France Reports Rise in Severe Neonatal Infections Caused by a New Enterovirus (Echovirus-11) Variant

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ABSTRACT: The surge in severe neonatal sepsis cases caused by a novel variant of Echovirus 11 (E-11) in France and several European countries has sparked concern. The affected infants, mostly premature and twins, displayed rapid clinical decline within days after birth, presenting symptoms akin to septic shock with hepatic impairment and multi-organ failure. Laboratory findings revealed profound coagulopathy, low platelet counts, and acute renal failure, indicating severe disease progression. Genetic analysis identified a distinct recombinant E-11 lineage, previously unseen in France before July 2022. Despite its novelty, the exact pathogenicity remains uncertain. Although the World Health Organization downplaying immediate public health risks, the absence of a robust global surveillance program hinders accurate prevalence assessment. To mitigate the impact of this novel E-11 variant, establishing robust surveillance, refining diagnostic capabilities, and exploring therapeutic interventions such as intravenous immunoglobulin (IVIg) and pocapavir are imperative for effective management and prevention strategies.

KEYWORDS: Neonatal infections, enterovirus, human enterovirus, echovirus-11, France

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Enteroviruses (EVs) are a group of viruses that cause seasonal epidemics and a wide range of ailments. In the neonatal period, transmission can occur either intrapartum by contact with maternal blood, secretions, or stool or postnatally through intimate contact with infected caretakers.[1,2] The positive-strand RNA virus known as echovirus 11 (E-11) is classified in the genus *Enterovirus*, family Picornaviridae. In newborns, these infections can lead to life-threatening inflammatory diseases such as acute hepatitis with coagulopathy.[3]

A rise in cases of severe newborn sepsis, caused by Enterovirus [Echovirus-11 (E-11)] was reported recently in France on May 5, 2023. As of June 26, 2023, a number of cases have been reported in several European nations, including Croatia (1 case), Italy (7 cases), Spain (2 cases), Sweden (5 cases), and the United Kingdom (2 cases).[4] Between July 2022 and April 2023, 4 hospitals in 3 different regions of France reported a total of 9 instances of newborn sepsis with hepatic impairment and multi-organ failure. Seven patients had passed away by May 5, 2023 and 2 have been discharged from the hospital and remain under follow-up. The present spike in prevalence and severity in neonates is linked to a recombinant lineage of E-11 that had not been found in France before, and it is notable for the very quick deterioration and high case fatality rate among affected infants.[5]

Nine infants presented with symptoms suggestive of late-onset sepsis, 8 of whom were born prematurely (born before 37 weeks of gestation). Moreover, a total of 4 sets of twins were delivered with gestational ages ranging from 31 to 36 weeks. The possibility of mother-to-child transmission was considered in all cases as symptoms manifested within the first week of the infant's life. In each instance, the infants exhibited 1 or more clinical indicators within 7 days of being born, indicating a potential route of transmission from the mother to the child.[5] The cases under consideration exhibited an atypical clinical presentation characterized by a remarkably rapid decline in health and a correspondingly high rate of mortality.

The onset of symptoms occurred between the third and fifth day of life for all patients. Fever and apnea were the first signs, followed quickly by other symptoms of septic shock after hospitalization. All the patients had undetectable levels of fibrinogen and blood coagulation factors V, II, VII, and X.[6] The patients had low platelet counts and high blood ammonia levels. At the outset of symptoms, acute renal failure was present in all infants.[1,7,8]

All 9 cases tested positive for EV, typed as Echovirus-11 (E-11), using reverse transcription polymerase chain reaction (RT-PCR) on blood, throat swabs, nasopharyngeal swabs, cerebrospinal fluid samples, and/or post-mortem biopsies. The

presence of E-11 in the blood of 4 out of 5 women was verified by RT-PCR and EV genotyping.[9] All of the pregnant women who were examined showed signs of nausea, vomiting, or diarrhea between 3 and 24 hours before giving birth. Sequence analyses of all typed EV infections in 2022 revealed the circulation of at least 2 lineages of recombinant origin, with the most prevalent one including all the sequences associated with the 9 cases as well as sequences associated with non-neonatal or mild neonatal infections. Investigations on the genetic makeup of the human population are still in progress.[6,8]

When looking at the epidemiological data collected from 2016 to 2022 in France through routine surveillance of EV infections among hospitalized patients, a significant increase in incidence and mortality was found for all severe neonatal infections associated with E-11. Historical data shows that in 2022, E-11 accounted for 55% (11 of 20) of all reported severe newborn infections with a known EV type, up from 6.2% in 2016 (3 of 48).[5,9]

Sequence analysis demonstrated the spread of at least 2 lineages of recombinant origin, one of which includes all sequences linked with the 9 severe cases as well as sequences associated with non-neonatal or mild neonatal infections. This new E-11 variant had not been seen in France before July 2022, and as of April 28, 2023, based on Genbank sequence data, it had not been seen anywhere else. As of May 5, 2023, all of the E-11 sequences from 2023 samples fall into this single, dominating lineage. The possibility of increased pathogenicity in this novel lineage cannot be ruled out, although the young age, premature birth, and lack of maternal immunity may also account for the severity of infections. The properties of this recombinant virus need to be defined; hence additional research is necessary.[5,8,10]

The World Health Organization (WHO) has determined that there is little threat to public health from this situation. However, EV infection is notable for the fact that it frequently causes asymptomatic viral carriage and shedding. Although instances of severe E-11 infection in twin newborns have been previously documented, it is worth noting that 4 pairs of twins were observed among the 9 reported cases. Since severe newborn EV infection is not a notifiable condition in many Member States, there may be more cases than are currently known.[6,8] Multiple factors contribute to the increased susceptibility of twins to preterm birth. Limited uterine space and heightened strain on the mother's body are well-established factors. Furthermore, the potential influence of an in-utero inflammatory process should not be disregarded, as it may exacerbate the already heightened risk of preterm birth in these instances.

Non-polio EVs are ubiquitous and found in every region of the planet. In a few cases, respiratory tract infections may be the only indication of an otherwise silent infection. Fever, a runny nose, and general malaise are common symptoms. Occasional outbreaks of clinical disease in a disproportionately high number of people due to these viruses have been linked to devastating outcomes. Clinicians caring for newborns and babies presenting with circulatory shock should suspect sepsis and conduct appropriate diagnostic tests, such as testing for EVs.[11,12]

Workers in the healthcare industry who handle samples that may contain non-polio EVs should undergo training in the safe collection, storage, and transportation of these samples. Strict adherence to national and international restrictions on the transit of infectious substances is required if samples are referred for confirmation, typing, or sequencing purposes either locally or internationally. Sequencing laboratories need to think about making their DNA sequence databases available to the public.[12,13]

Currently, there is a lack of a comprehensive global enterovirus surveillance program. Hence, accurately assessing the prevalence of severe neonatal E-11 infections or the circulation rates of E-11 viruses in the population poses a significant challenge. In the absence of enterovirus surveillance, it is probable that only the most severe cases will be identified by proactive measures aimed at testing and categorizing samples obtained from these cases. Due to the lack of mandatory reporting for non-polio enterovirus infection, it is possible that there exists a number of undiagnosed and/or unreported cases of severe neonatal enterovirus infection.[4]

Furthermore, possessing the capability to distinguish between Rhinovirus and Enterovirus is of great significance, given that these 2 viral families may exhibit similar symptoms; nevertheless, their clinical consequences and therapeutic approaches can vary. The ability to make precise diagnoses facilitates the provision of individualized and suitable medical treatment for every patient.

Treatment for echovirus infection is focused on avoiding consequences rather than curing the illness itself because no particular antiviral drug is available. In France, healthcare facilities that care for neonates should be aware of EV symptoms and be on the lookout for outbreaks of healthcare-associated infections in neonatal wards.[2]

In conclusion, at least in France, a novel variant of E-11 is now circulating, which is linked to an elevated risk of severe neonatal infection and death. Clinicians are on the front lines of detecting cases of severe clinical presentations in newborns, hence they need to be aware of the potential involvement of EV in such patients. France, like most European countries, uses a voluntary method for reporting EV-positive patients, which could result in an underestimation of the true number of severe cases if EV genome detection is ignored. Neonatal EV illness manifests as neonatal sepsis, which is clinically indistinguishable from bacterial or herpes simplex virus infections. Rapid evaluation for EV infection is warranted in neonates with myocarditis or liver failure with cytolysis and unexplained sepsis, particularly if the mother has acute symptoms of gastroenteritis in the days leading up to delivery. Samples of blood, respiratory fluid, cerebrospinal fluid, and feces should be taken for preliminary testing and potential sequencing. Two potential

therapeutic options that could be considered are intravenous immunoglobulin (IVIg) and pocapavir.

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Author Contributions

DC and SC, conceived the study and wrote the first draft. SKA and HC, revised and gave intellectual inputs in the manuscript. MRI and KD, conceived and supervised the work. All the authors approved the final version for submission.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Ethics Statement

It was an analysis of online available aggregate data. No Ethical approval was needed.

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