration of the surgery. Due to a history of radiotherapy and multifocal lytic-sclerotic lesions found on MDCT of the neck, we anticipated difficult intubation and, therefore, kept the fiber optic cable ready. With these precautions, we managed to do a successful operation on this patient and also received a good outcome.

Conclusions

General anesthesia in a patient with carotid artery stenosis allows us to control the ventilation and airway of the patient, but anesthetic agents reduce cardiac output and blood pressure. Thiopental has neuroprotective effects, while ketamine and nitrous oxide cause short- and long-term damage to brain cells by increasing brain metabolism and oxygen demand. Taking appropriate precautions in high-risk patients in terms of replacing clopidogrel with LMWH before surgery, using thiopental sodium instead of propofol for induction, maintaining an intraoperative MAP higher than 90 mmHg, avoiding nephrotoxic drugs, and using 0.45% saline instead of ringer lactate is crucial for a successful operation and good prognosis, as in our case.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Discussion: ICIPI is a rare complication of anti-PD-1/L1 therapy that should be promptly recognized as it can lead to irreversible pancreatic atrophy, as well as endocrine and exocrine insufficiency. Future work can be geared to better understand the pathophysiology of ICIPI and inform the management of affected patients.

S1587

Concurrent Acute Appendicitis and Cholecystitis in a Patient with Right Upper Quadrant Abdominal Pain

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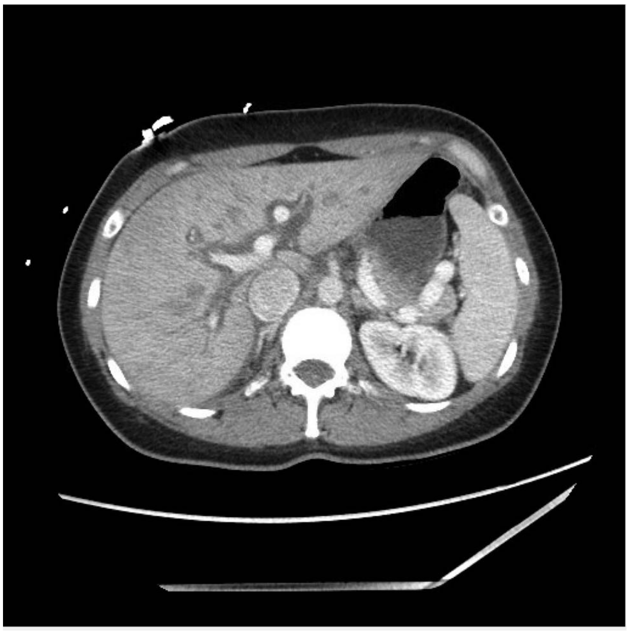
Introduction: The differential diagnosis for a patient presenting with right upper quadrant pain is broad, and it commonly includes hepatobiliary pathology. Appendicitis in the subhepatic region is a rare condition that can present as acute cholecystitis. We present a case of acute appendicitis, not diagnosed until surgery, presenting as right upper quadrant pain and causing inflammation of the gall bladder.

Case Description/Methods: A 35-year-old female with no significant past medical history presented to the hospital with constant, severe, and sharp right upper quadrant pain of one day duration. This was associated with nausea and chills. She reported no vomiting or similar pain in the past. On presentation, patient's vital signs were significant for a heart rate of 55 beats/min and a blood pressure of 88/43 mm/Hg. She was afebrile. Physical exam revealed right upper quadrant abdominal tenderness with no guarding or rebound tenderness. Labs showed a white blood cell count of 12.1 x 10^9/L. Liver function tests were within normal limits. CT abdomen and pelvis showed abnormal appearance of the liver diffusely, suggesting hepatocellular disease. Ultrasound of the abdomen revealed heterogeneously thickened gallbladder wall which might represent acute cholecystitis. HIDA scan showed no evidence of acute cholecystitis though gallbladder ejection fraction was at 0 percent suggesting biliary dyskinesia. During her hospital stay, patient was then taken to the operating room for presumed cholecystitis. During the surgery, an acutely inflamed appendix was identified in the right upper quadrant adjacent to the gallbladder. There was gallbladder wall edema and mild inflammation. Purulent fluid was noted in the peritoneal cavity. Laparoscopic appendectomy and cholecystectomy were performed with eventual improvement in patient's symptoms.

Discussion: Inflammation of a subhepatic appendix is rare, and it accounts for only 0.09 percent of all appendicitis cases. During embryonic development, failure of descent of the cecum can result in a subhepatic position of the appendix. This abnormal position makes it very challenging to diagnose appendicitis. In this patient, the acutely inflamed appendix adjacent to the gallbladder might have caused inflammation in the gallbladder wall resulting in concurrent cholecystitis. Concurrent acute appendicitis and cholecystitis is rare, but it should be considered when patients present with right upper quadrant paint.



[1587] **Figure 1.** CT abdomen and pelvis: abnormal appearance of the liver diffusely suggesting hepatocellular disease.

S1588

Extra Pancreatic Pseudocyst (EPP) as an Initial Presentation in an Alcoholic Woman With No Previous Medical History

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Introduction: Pseudocyst of pancreas is the most common complication of Acute and chronic pancreatitis. Pseudocysts can be intrapancreatic, peripancreatic and extra pancreatic. EPP in liver is a rare complication of Acute and chronic pancreatitis and only 26 cases have been reported so far. Here we are presenting a case of extra Pancreatic Pseudocyst located in the gall bladder fossa.

Case Description/Methods: A 59-year-old female with history of Chronic alcohol use presented with severe abdominal pain of 10 days duration. The pain was sudden in onset, sharp, constant located diffusely throughout her abdomen but was noted to be worse on the right upper (RUQ), radiating to her lower back and right shoulder. She drinks at least 2 glasses of wine daily for several years. Vital signs are stable on admission. On physical exam, the abdomen was soft, rigid with rebound tenderness in RUQ. Labs showed an elevated C-Reactive Protein 20.6, Sedimentation Rare 123, WBC 18.2, platelets 637, lipase 906. Ultrasound showed hepatic steatosis with complex fluid collection adjacent to the gallbladder in the right hepatic lobe. Computed Tomography scan demonstrated a severe colitis along with 4.8 cm x 3.3 cm complex fluid collection in the gallbladder fossa and an enlarged pancreatic head with loss of adjacent fat planes and tracking of fluid into the mesentery, and a 7 mm fluid collection within the pancreatic head. Patient was started on IV antibiotics along with continuous IV fluids for sepsis and questionable pancreatitis due to fever spikes (102.3F) and Interventional radiology (IR) placed a drain. The appearance of the fluid with elevated enzymes (Fluid Lipase and Amylase: 5104 and 605) was consistent with pancreatitis. MRI/MRCP showed a 2.7 cm fluid collection in the pancreaticoduodenal groove and marked inflammatory changes around hepatic flexure of the colon and a persistent fluid collection posterior to the gallbladder. IR drained collection regional to the liver and gallbladder. Resolution of the fluid collection following drainage was noticed. All cultures were negative, antibiotics were discontinued. Patient improved clinically.

Discussion: Most common location for EPP is lesser sac and least common site is Liver. Pathophysiology behind it is inflammatory disruption causing leakage of pancreatic fluid that migrates along hepatogastric, hepatoduodenal or by digesting tissue in the hepatic parenchyma. EPP are important to identify and surgical drainage would be mainstay of treatment to prevent severe complications.

S1589

A Rare Manifestation of COVID-19 in the Abdomen: Acute Pancreatitis

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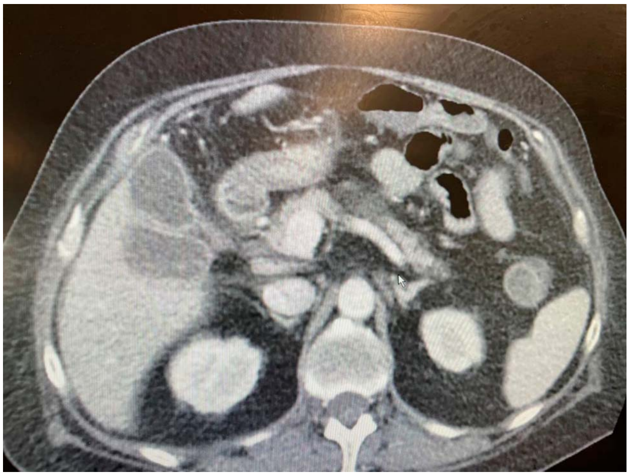
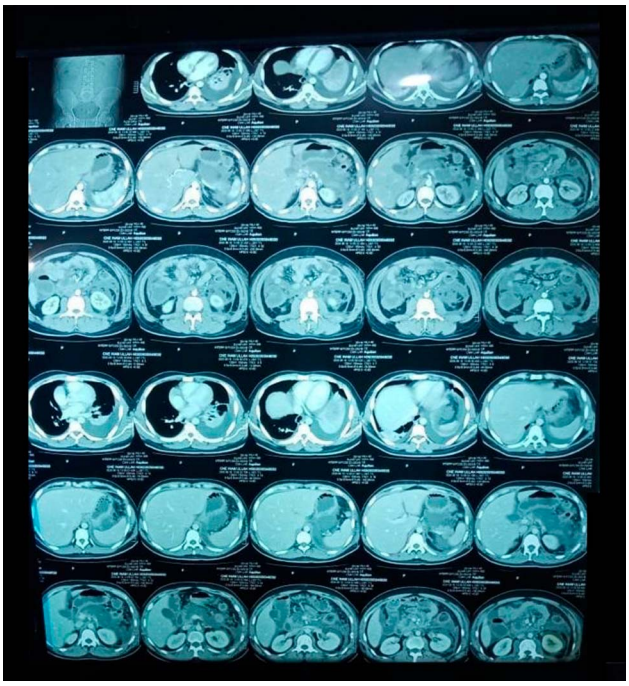
Introduction: Coronavirus, a novel menace, is exacting terrible human toll and mass death till date. It was thought that COVID-19 primarily affects the respiratory system, but recent studies have reported gastrointestinal manifestations as well. However, the incidence of acute pancreatitis in the setting of COVID-19 is a rising debate due to unknown mechanisms, especially in the absence of any precipitating factors for pancreatitis



[1588] **Figure 1.** CT scan showing collection in Gall Bladder fossa.



[1589] **Figure 1.** On non enhanced images pancreas appear enlarged and hypodense with irregular margins.

Case Description/Methods: An otherwise healthy 30-year-old female presented to the emergency department with pain in the lower abdomen radiating to the back, fever, cough, vomiting, diarrhea, and sore throat for the past seven to ten days. Her initial examination revealed a temperature of 100°F, a pulse rate of 85 beats /minute, blood pressure of 110/70 mmHg, respiratory rate of 20 breaths/minute, and oxygen saturation of 94% on room air. Her swab result for SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) came positive. Laboratory testing revealed a rise in serum lipase and serum lipase level. Her ultrasonography (USG) of the abdomen was suggestive of fatty liver changes (hyperechoic parenchymal echogenicity) and no gallstones. She was managed conservatively with intravenous fluid, analgesics and antibiotics for bacterial infection. Absence of any predisposing factor for pancreatitis in the setting of COVID led to the diagnosis of acute pancreatitis induced by COVID-19. Her contrast-enhanced computed tomography (CECT) of the abdomen also confirmed our suspicion.

Discussion: The rationale behind the development of acute pancreatitis in the presence of COVID-19 infection, with no past medical history and precipitating risk factor for pancreatitis, is suggestive of COVID-19 as a triggering factor. This case highlights the importance of pancreatic enzyme monitoring if patients have abdominal complications and without further delay, proper management can be set up if diagnosed early. Future complications such as chronic pancreatitis and pseudocyst formation can also be prevented if timely diagnosed.

[1589] **Table 1. Metabolic panel of the patient.**

Parameter	Day 3	Day 5	Reference range
Serum lipase (IU/L)	283	626	8-78
Serum amylase (IU/L)	171	820	25-125
Prothrombin time (seconds)	19	12.1	Control: 12
Activated partial thromboplastin time (seconds)	36	28.1	Control: 28
Blood glucose (mg/dL)	91	-	70-140
Blood urea (mg/dL)	35	-	10-50
Serum creatinine (mg/dL)	0.8	-	0.6-1.4
Total bilirubin (mg/dL)	0.4	-	Up to 1.0
Alkaline phosphatase (IU/L)	122	-	30-120
Aspartate aminotransferase (IU/L)	24	-	Up to 40
Alanine aminotransferase (IU/L)	12	-	Up to 40
Serum Na^+ (mmol/L)	143	-	135-147
Serum K^+ (mmol/L)	4.6	-	3.5-5.4
Total leukocyte count ($/mm^3$)	16,900	-	4,000-11,000
Total platelet count ($/mm^3$)	289,000	-	150,000-450,000

S1590

A Radiological Presentation and Surgical Excision of a 2-Year-Old-Male With Pancreatic Pseudocyst: A Case Report From a Low and Middle Income Country

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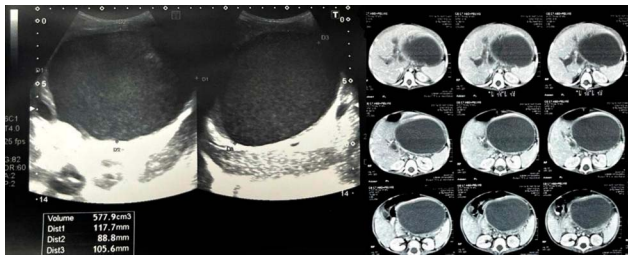
Introduction: While pseudocysts of the pancreases are not rare, spontaneous perforation or fistulization are noted in less than 3% of cases. The spontaneous rupture of pancreatic pseudocysts may occur in the bronchial treat, biliary tract, colon, duodenum, renal system, and stomach. Spontaneous ruptures associated with life-threatening symptoms necessitate surgical intervention. This vignette



[1590] **Figure 1.** Radiological findings of the patient. a (left): USG findings on admission, b (right): CT Scan of the Abdomen (post one-week of conservative treatment).

[1590] **Table 1. Laboratory findings of the patient during hospital stay.**

Laboratory test	Admission	Reference Range
WBC	7.8	4.5-11 x 10^7/L
Hgb	6.5	12-15.5 g/dL
MCV	62.8	80-100 fL
Plt	67	155-450 x 10^3/uL
Na	136	135-145 mEq/L
K	3.5	3.5 – 5.0 mEq/L
Cl	100	96-106 mEq/L
Cr	0.26	0.59-1.04 mg/dL
Ca	7.7	8.6-10.3 mg/dL
Amylase	135	30-110 u/L
D-Dimer	> 10,000	0-250 ng/mL

WBC – White blood cell, Hgb – Hemoglobin, MCV – Mean Corpuscular Volume, Plt – Platelet, Na – sodium, K – potassium, Cl – chlorine, Cr – creatinine, Ca – Calcium.

Brain and Spine
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Management of postoperative discitis with debridement and local antibiotic infusion: functional outcomes from a low-middle-income country

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Background: Postoperative discitis carries significant morbidity and mortality, especially in low-middle-income countries (LMICs), from where little contemporary data exists concerning outcomes of surgical management of medically-refractory disease. This study sought to determine functional outcomes of patients with postoperative discitis treated with debridement and a novel technique of antibiotic infusion in an LMIC.

Methods: This retrospective cohort study, conducted and reported in accordance with STROBE guidelines, included all postoperative discitis patients who had been debrided by one neurosurgeon in resource-limited setting in Southern India during January 2008-December 2020. Patients had undergone single-level discectomy elsewhere, later developing MRI-confirmed discitis not responding to minimum of two-week intravenous antibiotics. Patients underwent disc space debridement followed by drain placement for two-week continuous local antibiotic infusion and were followed up for one-year. Primary study outcomes were modified Kirkaldy-Willis criteria, Japanese Orthopaedic Association (JOA) score, and Visual Analog Scale (VAS) score for pain, assessed at one-year.

Results: 12 patients were included, ten males and two females, with median age of 46 (IQR=3.5) years. Three patients had diabetes, three were obese, two were smokers, and one each had Hepatitis-B and HIV-seropositivity. Discectomy had been performed at L4-L5 (N=10) and L5-S1 (N=2) levels, with debridement performed after median 82.5 (IQR=35) days, and taking median time 105 (IQR=17.5) minutes. VAS scores (mean±SD) decreased from 9.25±0.75 preoperatively to 0.67±0.89 postoperatively (Mean-difference 8.58, 95%CI 8.01-9.15, P<0.001). JOA scores (mean±SD) improved from 4.5±2.94 to 26.42±1.31 postoperatively (Mean-difference 21.92, 95%CI 20.57-23.26, P<0.001). Kirkaldy-Willis criteria-based outcomes were excellent in six (50%), good in five (41.7%), and fair in one (8.3%). No major complications were observed with patients becoming ambulatory within two weeks.

Conclusions: In resource-limited settings such as LMICs, patients with medically-refractory postoperative discitis may have good functional outcomes with debridement and utilization of two-week local antibiotic infusion therapy.

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Disappointed

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You gave me these elegant wings,
You gave me explicit privileges,
To treat you all, to heal you to health,
And to alleviate all your stresses.

I studied hard, I worked even harder,
I put in all those sleepless nights,
Not only to make my future bright,
But also to preserve your healthy lives.

I slogged hard for days and nights,
I made it through all those relentless shifts,
I worked diligently all this time,
Always missing my dear ones' presence.

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You beat me up, you pelt stones at me,
You hurl abuses, and worse, throw punches at me.
Your perfidy has cut my beautiful wings,
And tied my liberty with a thousand slings.

Is that not enough? I inquire of you all,
What will be then, if this is not?
Threatening my life as I fight at the front line,
Trying to eradicate that vicious, spiny and viral ball.

You were to stay home while I stayed at work,
This was all I asked and needed from you, but
You walked out of your homes, ignored my advice,
selfish, reckless fools, not even thinking twice.

Together we'll win over this pandemic,
Together we'll throw this out of our world,
If you support me and my community,
We'll have it run away, like a mouse, scrambling under the Earth's crust.

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