

Foot and Mouth Disease Virus

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Foot and mouth disease (FMD) is a devastating, highly contagious viral disease of all cloven-hoofed animals caused by the foot and mouth disease virus (FMDV) of the Picornaviridae family. The disease poses a severe threat globally, impeding the international trade of live animals and animal by-products. FMDV includes seven serotypes, namely, A, O, C, Southern African Territories (SAT)-1, SAT-2, SAT-3, and Asia1. Each serotype has antigenically distinct subtypes due to the high mutation rate.

Keywords: foot and mouth disease ; water buffalo ; Egypt ; serotype SAT-2 ; VP sequencing ; FMD outbreak ; cardiac marker

1. Overview

Spontaneous mutations are a common characteristic of the foot and mouth disease virus (FMDV), leading to wide antigenic variations resulting in the emergence of new topotypes and lineages of FMDV, which contributes to occasional vaccination failures. The objectives of the present study were to genetically characterize FMDV isolated from water buffaloes and study the biochemical and histopathological indicators of infected animals. Fifty-four water buffaloes of both sexes and different ages suffered from acute symptoms of FMD were clinically examined and randomly selected for inclusion in this study. Oral desquamated epithelial and oropharyngeal fluid samples have been tested for FMDV by reverse transcriptase PCR (RT-PCR). Tissue and serum samples were also collected from the diseased buffaloes and subjected to histopathological and biochemical analysis. Our findings showed that all examined samples were confirmed to be positive to FMDV serotype SAT-2 and were adjusted to be responsible for the recent disease outbreak in this study. Phylogenetic analysis revealed that the circulating viruses were of the SAT-2 serotype, closely related to the lineage of lib12, topotype VII, with 98.9% identity. The new lineage of SAT-2 showed a high virulence resulting in the deaths of water buffaloes due to heart failure, confirmed by high serum levels of inflammatory and cardiac markers, including haptoglobin, ceruloplasmin, cardiac troponin I and creatine phosphokinase-MB, indicating an unfavorable FMD-infection prognosis. In conclusion, we document the presence of new incursions circulating in water buffalo populations in Egypt in early 2019, explaining the high morbidity rate of FMD outbreak in early 2019. Furthermore, the newly identified serotype SAT-2 lib12 lineage, topotype VII, showed an aggressive pattern in water buffaloes of the smallholder production system.

2. FMD

Foot and mouth disease (FMD) is a devastating, highly contagious viral disease of all cloven-hoofed animals caused by the foot and mouth disease virus (FMDV) of the *Picornaviridae* family. The disease poses a severe threat globally, impeding the international trade of live animals and animal by-products ^{[1][2]}. FMDV includes seven serotypes, namely, A, O, C, Southern African Territories (SAT)-1, SAT-2, SAT-3, and Asia1. Each serotype has antigenically distinct subtypes due to the high mutation rate ^[3].

FMD is endemic in many countries in Africa, Asia, and South America ^{[4][5]}. In Egypt, FMDV serotypes O and A are endemic and cause sporadic outbreaks ^[6]. During 2012, widespread outbreaks due to FMDV serotype SAT-2 were reported in the Delta and Upper Egypt Governorates ^[7]. Since 2012, livestock in Egypt have suffered occasional FMD outbreaks due to different FMDV strains, resulting in significant losses among calves ^{[8][9]}; moreover, even co-infections with other infectious pathogens have been reported ^[10]. The appearance of new lineages from the different serotypes is associated with increased mortality rates in young ruminants and adults, inflicting severe economic losses ^{[11][12]}. All FMDV serotypes produce a clinically indistinguishable disease, but immunity to one serotype does not protect against the others due to the wide antigenic diversity. The affected livestock commonly exhibits fever; the cessation of rumination; ruby salivation; and the eruption of blisters on the lips, tongue, mouth, nose, between the toes, and sometimes on the teats; along with decreased milk production ^{[9][13]}.

Genetic analysis of viral protein 1 (VP1-coding region), the most variable protein among structural capsid polypeptides, can classify each serotype's strains into topotypes, lineages, and genotypes essential in tracing the cause of the newly emerging strains [14]. Serotype SAT-2 strains were clustered into 14 topotypes (I–XIV) by phylogenetic analyses. Topotype VII is the only one categorized in Egypt, which is predominantly endemic in south Sub-Saharan countries [10][15].

Domestic Nile water buffaloes (*Bubalus bubalis*) are essential animals for most farmers in Egypt, given their multiple advantages over cattle. In particular, water buffaloes are disease-resistant, produce high-fat milk and high-quality meat, and adapt to different environments with distinct climates. Egyptian farmers use water buffaloes for many purposes, including drafting animals and assisting with crop work in the fields. Numerous studies have reported and described FMD in cattle and other ruminant populations [10][16][17]. However, there has been little research on FMD in domestic water buffaloes.

The smallholder production system by traditional householders is a common livestock production system in Egypt, which is scattered throughout the country [18]. This traditional breeding system is typically used for small herds or small numbers of animals kept for subsistence or as a source of additional income by households. However, most studies on FMD have focused on farms with intensive production systems, which follow standard routine management, vaccination programs, and control measures against infectious diseases, including FMD [7][12][16]. Furthermore, variations in the microenvironment and management practices between these two production systems could influence the epidemiology and endemicity of FMD.

In early 2019, a massive outbreak of FMD hit livestock across Egypt, particularly in the Delta region. Thus, the objectives of this study were to (1) genetically characterize the circulating FMDV associated with the recent outbreak in the Sharkia and Dakahlia Governorates, Egypt, during the first quarter of 2019, and (2) study the histopathological profile and biochemical indicators in infected water buffaloes (*Bubalus bubalis*) to obtain a complete picture of the virulence of the circulating serotype.

3. Discussion

Various smallholders/householders from villages in Sharkia and Dakahlia Governorates, Egypt, reported clinical signs of FMD among vaccinated water buffaloes (*Bubalus bubalis*) in the first quarter of 2019. The present study aimed to genetically characterize the circulating FMDV virus strains associated with this outbreak. Furthermore, we assessed the virulence of the circulating serotype by examining the histopathological profile and biochemical indicators in FMD-infected buffaloes.

It is revealed that the SAT-2 serotype was responsible for the FMD outbreak in early 2019 in Egypt. This finding is consistent with an alert on the 2018 FMD outbreak [12], which reported the emergence of the FMDV Lib-12 lineage of topotype VII, serotype SAT-2, in Egypt. There are three predominant FMDV serotypes in Egypt: O, A, and SAT-2 [19][20][21]. However, in recent decades, several emerging topotypes, lineages, and genotypes within these three well-established serotypes have been documented in many reports [6][12][16][19].

Sequenced strains from the 2019 outbreak isolates (MN864514–MN864518) showed close relatedness to Ghanaian strains reported in the 2018 outbreak (LC456875) with an identity 91.10% and West and Central Africa strains reported in 2016 (KX266288) with an identity 94.14%. However, the SAT-2 serotype isolated in the present study showed less similarity to the SAT-2 serotype reported in Ethiopia during 2009 outbreaks (KF112952) with 72.51% similarity, the SAT-2 serotype identified in Sudan in 2008 (GU566073) with 72.51% similarity and the SAT-2 serotype isolated in Uganda in 2009 (FJ461346), with an identity 79.59%. This finding suggested that the new SAT-2 serotype lineage circulating in Egypt in 2019 might have been introduced to Egypt from Ghana and/or West and Central Africa, possibly through importing animals and animals' by-products. On the contrary, Ahmed et al. [6] reported that serotype SAT-2/VII/Ghb-12 (JX570618) had emerged in Gharbia Governorate, Egypt, during 2012 and caused devastating losses to cattle. Furthermore, Soltan et al. [12] detected SAT-2 Alx-12 lineage of topotype VII (SAT-2/Fayoum1/Egy/2017; MF322696) in nonvaccinated cattle in Dakahlia and Fayoum Governorates, Egypt, between 2016 and 2017.

The phylogenetic tree revealed a substantial degree of relatedness between the representative Egyptian isolates ($n = 5$) with a similarity of 98.9%, although these isolates were recovered from two different districts of Egypt. However, it showed a 12.2–12.7% variance from the vaccine strain registered under accession number (JX570618); namely, FMDV SAT-2 EGY/3/2012 topotype VII, lineage Gharbia 12. The variation between the isolated and vaccine strains explains the widespread and aggressiveness of the FMDV involved in the new outbreak in early 2019. Moreover, this clarifies the

markedly high morbidity in livestock and the high mortality, particularly among young calves, despite the annual vaccination program.

After the end of this study, the Egyptian Veterinary Authority responded to the farmers' warnings about the early 2019 FMD outbreak via an emergency vaccination campaign using the regularly used trivalent vaccines. However, our findings show that this strategy was inadequate to provide complete protection based on the sequence data and phylogenetic analysis. A similar conclusion was previously reported [12] and suggested the manufacture of local monovalent vaccines containing this recent strain (SAT-2 serotype, topotype VII, lib12 lineage).

FMD is known to cause high mortality rates (sometimes 100%) among calves younger than 2 months due to FMDV tropism switching to the cardiac muscle, causing myocarditis [22][23]. In the present study, the mortality rate among adult buffaloes aged more than 2 years was unexpectedly as high as 14/54 (25.9%). A previous study suggested using cardiac biomarkers such as cTnI to assess the prognosis of FMD [24]. The cardiac biomarkers from clinically FMD-infected buffaloes were highly elevated compared with the standard reference ranges. This reflects the aggressiveness and high virulence of the circulating FMD serotype, which was also confirmed by histopathological analysis of the newly deceased buffaloes' hearts and elevated acute-phase proteins such as haptoglobin and ceruloplasmin [25][26]. However, we think these findings were exacerbated by complications associated with other factors, such as emaciation due to parasitic infections and malnutrition of the livestock raised under the smallholder production system [18].

In addition, farmers raising animals under the smallholder production system tend to overlook the registration of newborn calves, either to avoid paying extra taxes or to sell them to local merchants for extra income (personal communications). Thus, these animals are not registered and subsequently are not listed for the annual FMD vaccination program. Therefore, they lack immunity against FMD and are particularly susceptible to FMDV [27]. Unlike large-scale animal production farms, the hygiene and biosecurity measures in smallholder farms are insufficient. Therefore, the disease spread and the consequences of this among smallholder farmers are devastating.

4. Conclusions

This entry documented new incursions circulating in water buffalo populations in Egypt in early 2019, which explains the high morbidity rate of FMD outbreak in early 2019. The newly identified serotype SAT-2 lib12 lineage, topotype VII showed an aggressive pattern in water buffaloes of the smallholder production system. Implementing strict control measures against FMD under a smallholder production system is crucial, and the inclusion of the new serotype SAT-2 lib12 lineage, topotype VII, is important for efficient vaccination and its subsequent protection.

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