

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



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



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)



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

CDC

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

CDC

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

CDC

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

CDC

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

CDC

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**

CDC

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Additional Slides

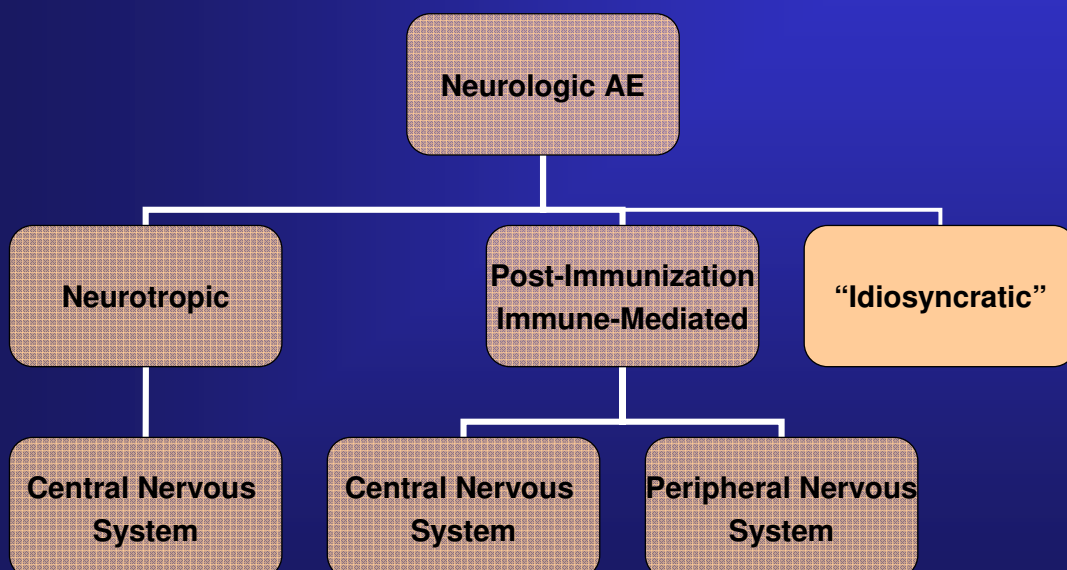


GBS and Influenza Illness

- 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

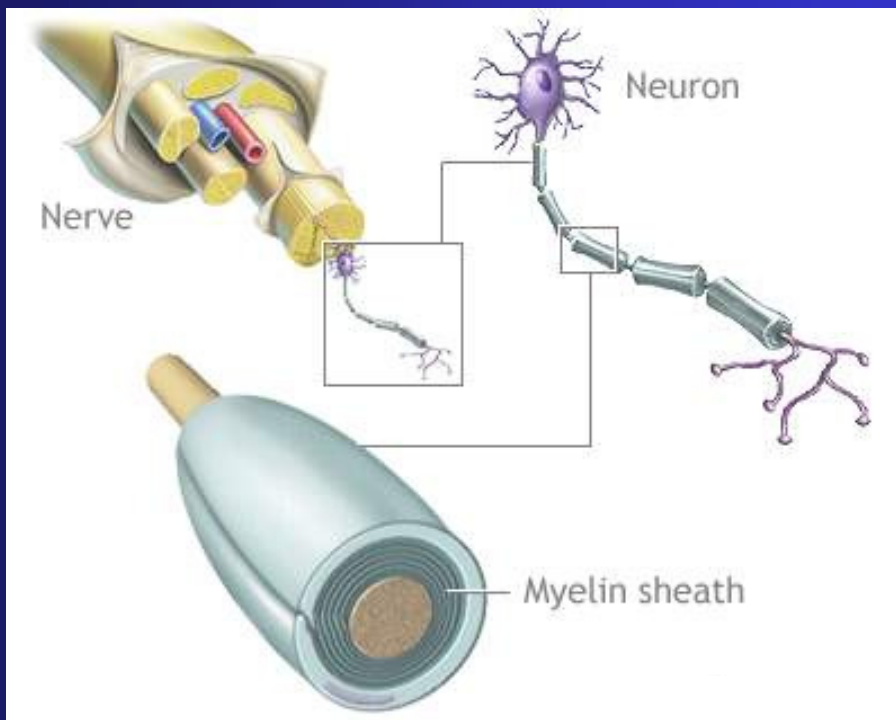
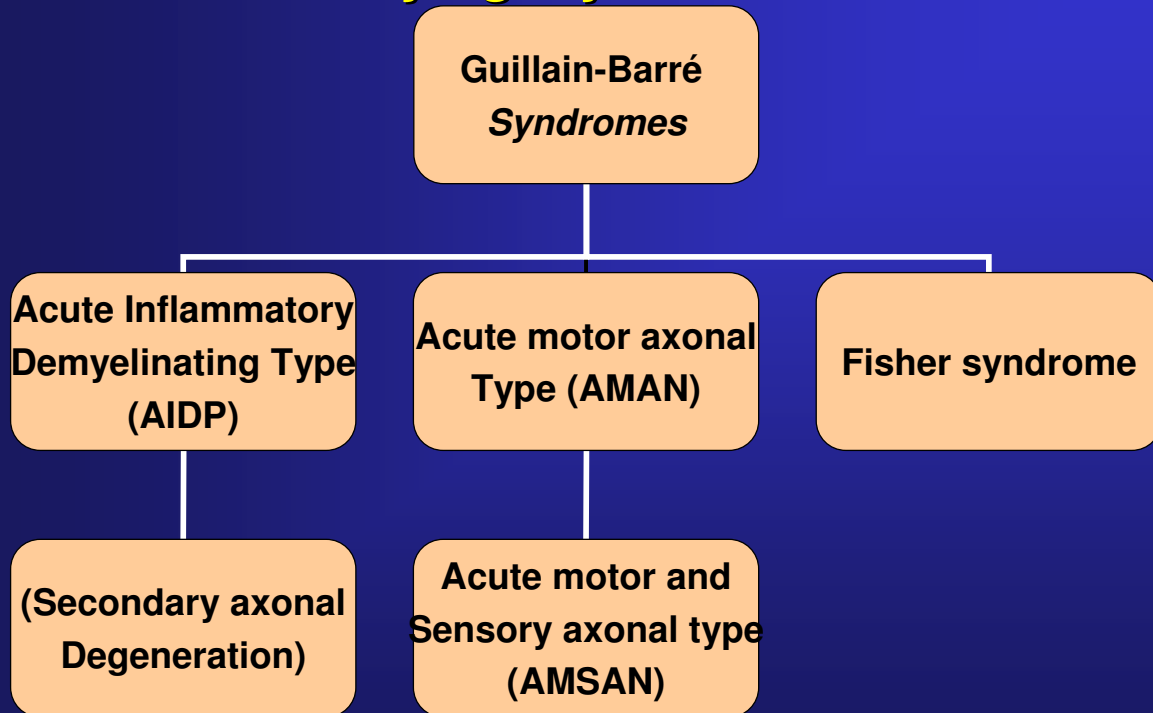
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Vaccine-Associated Neurologic Disease



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“Phylogeny” of GBSs



Guillain-Barré 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?

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

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



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

