P0011
Poster Session I
News from the fungal frontier

CENTRAL NERVOUS SYSTEM FUNGAL INFECTIONS AND CARD9 DEFICIENCY

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Objectives

Invasive fungal diseases occur mainly in patients withacquired, but also inherited immunodeficiencies. However, few patients developinvasive fungal disease without known risk factor. We therefore hypothesizedthat these infections might have an unidentified genetic etiology. We studiedpatients who developed central nervous system (CNS) fungal infections; onepatient with CNS *Exophiala dermatitidis* infection and three patientswith CNS *Candida* spp. infection. Invasive *E. dermatitidis*infections are rare, with frequent CNS location, mainly reported in patientswithout known immunodeficiencies. CNS candidiasis are also rare infectionsusually occurring in preterm neonates or following neurosurgery.

Methods

Based on literature data previously reporting a largeconsanguineous Iranian family with CARD9 deficiency that developed chronic mucocutaneousand central nervous system candidiasis, we used a candidate gene approach andsequenced *CARD9* in all patients.

Results

CARD9 is an adaptor protein expressed by myeloid cellsthat signals at least downstream Dectin-1, Dectin2 and MINCLE, receptors implicatedin antifungal immunity. We identified homozygous *CARD9* mutations in 4/4patients studied: the patient who developed invasive *E. dermatitidis* was found homozygous for the R18W *CARD9* mutation, and the three patientswho developed CNS candidiasis were found homozygous for the R35Q and R70W missenseand the Q289X nonsense mutations. Transmission was found to be autosomalrecessive for all patients, except for the patient with *E. dermatitidis* infectionwho displayed a parental unidisomy. In comparison to the controls tested, CARD9expression was reduced in R70W and normal in R18W myeloid cells. CARD9deficient whole blood and dendritic cells displayed a selective response defectto *Candida albicans* and *Saccharomyces cerevisiae* with impairedIL-6 or TNF-α production. This defect might explain theselective susceptibility of CARD9 deficient patients to invasive fungalinfections.

Conclusion

This work evidenced that CARD9 deficiency isassociated with *Exophiala dermatitidis* and *Candida* spp. CNSinfections. This susceptibility is associated with an impaired proinflammatorycytokine production by dendritic cells and whole blood specifically upon fungalagents. Occurrence of CNS fungal infections in CARD9 deficient patients demonstratesthe central role of CARD9 in central nervous system antifungal immunity.