Guillain-Barré Syndrome and Influenza Vaccine

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Guillain-Barré Syndrome (GBS)

- Immune-mediated polyradiculoneuropathy
  - Acute – subacute "ascending" limb weakness with decreased reflexes
  - Cranial nerve palsies, respiratory failure
- Several potential mechanisms hypothesized
  - Humoral or cellular immune response to antigenic stimulus, resulting in attack on nerve self-proteins
  - Numerous infectious agents and immunizations temporally associated
  - Strongest association with *Campylobacter jejuni* infection – "molecular mimicry"
- Incidence increases with age, particularly over 50
- Characteristic clinical, laboratory, electrodiagnostic features
- Outcome generally favorable
  - Case fatality 5 – 10%
  - Neurologic sequelae in 20%
  - Older age with worse prognosis

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GBS and Influenza Vaccine: Methods

- All available literature reviewed (limited to controlled studies)
- Use of swine-antigen containing influenza vaccines, including A/NJ/76 (H1N1), used pre- and post-1976 assessed
- Archived WHO, CDC, CBER records
  - AFEB records
  - Personal communications
- Comparison data on virologic, molecular characteristics of A/NJ/79 influenza virus, current A/CA/09 virus, other SW-OI viruses
- Best available data for "background" rates of GBS:
  - 1.0 – 1.7 / 100,000 population / year in developed countries
  - When possible, published rates converted to incidence / 100,000 for comparison

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GBS and A/NJ/76 (H1N1) Vaccine

- 1976: human-to-human transmission of swine-origin H1N1 influenza virus on US military base
  - 40 million doses of vaccine among US civilians, military
  - Influenza epidemic never materialized
- "Cluster" of GBS cases noted though AE surveillance early in campaign
  - Campaign discontinued Dec. 16, 1976
- Subsequent assessment of US civilians by CDC, state health depts.
  - Active, national case-finding between December 16, 1976 and Jan 31, 1977
  - GBS among adult vaccinees compared to non-vaccinees ("expected" rate)

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1. Based on 8 controlled assessments, A/NJ/76 (H1N1) influenza vaccine associated with increased risk of GBS in adults

- RR of 7.6 (95% CI 6.7 – 8.6)
- Reporting rate of 8.6 cases / 100,000 / yr
  - Non-vaccinees: 1.7 / 100,000 / yr
- Attributable risk of 0.95 / 100,000 vaccinees
- Features consistent with biological plausibility
  - Risk concentrated within first 6 weeks of vaccination (peak at week 2 – 3)
- Not a lot- or manufacturer- specific phenomenon
- Several re-analyses with same conclusions

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2. There are limited data on GBS risk among other populations receiving vaccine.

- U.S. Military
  - A/NJ/76 formulation (bivalent) same as civilian, but higher dose (1.0 ml vs. 0.5 ml); also received B vaccine
  - Single study: "no increased risk of the magnitude reported by CDC"; limitations in data*
  - No additional controlled data
- Use of A/NJ/76 vaccine outside US
  - UK: ? Anecdotal reports, but no confirmation
  - Canada: 800,000 doses of monovalent and bivalent vaccine distributed
    - Limited mechanisms to detect risk of GBS; small population of vaccinees
  - Netherlands
    - 2.4 million doses apparently delivered
    - None apparently used

*Johnson, D. Arch Neurol 1982;39:21

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3. There are limited data on risk of GBS from swine-antigen-containing influenza vaccines pre--1976

- 1955 – 1969: Swine antigen (A/swine/Iowa/1976/31 H1N1) routinely incorporated into U.S. military vaccines
- 1956 – 1959: same antigen incorporated in some civilian vaccines
- No suggestion of increased risk
  - Limited passive surveillance infrastructure
  - No systematic assessments
  - In limited exposed population, no risk of sufficient concern enough to be reported to public health authorities or published
- Swine antigens not used since 1976 (Netherlands 1977?)

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4. Most data suggest little, if any, significant risk of GBS following subsequent influenza vaccines

- Association between other influenza vaccine formulations and GBS less clear
- 9 well-designed, controlled assessments between 1977 and 2009
- Two suggesting a small but statistically significant increase in risk of GBS
  - Lasky et al*:
    - increased risk following influenza vaccine for combined 1992-93 and 1993-94 seasons (RR 1.7; 95% CI 1.0 – 2.4; AR 0.06 / 100,000 vaccinations);
    - no such risk with each season separately.
  - Juurlink et al#:
    - increased risk of GBS following presumed influenza vaccination over period of 1993 – 2004 (RR 1.45, 95% CI 1.05 – 1.99)
    - No increase in incidence of hospital admissions for GBS following universal influenza vaccination in Ontario in 2000.
- Differences in methodologies, case ascertainment methods, analyses
- No clear, consistent association
- Potential GBS risk likely outweighed by influenza-associated morbidity / mortality in any particular season

*N Engl J Med 1998;339:1797 #Arch Int Med 2006;166:2217

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5. Biological data on possible mechanisms for association of GBS and A/NJ/76 (H1N1) vaccine are largely absent

- No association with particular human leukocyte antigen (HLA) haplotypes
- A/NJ/76 vaccine, ***but also other formulations***, induces anti-myelin ganglioside antibodies in mice *(Nachamkin et al. 2008)*
  - Provides biological basis, but significance unclear
- No robust data suggesting a biological basis for association

*Kaslow et al. Neurology 1987;37:685 #J Infect Dis 2008;198:226

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6. There are both molecular and antigenic similarities and differences between A/NJ/76 (H1N1) and 2009 A/H1N1 viruses

- A/NJ/76 (HswN1): "classical" swine influenza virus
  - All gene segments derived from viruses since 1930
- 2009 A/H1N1: novel combination of gene segments
  - 6 genes – "triple reassortant"; gene segments from swine H1N1, North American avian and human H3N2
  - NA, M – Eurasian lineage of Hsw1N1 viruses
  - HA antigenically and genetically different from A/NJ/76
- Biological properties of 2009 A/H1N1 HA and NA not fully characterized

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Conclusions (1)

- A/NJ/76 (H1N1) influenza vaccine associated with increased risk of GBS in adults 6 - 8 weeks following vaccine in US civilians
  - Reasons unknown
  - No clear biological explanation
- Data on risk of GBS following other swine-antigen containing vaccines too limited to allow for conclusions
- Most data suggest little or no risk of GBS following subsequent influenza vaccines
- A/NJ/76 (H1N1) and 2009 A(H1N1) viruses differ virologically and antigenically
  - Without biological underpinning for 1976 event, unclear what significance any similarities might have on risk of vaccine

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Conclusions (2)

- 1976: No significant influenza disease
- 2009: Already associated with morbidity and mortality
  - Future epidemiology, potential virulence unknown
- Risk in 1976 may have been acceptable in the setting of significant influenza-associated disease

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Additional Slides

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GBS and Influenza Illness

- Case reports of GBS following influenza / ILI
- No substantial evidence of strong association
  - No seasonal pattern of GBS
  - No increase in GBS following large epidemics
- Several reports suggest risk, but data conflicting

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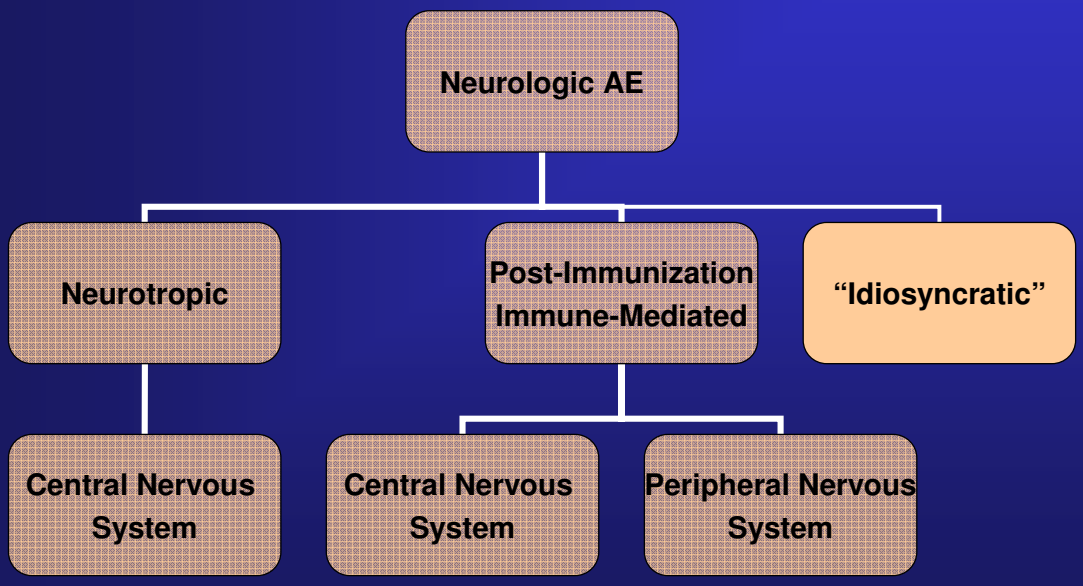
Vaccine-Associated Neurologic Disease



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"Phylogeny" of GBSs

Guillain-Barré *Syndromes*

- **Acute Inflammatory Demyelinating Type (AIDP)**
  - **(Secondary axonal Degeneration)**
- **Acute motor axonal Type (AMAN)**
  - **Acute motor and Sensory axonal type (AMSAN)**
- **Fisher syndrome**

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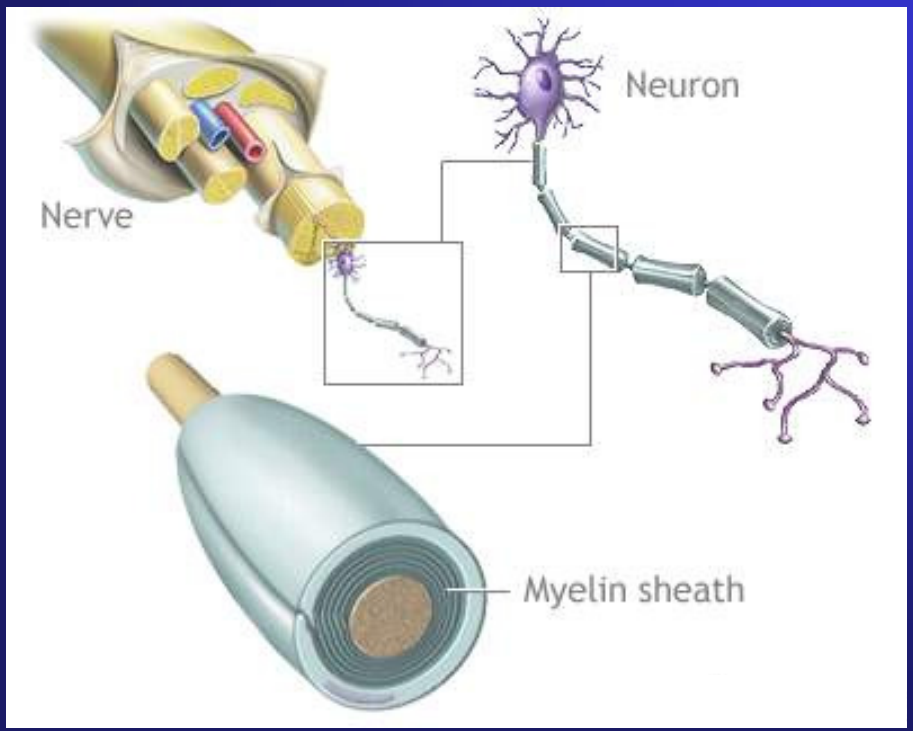

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Guillain-Barré Syndrome

- Acute inflammatory demyelinating polyradiculopathy--most common form of GBS in North America, Europe
  - Primarily axonal form more common in developing world
- Incidence 0.5 – 4 / 100,000, depending on study design; incidence increases with age
- Demyelination > axonal damage; cross - reactive epitopes on peripheral myelin sheath or axons
  - Various structural glycoproteins on myelin / axons induce antigenic response
- Antecedent viral-like illness or immunization reported in over 2/3

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GBS

- Acute – subacute onset of weakness– evolve over days to weeks
  - Most– maximal deficit within 2 weeks
  - Hypo- or areflexia
- "Ascending" weakness—legs to arms; generally symmetric
- Sensory abnormalities
  - Ascending pain or dysesthesias
  - Objective numbness generally absent
- Autonomic dysfunction
  - Tachy / bradycardia, hypotension, arrhythmias
- Cytoalbuminologic dissociation – elevated CSF protein in absence of pleocytosis
- Characteristic electrophysiologic profile – reduced conduction velocities and decreased amplitudes indicative of demyelination
- Fisher Syndrome: "ataxia, areflexia, ophthalmoplegia"

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GBS and Glycoconjugate Antibodies

- Gangliosides: glycosphingolipids in plasma membrane of tissues
  - Major surface molecules of PNS & CNS tissues
- Strong association of antiganglioside antibodies with GBS; thought to play a role in pathogenesis
  - Anti-GM1: AMAN
  - Anti-GQ1b: FS
- Natural infection with certain serotypes of *Campylobacter jejuni* associated with GBS
  - Cross-reactive antibodies to gangliosides and *C. jejuni* lipopolysaccharide moieties
  - Biological plausibility?

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GBS

- Outcome generally favorable; complete recovery with or without treatment
  - Advanced age, mechanical ventilation associated with poorer outcome
- Treatment modifies disease progression and outcome
  - Intravenous immune globulin (IVIG)
  - Plasmapheresis
  - Corticosteroids contraindicated

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GBS vs. CIDP

	GBS	CIDP
Antibodies	AIDP: Variable AMAN: GM1 FS: GQ1b	No antibodies
Antecedent event	70%	None
Course	Monophasic	Relapsing / remitting
Treatment	IVIG, PLEX	Steroids, IVIG, PLEX
Pathology	Axonal and demyelinating	Demyelinating

Differentiation between GBS and CIDP requires longitudinal follow-up to identify relapses and remissions

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GBS and Vaccines

Influenza

- 1976 swine influenza: small but significant risk for GBS (1 additional case / 100,000 vaccinees) 1 – 6 weeks post-immunization
  - IOM: "evidence favors a causal association..."
- Association between other influenza vaccine formulations and immunizations less clear
  - 19 well-designed, controlled studies in the literature between 1977 and 2009
    - 2 (Lasky et al., 1998 [flu]; Kinnunen et al., 1989 [OPV]) suggest slightly increased risk...(maximal odds ratio 1.7)
  - No clear, consistent association
- Biological data: swine influenza vaccine, ***but also other formulations***, induces anti-myelin ganglioside antibodies in mice *(Nachamkin et al. 2008)*
  - Provides biological basis, but significance unclear

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