HUNTINGTON Disease or Corea
1872

George Huntington
USA 1850-1916
• HEREDITARY PATHOLOGY (autosomal dominant)
• MOTOR INCOORDINATION
• COGNITIVE DECLINE IN MIDDLE AGE

SYMPTOMS
• intermittent movements of the limbs, trunk, face and neck (chorea)
• personality changes
• memory impairment

OUTCOME
during the 15-30 years communication incapacity; death by immobilization
Repetitive trinucleotide sequence CAG short arm of chromosome 4 in position 16.3 (4p16.3) Autosomal dominant mutation
CHARACTERISTICS OF THE DISEASE

• Severe neuronal loss in the caudate / putamen (posterior and anterior)

• Disease onset: 35-45 years

• Genetic alteration on chromosome 4

• Genetic mutation of IT15, which codes for huntingtin (Htt)

• IT15 gene mutation could lead to metabolic alterations
  CAG (normally repeated 11 to 34 times)
  + glutamine residues expressed in the protein
  the disease is the earlier the greater the number of repetitions
Organization of piramidal and extrapyramidal system

Motor cortex ➔ Glutamate ➔ Corpus striatum ➔ ACh ➔ Substantia nigra

Movement ➔ Parkinson's disease ➔ Dopamine ➔ Substantia nigra

Corpus striatum ➔ Glutamate ➔ Huntington's disease ➔ Thalamus ➔ GABA

P comp ➔ P retic ➔ Substantia nigra

Thalamus ➔ GABA
Gene on the short arm of chromosome 4 in position 16.3 (4p16.3) "huntingtin" (Htt)

Important htt in the axonic vesicular transport mechanism. It would act as an accelerator of the dynein complex, and its mutation limits if not eliminates this propulsive effect

Huntingtin interacts with regulatory proteins such as caspases (important for neurodegeneration). The mutated protein undergoes misfolding
Dynein is a "protein engine" functionally and structurally related to myosin and kinesin. Like all protein engines, it is able to couple the hydrolysis of ATP with the generation of mechanical energy of movement.
The most important protein compound on neurodegeneration is BDNF (Brain Derived Neuronic Factor) which keeps neurons alive by avoiding apoptosis. Its transfer from the cortex to the striatum takes place via axon transport.
SYMPTOMATIC THERAPY

- FLUOXETINE (irritability, depression)
- CARBAMAZEPINE (depression)
- CLONAZEPAM and VALPROIC Acid (myoclonic convulsions)
  BACLOFEN (GABA agonist)
- CLOZAPINE, RISPERIDONE (psychosis, hallucinations)

RESERPINE, TETRABENAZINE (movement)

Caloric requirement
Fluoxetine
Valproic acid, carbamazepine: mechanism of action

**Fig. 2.** Possible sites of interaction of antiepileptic drugs on GABA-mediated transmission. GABA is formed from glutamate by the action of glutamic acid decarboxylase (GAD), and can be metabolized by GABA aminotransferase (GABA-T) to form succinic acid semialdehyde (SSA). The GABA_A receptor is associated with an ion channel permeable to Cl^-; GABA increases the probability of ion channel opening, which leads to an elevation of intracellular Cl^- levels and hyperpolarization. Barbiturates and benzodiazepines act via associated modulatory sites to potentiate the effect of GABA on Cl^- conductance.

**Fig. 3.** Possible sites of interaction of antiepileptic drugs on glutamate-mediated transmission. The NMDA receptor is associated with an ion channel permeable to Na^+ and Ca^{2+}, and is associated with a number of modulatory sites, including a strychnine-insensitive glycine-binding site. Glycine is an absolute requirement for the receptor–channel complex to enter the open state. CPP, 3-(2-carboxypiperazin-4-yl)-1-propenyl-phosphonic acid.
Reserpine
Tetrabenazine
MULTIPLE SCLEROSIS - MS
(disseminated sclerosis)
Jean-Martin Charcot

1825-1893

Macrofage in the demyelination of MS
MULTIPLE SCLEROSIS ORIGIN

autoimmune disease: demyelination

infections, genes, inflammation, environment

young women

prognosis

impediment communication between neurons

symptoms (sensitivity, muscle weakness, ataxia, dysarthria, dysphagia, vision problems)

↑ cholesterol, ↓ vitamin D
- Relapsing-Remitting MS (RRMS)
- Secondary-Progressive MS (SPMS)
- Primary-Progressive MS (PPMS)
- Progressive-Relapsing MS (PRMS)
Multiple Sclerosis

Healthy brain

Brain with damage (lesions or plaques) caused by MS
T cells attack myelin

They enter the CNS through BEE made permeable by infections or viruses

Increase Th1 CD4 (interferon gamma, TNF)

Decreased Th2 CD4 (cytokines, IL4, 5, 13)

Th17 CD4 (IL 17)
THERAPY

Receding and remitting forms; progressive; secondarily progressive

Corticosteroids: methylprednisolone (acute attack)

Interferon beta (i.m. or s.c.)

Glatiramer (s.c), immunomodulator; Mitoxantrone, immunosuppressant

Natalizumab (i.v.), monoclonal antibody (prevents Immune System infiltration in the CNS, blocks adhesion molecules)

Cannabinoids (dronabinol), acts on symptoms: spasticity and pain
Interferon production
- From cells of the immune system and tissue cells in response to external agents such as viruses, bacteria, parasites, cancer cells

Interferon functions

Interferon effects:
- inhibits the replication of viruses within infected cells
- prevents viral spread to other cells
- strengthen the activity of the cells responsible for immune defenses, such as T lymphocytes and macrophages
- inhibits the growth of some cancer cells

Interferons mechanism:
- they bind to the cell membrane and stimulate the production of antiviral enzymes
- the virus that attacks an interferon-activated cell cannot multiply due to antiviral enzymes
- stopping or attenuating the infection
1) Interferon beta 1a and 1b (Avonex < Rebif < Betasoren) (fever)
2) Natalizumab (Tysabri) (monoclonal antibody) immunomodulator (prevents system infiltration of immune system in the CNS, blocks adhesion molecules). Encephalopathy
3) Glatiramer (copaxone) (immunomodulator)
4) Corticosterone (only in the acute phase)
5) Mitoxantrone (immunosuppressant also used in cancer chemotherapy) more advanced stages
6) Teriflunomide Pyrimidine synthesis inhibitor, decrease inflammation, lower number of white blood cells in the CNS

Dalfamprine, Ampyra (K channel blocker)
Dimethyl fumarate (immunomodulator)
Fingolimod (prevent lymphocytes from getting into the CNS)
Mitoxantrone, Ocrevus (ocrelizumab) monoclonal antibody CD20-positive B cells
**Cladribine** is a nucleoside analogue of deoxyadenosine. Used as a second choice

The mechanism of action of cladribine, a tablet drug, consists of a reduction in the number of lymphocytes that feed the inflammation processes underlying the alterations of the nervous system that are characteristic of multiple sclerosis. Like other products recently introduced in clinical practice for the treatment of multiple sclerosis, cladribine is also used in other fields, such as hematology, for the treatment of some forms of leukemia.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action for B Cells</th>
<th>Effect on Circulating B Cells</th>
<th>Vaccine Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta</td>
<td>Increased BAFF&lt;sup&gt;5,6&lt;/sup&gt; Decreased expression of costimulatory molecules&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Increased total numbers&lt;sup&gt;5,9&lt;/sup&gt; Relative increase in transitional cells&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Normal&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Impaired antigen presentation&lt;sup&gt;11,12&lt;/sup&gt; Increased anti-inflammatory cytokines (IL-10)&lt;sup&gt;5,11,12&lt;/sup&gt;</td>
<td>Relative decrease in class-switched memory cells&lt;sup&gt;5&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Inhibits proinflammatory cytokines (eg, IL-1β, IL-23)&lt;sup&gt;12&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Glatiramer acetate</td>
<td>Decreased BAFF&lt;sup&gt;14,a&lt;/sup&gt; Impaired antigen presentation&lt;sup&gt;15,b&lt;/sup&gt;</td>
<td>Decreased total numbers&lt;sup&gt;16,a&lt;/sup&gt; Relative increase in naive cells&lt;sup&gt;16,a&lt;/sup&gt;</td>
<td>Impaired relative to healthy and</td>
</tr>
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<td></td>
<td>Increased anti-inflammatory cytokines (IL-4, IL-10)&lt;sup&gt;14-16&lt;/sup&gt;</td>
<td>Relative decrease in plasmablast and memory cells&lt;sup&gt;16&lt;/sup&gt;</td>
<td>interferon-treated controls</td>
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<tr>
<td></td>
<td>Inhibits proinflammatory cytokines (eg, IL-17, IL-6, TNF-α, LT)&lt;sup&gt;14,16&lt;/sup&gt;</td>
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<td>(influenza)&lt;sup&gt;13&lt;/sup&gt;</td>
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<td>Fingolimod</td>
<td>Sequesters B cells in lymphoid tissue; impedes access to CNS</td>
<td>Decreased total numbers&lt;sup&gt;17&lt;/sup&gt; Relative increase in naive cells&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Impaired relative to placebo treated,</td>
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<td>Decreased expression of costimulatory molecules&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Relative decrease in newly produced B cells and memory cells&lt;sup&gt;17,19&lt;/sup&gt;</td>
<td>but seroprotection usually achieved&lt;sup&gt;13,20&lt;/sup&gt;</td>
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<td>Increased anti-inflammatory cytokines (IL-10)&lt;sup&gt;17&lt;/sup&gt;</td>
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<td>Inhibits proinflammatory cytokines (eg, IL-17, TNF-α)&lt;sup&gt;17&lt;/sup&gt;</td>
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<tr>
<td>Dimethyl fumarate</td>
<td>Unknown</td>
<td>Slight decrease in total numbers&lt;sup&gt;22,23&lt;/sup&gt;</td>
<td>Unknown</td>
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<td>Teriflunomide</td>
<td>Impairs proliferation of rapidly dividing cells Less infiltration into CNS&lt;sup&gt;13,b&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Generally intact; may be slightly</td>
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<td>diminished for some antigens&lt;sup&gt;13&lt;/sup&gt;</td>
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<td>Natalizumab</td>
<td>Impairs transmigration into CNS and other tissues</td>
<td>Increased in precursor, regulatory, marginal zone-like, and memory cells&lt;sup&gt;30,31&lt;/sup&gt;</td>
<td>Decrease in plasma IgG and IgM&lt;sup&gt;30&lt;/sup&gt;</td>
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<td></td>
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<td>Possibly impaired; data are conflicting&lt;sup&gt;13&lt;/sup&gt;</td>
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<td>Alemtuzumab</td>
<td>Increased BAFF&lt;sup&gt;41&lt;/sup&gt; Temporary depletion of B cells with subsequent reconstitution; long-term depletion of T cells</td>
<td>Increase in newly produced cells (immediately after infusions) and mature naive cells&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Normal&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Cytotoxic for rapidly dividing cells Increased anti-inflammatory cytokines (IL-10)&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Decreased total numbers after infusions&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Impaired&lt;sup&gt;13&lt;/sup&gt;</td>
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<td>Inhibits proinflammatory cytokines (eg, LT, TNF-α)&lt;sup&gt;45&lt;/sup&gt;</td>
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<td>Rituximab or ocrelizumab</td>
<td>Long-term (months) depletion of CD19&lt;sup&gt;+&lt;/sup&gt; B cells specifically (circulation and CNS)&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Complete depletion of CD19&lt;sup&gt;+&lt;/sup&gt; cells Mature plasma cells spared</td>
<td>Impaired for recall antigens&lt;sup&gt;13,c&lt;/sup&gt;</td>
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<td></td>
<td>Increased anti-inflammatory cytokines (IL-10)&lt;sup&gt;50&lt;/sup&gt;</td>
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<td>Live viral vaccines contraindicated</td>
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