Theiler`s murine encephalomyelitis virus

Host species

- natural hosts: wild mice [1], laboratory mice, [2] [3] [4], water, bank and meadow voles (family Microtinae) [5] [6]
- positive serological reactions in laboratory rats [7] [8]; virus might be related to TMEV-virus, only one report on clinical signs and lesions in rats (MHG-strain) [9], positive serological findings may indicate the presence of a yet uncharacterised virus (?rat cardiovirus?) [10]
- guinea pigs: the presence of antibodies to TMEV in guinea pigs suffering from lameness indicates that the causative agent of guinea pig lameness might be a cardiovirus [11]
- mice, rats, hamsters and cotton rats are susceptible to intracerebrally inoculated virus (GDVII strain) but not guinea pigs [12] [13].

Serological prevalence of TMEV in mouse and rat colonies:

Canada: 1980/1986: 40% of mouse colonies, 58% of rat colonies [8]

Germany: 1987-1988: 11% of mouse colonies, 20% of rat colonies [3]

France: 1996/1997: 26% of mouse colonies, 13% of rat colonies [2]

United States: 1996: 30% of mouse colonies, 5-10% of rat colonies [14]

Properties of the Virus

RNA-virus, family Picornaviridae, Genus Cardiovirus; all TMEV strains (see below) are of the same serotype and cross-neutralize with polyclonal antisera [15] [16].

- different subgroups exist:
  - subgroup TO (DA, BeAn 8386, WW, TO, Yale) may produce chronic persistent infection of the CNS, accompanied by demyelinating lesions of the spinal cord; small plaques in cell culture;
  - subgroup GDVII (FA, GDVII) produce acute fulminant encephalomyelitis; large plaques in cell culture [17] [18];
- virus can be stored for a long period at –60°C
- optimal stability of the virus in the vicinity of pH 8 and pH 3,3
- exposure to air has little influence on the stability of the virus
- TMEV is rapidly destroyed at temperatures above 50°C
- virus is completely inactivated by 1% H2O2 at 37°C and by 50% acetone or alcohol [19].

Strain susceptibility

different susceptibilities of various mouse strains after experimental intracerebral inoculation [17] [20]:

- high susceptibility: SJL/J, DBA/1, DBA/2, SWR, PL/J and NZW mice
- intermediate susceptibility: C3H, CBA, AKR, C57BR mice
- resistant: BALB/C substrains, C57BL/6, C57BL/10, C57/L, 129/Jm and H-2D(b) mice; resistance to DA-virus in H-2(b) mice maps to the H-2D gene and is associated with a potent antiviral cytotoxic T-lymphocyte response [21]
- with cyclophosphamide (cy), mice can be made susceptible but resistance was restored by adoptive transfer of splenic cells from non cy treated donors, only C57Bl/6 could not be made susceptible; high doses of gamma irradiation increase susceptibility of mice [20]

Organotropism

replication of the virus in gastrointestinal mucosa [22] [23]; natural infection rarely spreads from intestine to spinal cord or brain; macrophages are a reservoir of the virus (Da, To, WW, BeAn) [24] [25] as well as oligodendrocytes, astrocytes and microglia [26] [27]; placentas and foetuses (only in early gestation) can be infected [28];

Clinical disease

- **mice, natural infection, subgroup TO (DA, BeAn 8386, WW, TO, Yale):** in mice asymptomatic gastrointestinal infection (except immunodeficient mice [29]), the virus rarely spreads to the central nervous system [30] [13], symptoms are flaccid posterior paralysis and seldom anterior paralysis in mice that are otherwise clinically normal; incubation period: 7-30 days
- **mice, natural infection, subgroup GDVII (FA, GDVII):** encephalomyelitic form may be expressed clinically by excitability, circling, rolling, tremor and convulsions on noise stimulation (incubation time: 2-9 days); most of the infected mice die soon after onset of clinical signs [23]
- **Rats,** MHG-virus strain: case report of symptoms in 3 rats of a colony with symptoms like circling, incoordination, tremor, torticollis [9]
- **experimental infections in mice and rats (intracerebrally, intranasally or footpad inoculation): strains DA, BeAn, WW, TO, Yale:** wobbling gait, about 2 to 4 weeks p.i., followed by weakness of the posterior limbs, spastic paralysis, urinary incontinence and priapism [31] [32]; weanling rats die within 2-3 days without paralytic symptoms [12] strains FA, GDVII: hyperexcitability, circling, and flaccid paralysis which lead to death within one week [23] [33] [34]

Pathology

- **mice, natural infection, subgroup TO (DA, BeAn 8386, WW, TO, Yale):** non-suppurative encephalomyelitis with gliosis and necrosis of ventral horn neurons of the spinal cord and neuronal necrosis in posterior regions of the brain, satellitosis,

Cowdry type B intranuclear inclusion bodies in neurons are not a consistent feature of the disease [22], inflammation may persist for several months after necrosis subsides and is then accompanied by astrocytosis and focal mineralization [35]

- **mice, natural infection, subgroup GDVII (SCID-mice):** severe degeneration (often spongiform) and necrosis of neurones and glial cells of the ventral horns (lesser involvement of the dorsal horns of the spinal cord) [29]
- **experimental infections in mice (intracerebral inoculation)**:
- **subgroup: DA, BeAn, WW, TO, Yale:** acute neuronal degenerative changes and microglial proliferation primarily in the spinal cord anterior horn, brain stem and thalamus and perivascular inflammation also in the spinal cord leptomeninges, followed after 1 month p.i. by persistent viral infection of the spinal cord (white matter) with varying degrees of chronic progressive demyelinisation and inflammation and remyelinisation after a few months (resembles multiple sclerosis in man [31] [12] [33]); Hydrocephalus and pachymeningitis in mice after inoculation of an DA virus variant (H101 virus), without viral persistence, no demyelination [36]•subgroup: FA, GDVII: acute polioencephalomyelitis with necrosis of ganglion cells and neuronophagia of hippocampus, cortex and spinal cord anterior horn and nonsuppurative inflammation, high apoptosis rate in neurons, little if any demyelinisation, no viral persistence in the CNS [37] [38] [39]

Morbidity and mortality

- **natural infection**: subgroup TO (DA, BeAn 8386, WW, TO, Yale): morbidity low, little or no mortality (except immunodeficient mice with high morbidity and mortality [29]); strains FA, GDVII: morbidity and mortality high
- **experimental infection**: (intracerebral inoculation): subgroup TO (DA, BeAn 8386, WW, TO, Yale): morbidity high, mortality low; strains FA, GDVII: morbidity high (100%), mortality high

Zoonotic potential

- none

Interference with research

- chronic CD4+ response which is initially directed at viral determinants but persists in the CNS and is directed against multiple myelin autoepitopes; T cell proliferative response in spleen [32]
- increase of CD4+ Th1-cells producing IFN-gamma (DA-strain) [40]
- high m-RNA expression of proinflammatory cytokines in brain and spinal cord of SJl/J mice beginning at day 5 post infection for tumour necrosis factor-a (TNF-a) and interferon-g (INF-g); with DA additionally for lymphotoxins LT-a and LT-b, and with GDVII additionally for interferon-b (IFN- b) and interleukin-6 (IL-6) and high m-RNA chemokine expression after DA, GDVII and H101-virus infection for Rantes, monocyte chemotactic protein-1 (MCP-1), IP-10 and macrophage inflammatory proteins (MIP-1b, MIP-1a, MIP-2) [41] [42] [43]
- Increase of INF-a and INF-b in SJL CD4-/- mice (DA-strain) [44]

- Interleukin-1 receptor declines in hippocampus in susceptible strains (SJL/L) [45]
- high apoptosis rate in neurons in GDVII infected mice, in DA infected mice high apoptosis rate in oligodendrocytes [39]
- inhibition of alpha/beta interferon synthesis in infected L929 cells [46]
- restraint stress has an effect on infected (BeAn strain) animals (increased mortality, increased viral titres, decreased number of lymphocytes) [47]

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