Primary generalized epilepsy: clinical variability from childhood to adult

Kanokwan Boonyapisit, M.D.
Siriraj Hospital

Outline

- IGE in adult: Is this common?
- Clinical spectrum of IGE in adult
- Is IGE in adult different from childhood IGE?
- Clinical implications

IGE in adult: Is it common?

- Idiopathic generalized epilepsy is common and accounts for 20-40% of all epilepsies
- Before 1989 classification, Gastaut reported that in his series seizures began after adolescent in 35% of IGE patients

IGE in adult: Is it common?

- Loiseau J, et al 1998
- Review in literatures and 4 large epilepsy database in France for IGE of very late onset (>60 yr old)
- Found 5 case reports in literature
  - All female
  - 4 presented with GTCs and one with myoclonic seizure
- Found no pts in the databases with very late onset IGE

Loiseau J, et al. Seizure 1998;7:485

IGE in adult: Is it common?

	Cutting 2001	Marini 2003	Nicolson 2004
No. of pts with IGE	313	121	844
Adult onset IGE	42 (13%)	34 (28%)	72 (8.5%)
Mean age of onset	23.8	33	23.8

Nicolson A, et al JNNP 2004;75:72
Marini C, et al JNNP 2003;74:192

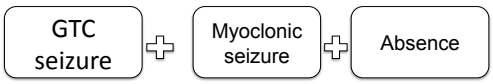
Classic syndromes of IGE that can be found in adult

- Childhood absence epilepsy
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Epilepsy with grand mal seizures (generalized tonic-clonic seizures) on awakening

Clinical spectrum of IGE in adult

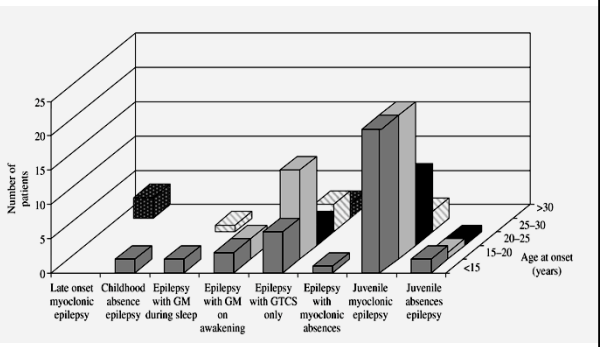
- GTC seizure alone
- GTC seizure +/- myoclonic seizure +/- absence seizure
- Absence status
- Absence status in the elderly

Clinical spectrum of IGE in adult



	Cutting 2001	Marini 2003	Nicolson 2004
Adult onset IGE	42 (13%)	34 (28%)	72 (8.5%)
Mean age of onset	23.8	33	23.8
Seizure types			
GTC seizure	41 (97%)	32 (94.1%)	69 (95.8%)
Myoclonic	21 (50%)	6 (17.6%)	30 (41.7%)
Absence	16? (38%)	3 (8.8%)	11 (15.3%)
Epilepsy type			
AME	21 (50%)	6 (17.6%)	30 (41.7%)
GTS-A/ GTC	3 (7%)	25 (73.5%)	35 (48.6%)
Absence E	-	3 (8.8%)	7 (9.7%)
Unclassified	1 (3%)	-	-

Nicolson A, et al JNNP 2004, Marini C, et al JNNP 2003



Mohanraj R, Brodie MJ. Acta Neurol Scand 2007:115:204

Generalized tonic clonic seizure

Epilepsy with GTC seizures only

- Appeared in recent proposed classification scheme in 2001
- This appeared to include the classically described “epilepsy with GTC seizures on awakening”
- Peak age of onset at the end of second decade (range 5-50 year)

Engel J Jr. Epilepsia 2001;42:796

Epilepsy with GTC seizures only

- Seizure types: GTC seizures, few also have myoclonic and absence seizures
- Seizures are mainly provoked by alcohol or sleep deprivation
- In GTC seizures on awakening, 90% of all seizures occur within 1-2 hrs after awakening or at the end of the day

Epilepsy with GTC seizures only

- EEG
  - Interictal: generalized 4-5 Hz swc, generalized polyspikes
- Genetics
  - Frequently have positive family history
  - Different mutations of chloride channel 2 gene (CLCN2) on chromosome 3q26 are associated with GTC on awakening

Epilepsy with GTC seizures only

- Treatment
  - Valproate, lamotrigine
  - Topiramate, levetiracetam, zonisamide
- Prognosis
  - Good chances of seizure control and 2-5 yrs seizure fredom: 70-90%

Myoclonic seizure

Adult onset myoclonic epilepsy

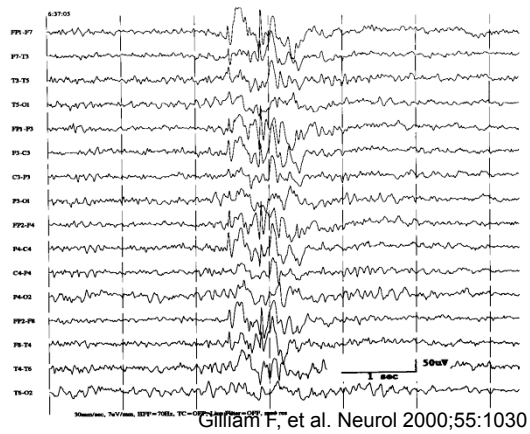
- Gilliam, et al 2000
- 11 cases of adult onset myoclonic epilepsy
- Mean age of onset 39 yrs (range 28-53 yrs)
- Seizure types
  - Myoclonic seizures
  - Absence seizures
  - GTC seizures (less than 1 per year)

Gilliam F, et al. Neurol 2000;55:1030

Adult onset myoclonic epilepsy

Patient no.	Age at onset of myoclonic seizures, y	Age at onset of absence seizures, y	Age at onset of GTC seizures, y	EEG	Family history
1	37	37	—	poly S/W	+
2	34	34	—	poly S/W	—
3	53	53	53	S/W	—
4	38	38	38	S/W	+
5	28	—	28	PPR	—
6	41	—	41	PPR	+
7	32	—	32	S/W	Sister with febrile seizures
8	35	—	51	S/W	+
9	25	27	27	S/W	—
10	29	—	29	S/W	—
11	41	—	38	poly S/W	Sister with febrile seizures

Gilliam F, et al. Neurol 2000;55:1030



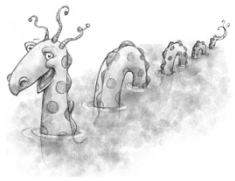
Gilliam F, et al. Neurol 2000;55:1030

Adult onset myoclonic epilepsy

- Seizures were controlled in all pts with VPA or LTG
- Authors' conclusion
- Except for the age of onset, the clinical and EEG features were similar to classic IGE

Gilliam F, et al. Neurol 2000;55:1030

Absence



IGE with phantom absences

- Found in 3% (13pts) of 410 consecutive epilepsy pts over 16 yrs old in one series
- Clinical manifestations
  - Phantom absences that are difficult to recognize and never appreciate prior to GTC onset
  - Infrequent GTC seizures, usually starting in adulthood
  - Absence status epilepticus occurs in 50% of patients

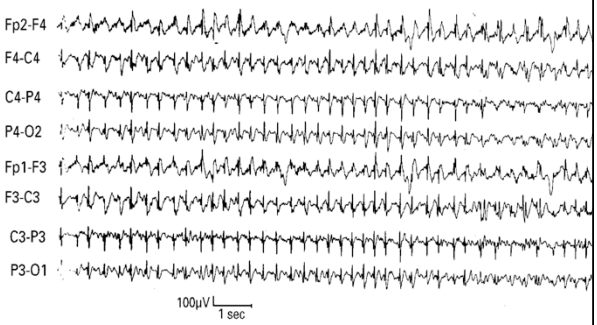
Panayiotopoulos CP, et al. JNNP 1997;63:622

IGE with phantom absences

- 3 of 13 pts have family history
- Absence status were wrongly diagnosed as complex partial seizures in 4 pts
- EEG: generalized 3-4 Hz spike/polyspikes and wave complexes, no photoparoxysmal response

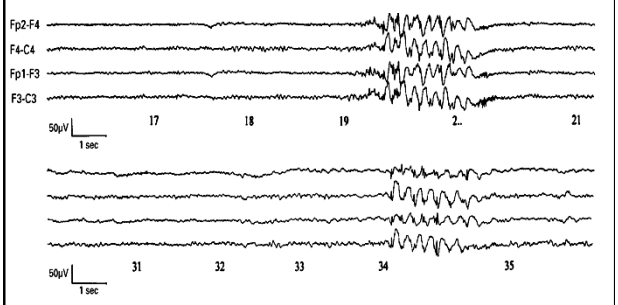
Panayiotopoulos CP, et al. JNNP 1997;63:622

IGE with phantom absences



Panayiotopoulos CP, et al. JNNP 1997;63:622

IGE with phantom absences



Panayiotopoulos CP, et al. JNNP 1997;63:622

IGE with phantom absences

- Prognosis:
  - Most of the patients were seizure free with treatment
  - Some patients refused to take medication

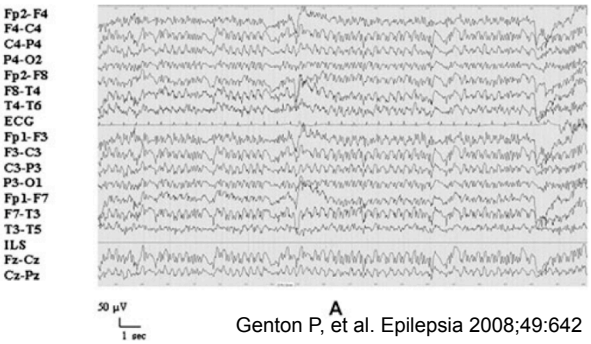
Panayiotopoulos CP, et al. JNNP 1997;63:622

Absence status epilepsy

- 11 cases
- Main type of seizure is recurrent, unprovoked absence status
- Rare typical absences
- Infrequent GTC seizures
- Onset of absence status is usually after puberty or early adult
- No family history

Genton P, et al. Epilepsia 2008;49:642

Absence status epilepsy



Genton P, et al. Epilepsia 2008;49:642

Absence status epilepsy

- All patients were given wrong diagnosis of complex partial seizures with secondarily GTC or just “grandmal seizure”
- Prognosis is quite good with adequate treatment (VPA, LTG)

Genton P, et al. Epilepsia 2008;49:642

Late onset absence status

- Absence status in the elderly
- Presence of absence status epilepticus at the age of 60-80
- Most occurs “de novo”
- A portion of patients had prior history of IGE when they were young in some series
- Almost half of patients had precipitating factors

eg. Benzodiazepine withdrawal

Late onset absence status

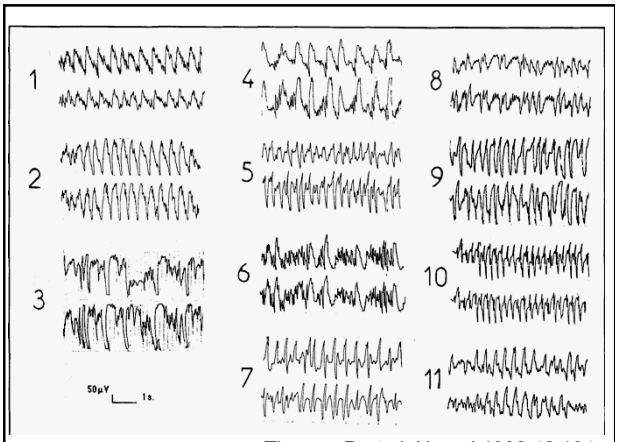
- Thomas P, et al.
- Reported 11 cases of “de novo” absence status at the age onset >40 years
- Mean age of onset 58.9 yrs (48-81 yrs)
- One pt had one prior GTC seizure due to benzodiazepine withdrawal

Thomas P, et al. Neurology 1992;42:104

Late onset absence status

- 9 pts received psychotropic drugs include benzodiazepines and in 8 of 9 pts benzodiazepine was discontinued 2-3 days prior to AS
- AS were stopped with benzodiazepine or phenobarbital in all cases

Thomas P, et al. Neurology 1992;42:104



Thomas P, et al. Neurol 1992;42:104

Authors	No. pts	Age
Elian (1969)[3]	1	55
Amand (1971)[4]	3	60,63,66
Schwartz and Scott (1971)[5]	4	56,62,42,54
Wells (1975)[37]	1	62
Richard and Brenner (1980)[38]	1	84
Van Zandycke et al (1980)[39]	2	52,70
Weiner et al (1980)[20]	1	30
Goldman et al (1981)[40]	1	59
Rumpl and Hinterhuber (1981)[19]	1	58
Vercelletto and Gastaut (1981)[41]	1	65
Bateman et al (1983)[42]	1	50
Pritchard and O'Neil (1984)[43]	1	
Lee (1985)[26]; Ellis and Lee (1977)[7]	11	
Courjon et al (1984)[24]	3	
Van Sweden (1985)[6]	4	
Vollmer et al (1985)[44]	1	
Bourrat et al (1986)[9]	8	
Dunne et al (1987)[10]	5	
Hersch and Billings (1988)[16]	1	
Van Sweden and Mellerio (1988)[11]	12	58,66,39,43,43,44, 50,52,52,52,61,73
Vickrey and Bahls (1989)[21]	1	64

Mean age* (55 patients): 61.7 yrs.
Sex ratio* (58 patients): F = 38 (66%), M = 20 (34%).

* In some cases, this information was not available.

Review of 64 cases
In the literature

Middle age or elderly pts
No prior history of epilepsy
Female predominance
72% had precipitating factors

Thomas P, et al.
Neurology 1992;42:104

No definite factor, 19[3-5,9,10,24,37-41]
Psychotropic drugs, 36
- Benzodiazepine withdrawal, 8[10,11,16]
- Benzodiazepine, 3[8,9,11]
- Neuroleptics, 5[8-11]
- Tricyclic antidepressants, 7[8,9,11,19]
- Barbiturates, 3[11]
- Lithium carbonate, 4[7,10,20]
- Meprobamate, 2[11]
- Viloxazine, 2[8]
- Methaqualone, 1[11]
- MAO inhibitors, 1[9]

Other drugs, 6
- Cimetidine, 2[8]
- Diuretics, 2[9]
- Metformin, 1[9]
- Theophylline, 1[21]

Metabolic and toxic factors, 17
- Hyponatremia, 5[7,9]
- Hypokalemia, 3[9]
- Metrizamide, 1[21]
- Alcohol, 5[7,9,11,16,24]
- Dehydration, 1[9]
- Hepatic abnormalities, 1[7]
- Psychogenic polydipsia with metabolic imbalance, 1[7]

Miscellaneous, 6
- Cancer, 2[7,26]
- Mild dementia, 1[9]
- Shock therapy, 2[19,20]
- Stroke, 1[7]

* In some cases, more than one possible factor was present.

Precipitating factors

Thomas P, et al.
Neurology 1992;42:104

Generalized epilepsy with febrile seizure plus (GEFS+)

- Phenotypic spectrum are extremely variable
- Multiple febrile seizures in early childhood and persists beyond 6 years old
- History of febrile seizures in the family

Generalized epilepsy with febrile seizure plus (GEFS+)

- Generalized seizure or focal seizures
- Seizures remitted in early teenage although in some cases can persist until late adolescent or older
- Seizure types
  - GTCs, absence, myoclonic, atonic, tonic seizures
  - Unilateral clonic seizures, visual, psychic aura

Generalized epilepsy with febrile seizure plus (GEFS+)

- Genetics
  - AD with incomplete penetrance
  - Different mutations
    - SCN1B gene (19q13.1) µ1 subunit of sodium channel
    - SCN1A gene (2q21-33) α1 subunit of sodium channel
    - GABRG2 gene (5q31-33) Y2subunit at the benzodiazepine binding site of $GABA_A$ receptor

Is IGE in adult different from childhood IGE?

- Nicolson, et al
- Study clinical manifestation of 72 cases late onset IGE compared to 844 cases of early onset IGE

Nicolson A, et al JNNP 2004

Variable	Age of onset <20 years (n=772)	Age of onset >20 years (n=72)
Sex		
Male	317 (41.1)	40 (55.6)
Female	455 (58.9)	32 (44.4)
Family history	169 (21.9)	20 (27.8)
Febrile convulsions	81 (10.5)	4 (5.6)
Mean age of onset (years)	12.0	23.8
Mean length of follow up (years)	17.6	11.4
EEG*		
GSW	548 (76.5)	46 (66.7)
PPR	191 (26.7)	20 (29.0)
Focal abnormality	80 (11.2)	6 (8.7)

Nicolson A, et al JNNP 2004

Variable	Age of onset <20 years (n = 772)	Age of onset >20 years (n = 72)
Seizure types		
Absence	358 (46.4)	11 (15.3)
Myoclonus	363 (47.0)	30 (41.7)
Tonic–clonic	718 (93.0)	69 (95.8)
Epilepsy type		
Absence epilepsy	216 (28.0)	7 (9.7)
Myoclonic epilepsy	363 (47.0)	30 (41.7)
TC seizures only	193 (25.0)	35 (48.6)
Remission rate†		
Absence epilepsy	112 (54.1)	35 (55.6)
Myoclonic epilepsy	173 (49.4)	15 (53.6)
TC seizures only	124 (70.5)	18 (62.1)
Overall	409 (55.8)	68 (56.7)

Nicolson A, et al JNNP 2004

Prognosis in adult onset IGE

Syndrome	Remission (%)	Relapse (%)	Uncontrolled (%)	Total
Juvenile myoclonic epilepsy	40 (73)	4 (7)	11 (20)	55
Epilepsy with generalized tonic–clonic seizures	15 (54)	5 (18)	8 (29)	28
Epilepsy with generalized tonic–clonic seizures on awakening	5 (71)		2 (29)	7
Juvenile absence epilepsy	3 (75)		1 (25)	4
Late-onset myoclonic epilepsy		1 (33)	2 (67)	3
Epilepsy with generalized tonic–clonic seizures during sleep	2 (67)		1 (33)	3
Childhood absence epilepsy	1 (50)		1 (50)	2
Epilepsy with myoclonic absences			1 (100)	1
Total	66 (64)	10 (10)	27 (26)	103

Mohanraj R, Brodie MJ. Acta Neurol Scand 2007:115:204

Implication to our practice

- IGE in adult does exist although uncommon
- Clinical syndromes of IGE in adult are still not well defined
- Through history of seizure characteristics and EEG (sleep deprived, hyperventilation and photic stimulation) may be helpful for diagnosis of IGE in this age group
- Beware of frontal lobe epilepsy that may mimic IGE

Implication to our practice

- Importance of diagnosis of IGE in adult
  - Select appropriate medication
  - Reduced cost of neuroimaging
  - Importance of avoiding precipitants