AARHUS UNIVERSITY

Press release

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Basic information

Name: Nanna-Sophie Brinck Andersen Email: nsbj@clin.au.dk Phone: 28555528

Department of: Clinical Medicine

Main supervisor: Trine Hyrup Mogensen

Title of dissertation: Host genetic susceptibility to poliovirus infection

Date for defence: 24.01.2020 at (time of day): 1.00 pm Place: Auditorium A1 (Building 1333, room 101), Bartholins alle 7, 8000 Århus C.

Press release (Danish)

Host Genetic Susceptibility to Poliovirus infection

I årene før poliovaccinen, var poliovirus (PV) et almindeligt infektiøst patogen, der normalt forårsagede mild eller asymptomatisk sygdom. I sjældne tilfælde invaderede virus centralnervesystemet (CNS) hvilket resulterede i paralytisk poliomyelitis (børnelammelse) eller død. Den dag i dag kan man i langt de fleste tilfælde stadig ikke forklare, hvorfor PV infektion udvikler sig fra mild til alvorlig sygdom. På trods af den globale indsats for at udrydde virus, forbliver PV endemisk i Afghanistan, Pakistan og Nigeria. Dette studie har fokuseret på genetiske undersøgelser af patienter der lever med udtalte lammelser forårsaget af PV, med det formål at identificere genetiske varianter i det medfødste immunforsvar, der kan disponere til dette alvorlige sygdomsforløb. Studiet er et nyt ph.d.-projekt fra Aarhus Universitet, Health. Projektet blev udført af Nanna-Sophie Brinck Andersen, der forsvarer sin afhandling den 24.01.2020

I samabejde med Polio Foreningen og Specialhospitalet for Poliopatienter, inkluderede vi 18 patienter, der i barndommen blev diagnosticeret med alvorlige lammelser efter PV infektion, og overlevede med betydelige neurologiske følger. Vi identificerede en række genetiske varianter der tilhører fælles cellulære signaleringsmekanismer, blandt andet antiviral immunitet, autofagi og apoptose, og som alle potentielt kan have indflydelse på PV replikation, neuroinvasion og sværhedsgrad af sygdommen. Af særlig interesse, identificerede vi en patient med en variant i autofagi relateret (ATG) 7, et centralt molekyle for den normale udvikling af autofagosomer. Vi fandt at PV-induceret autofagi var nedsat i patientens celler og associeret med øget mængde virus og mere celledød. Rekonstituering af patientens hudceller med vildtype ATG7, men ikke med variant ATG7, genoprettede patientcellernes evne til kontrollere infektionen, samt til at inducere autofagi under PV infektion. Genetisk ændring af ATG5, ATG6 eller ATG7 i en cellelinje der stammer fra CNS, forhindrede derudover kontrol af PV infektion. Tilsammen indikerer data fra dette studie, at varianten i ATG7 bidrog til den svære kliniske forløb af PV infektion hos denne patient.

Forsvaret af ph.d.-projektet er offentligt og finder sted den 24.01.2020 kl. 13.00 i Auditorium A1, bygning 1333, lokale 101, Aarhus Universitet, Bartholins alle 7, 8000 Århus C. Titlen på projektet er ”Host genetic susceptibility to poliovirus infection”. Yderligere oplysninger: Ph.d.-studerende Nanna-Sophie Brinck Andersen, e-mail: nsbj@clin.au.dk, tlf. 28555528.

Bedømmelsesudvalg:

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Press release (English)

Host Genetic Susceptibility to Poliovirus Infection

Poliovirus (PV) infection was in the pre-vaccination years a common infectious pathogen usually causing mild or asymptomatic disease. In rare cases, viral neuroinvasion resulted in devastating paralysis or death. To date, the disease determinants remain largely unknown, and despite global efforts to eradicate the virus, PV remains endemic in Afghanistan, Pakistan, and Nigeria. The focus of this study was to perform genetic and immunological investigations of patients living with severe paralysis due to PV infection. The aim was to identify genetic variants in the innate immunedefence that may predispose individuals to this devastating disease outcome. The project was carried out by Nanna-Sophie Brinck Andersen, who is defending her dissertation on 24.01.2020.

In collaboration with the national polio association, we collected a cohort of 18 patients who suffered from severe paralytic poliomyelitis in infancy or early childhood and survived with significant neurological sequelae. We identified several variants in a set of common cellular pathways involved in antiviral immunity, autophagy, or apoptosis, which, we suggest, might influence PV replication, neuroinvasion, and disease severity. Of great interest, we identified a patient with a variant in autophagy related (ATG) 7, a central molecule for autophagosome biogenesis. We found that PV-induced autophagy was impaired in patient fibroblasts and associated with an increased viral burden and enhanced cell death. Rescue of patient fibroblasts with wild-type ATG7, but not the variant ATG7, restored PV-induced autophagy and control of infection, thus reconstituting back to a phenotype resembling fibroblasts from healthy controls. Moreover, genetic editing of ATG5, ATG6, or ATG7 prevented control of PV infection in a cell line originating from the central nervous system. Collectively, this study proposes that the variant in ATG7 contributed to the severe clinical disease course of PV infection in this patient.

The defence is public and takes place on 24.01.2020 at 13.00 in Aarhus University, Auditorium A1 (Building 1333, room 101), Bartholins alle 7, 8000 Århus C. The title of the project is "Host genetic susceptibility to poliovirus infection". For more information, please contact PhD student Nanna-Sophie Brinck Andersen, email: nsbj@clin.au.dk, phone +4528555528.

Assessment committee:

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