Neurology Update for Psychiatrists

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• Horearium: Bayer-Schering, Biogen Idec, Lundbeck
The Dublin Neurological Institute at the MMUH (www.neurologicinstitute.ie)
Burden of Mind & Brain Disorders

<table>
<thead>
<tr>
<th>Rank</th>
<th>Cause</th>
<th>Worldwide</th>
<th>DALYs (millions)</th>
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<td>Post-traumatic stress disorder</td>
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<td>Multiple sclerosis</td>
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<td>Parkinson’s disease</td>
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*Data from ref 1. Examples of MNS disorders under the purview of the Grand Challenges in Global Mental Health Initiative. 
World Bank criteria for income (2009 gross national income (GNI) per capita): low income is US$995 equivalent or less; middle income is $996–12,195; high income is $12,196 or more. 
A disability-adjusted life year (DALY) is a unit for measuring the amount of health lost because of a disease or injury. It is calculated as the present value of the future years of disability-free life that are lost as a result of the premature deaths or disability occurring in a particular year.
New Treatments for Brain Disorders
Case I - Mrs. X

- 54 year old woman
- Recurrent depression with anxiety symptoms
- 3 psychiatric admissions
  - 1976, 19 years old
  - 18 July-8 September, 2011
  - 4 November, 2011 to present
Thirty year outpatient course

- 1976
  - “Neurotic anxiety disorder with obsessional features”
  - Melleril (Thioridizine), Clomipramine
- Paroxetine
- Retroverted uterus, Costochondritis, Tietze syndrome
- 2007-2011, Fibromyalgia
  - Paroxetine, Duloxetine, Clomipramine

- Married, 3 children, one grandchild
July, 2011- psychiatric admission

- Noncompliance with medication, self-reported
- Paroxetine recommenced
- Olanzapine 5mg
- Brief period improvement…

- Treatment refractory depression
Trials of medication

- Paroxetine, Olanzapine, Lithium augmentation
- Paroxetine, Olanzapine, Pregabalin
- Mirtazapine, Olanzapine
- Mirtazapine, Olanzapine, Venlafaxine
- Mirtazapine, Venlafaxine, Propranolol
- Dothiepin…23 November, 2011
Dothiepin trials

- Dothiepin, propranolol, diazepam
  - Venlafaxine, mirtazapin cross tapered
- Dothiepin, quetiapine
- Dothiepin, Phenylzine
  - Diazepam, quetiapine cross-tapered

- 25 January, 2012
  - First noted improvement in mood
29 January, 2012

• Sedation, ataxia, fall
• “frothing at mouth”
• Respiratory distress/?airway obstruction
  – Flumazenil
  – Transferred to Medical ward
• Urinary retention
• Hypotensive; Raised CK; CT brain
• Medications discontinued
4 February, 2011

• Transferred back to psychiatric care
• Dothiepin 75mg, Phenylzine 30 mg BD
• Discharge planned, mood significantly improved

• Sedation, “tremor inside,” ataxia, syncope
• ?Tolerable side effects with resolving depression
• Discharge delayed
• 17 February, blood pressure 73/40
• Day 1, 17 February
  – Dothiepin held
    • Minimal improvement BP
    • Temperature, pulse – within normal limits
      • sleep disturbance

• Day 4
  – Dothiepin 50mg nocte

• Day 5
  – Marked EPSE, cogwheel rigidity ++
  – Marked distress
  – Dothiepin held
• Day 7, Friday
  – “I’ve lost everything…It doesn’t matter anymore.”
  – Dothiepin 50mg
  – Syncope, “tremor”

• Day 9
  – Refused food and fluids

• Day 10
  – Cogwheel rigidity +++
  – Catatonia-like postures
  – Clonus, myoclonus
The Serotonin Syndrome

- 1960 Oates & Sjoerdsma encephalopathy, ataxia, restlessness, legs hyperreflexia, diaphoresis following high dose tryptophan & MAOI in 4
- Variable agitation, confusion, disorientation, “drunkenness”, restlessness, coma
- Myoclonus, rigidity, leg hyperreflexia, clumsy
- Fever, nausea, flushing, diaphoresis, dilated pupils, tachycardia, tachypnea, fluctuating BP
- May have warning symptoms (jerks/ agitation)
• Rarely hyperthermia, seizures, oculogyric crisis, opisthotonus, nystagmus, dysarthria, Babinski signs, DIC, myoglobinuria, ARF, arrhythmia, coma & death
• Can occur with serotomimetic agents alone or in combination with MAOIs (often due to the premature start of new agent)
• Occurs shortly after initiation/increase of agent & persists for hrs to days
• Raised CPK, leukocytosis
Sternbach Diagnostic Criteria

1. Symptoms coincide with initiation/increase of serotomimetic agent (within hrs or days)
2. Three of following: fever, mental status change, agitation, incoordination, myoclonus, tremor, hyperreflexia, diaphoresis, shivering, diarrhoea,
3. Other aetiologies excluded (infection, metabolic, substance abuse or withdrawal)
4. No neuroleptic initiated/increased prior to onset
SS Pharmacology

Drug
• Tryptophan
• Fluoxetine
• Clomipramine
• Moclobemide
• Bromocriptine
• Meperidine
• Phenelzine
• Dextromethorphan
• Sertraline
• Trazodone
• Fluvoxamine

Combination
• Fluoxetine, MAOI
• CBZ, pentazocine, selegiline
• Alone, MAOI, trazodone
• Citalopram, imipramine
• L-dopa
• Iproniazid, MAOI
• Ecstasy (MDMA)
• MAOI
• MAOI, nortriptyline
• Buspirone
• Alone
Rx Serotonin Syndrome

- Supportive: ABC, hydrate, antipyretics, cooling
- Immediately withdraw causative agents
- Specific serotonin antagonists e.g., methysergide, cyproheptadine, propranolol
- Other: clonazepam, lorazepam, benztropine, diphenhydramine, unclear role for muscle relaxants (pancuronium, succinylcholine) or membrane stabilizers (dantrolene)
Case II

65 yo woman 1 week post medication change
Clinical Features of Malignant Catatonia

- Excitement and/or stupor
- Other catatonic features: mutism, negativism, catalepsy, posturing, echolalia, echopraxia, staring
- Muscle rigidity
- Altered consciousness
- Autonomic instability: profuse sweating, tachycardia, labile BP, tachypnea, cyanosis
- Laboratory findings raised CPK & WCC; low serum iron; sometimes abnl LFTs, slow waves on EEG, hyperglycemia, raised creatinine, hyponatremia, hypernatremia, dehydration
- Frontal atrophy on brain imaging, frontal hypoperfusion on SPECT
Disorders associated with Malignant Catatonia Syndrome

- **Psychiatric disorders**: Schizophrenia, mood disorders, periodic catatonia, psychotic disorders
- **Cerebrovascular disorders**: basilar artery thrombosis, bilateral infarction of the anterior cingulate gyri, bilateral hemorrhagic lesions of the temporal lobes
- **Other CNS problems**: normal pressure hydrocephalus, seizures, cerebral anoxia
- **CNS tumors**: periventricular diffuse pinealoma, glioma of 3rd ventricle or splenium, angioma mesencephalon
- **Head trauma**: closed head trauma, surgical removal of lesions near the hypothalamus
- **Infections**: viral encephalitis, borrelia encephalitis, bacterial meningoencephalitis, general paresis, viral hepatitis, bacterial septicemia
- **Metabolic disorders**: hyperthyroidism, Addison’s disease, Cushing’s disease, uremia, Wernicke’s encephalopathy, SLE
- **Toxic disorders**: postoperative states, sedative-hypnotic withdrawal, tetraethyl lead poisoning, cyclobenzaprine toxicity, toxic epidermal necrolysis, NMS, serotonin syndrome
Neuroleptic Malignant Syndrome

- Hyperthermia, rigidity, fluctuating encephalopathy, autonomic instability
- Exposure to neuroleptics (immediately after 1st dose or years later), dopamine depleting agents, or withdrawal of L-dopa or dopamine agonists
- Precipitated by dehydration, fever or high environmental temperatures
- Sometimes associated with a rapid dose increase
- Raised CPK, WCC, LFTs, EEG generalised slowing, normal CSF & brain imaging
Treatment of NMS

• 20-30% fatal
• Respiratory failure due to rigidity, renal failure due to myoglobinuria
• Immediate withdrawal of all neuroleptics or dopamine depleters at the earliest sign
• Supportive care: rehydration & maintain adequate urine output, lower body temp, protect airway (+/- ET), ventilation with muscular paralysis in rare cases
Treatment of NMS

• Dantrolene 1-10mg/kg/day IV/NG, direct acting muscular relaxant, no systematic studies done

• Bromocriptine 2.5 to 10 mg IV/NG q4-6h, no systematic studies done

• Other Gabaergic agents: benzodiazepines, sodium valproate, vigabitrin
Case III History:

- 2 prior miscarriages
- Cocaine twice in distant past
- 6/52 headaches, nausea, dizziness
- Pregnant
- Acute urinary retention/constipation
- Psychosis within following 24 hours
Examination:

- Elated, prominent auditory and visual hallucinations, talking, repeating phrases, insomnia
- ‘dead aunt on the ceiling talking to her’
- ‘people going to take her baby, going to do experiments’
- Some insight, agreed she needed oral medication
Examination

• Tachycardia, Febrile, urinary retention, constipation, labile BP on occasion
• Fluctuating level of consciousness
• Forced eye closure, neck rigidity, mouth open
• Intermittent stereotypic movements of R hand
• Catatonia, ‘Waxy flexibility’
• Brisk DTRs, Unresponsive plantars
• Noted to ‘awaken’ post IV lorazepam
Differential:

- Autoimmune
- Neuroleptic malignant syndrome
- Paraneoplastic
- Drug induced psychoses
Treatment:

- Initially with olanzapine, lorazepam and haloperidol prn
- Plasmaphoresis (5 exchanges) / IV M-Pred *5/7
- AEDs...
- IVIG * 5/7
- Return to plasmaphoresis and commenced on Azathioprine (18th & final exchange today)
Diagnosis:

- **Anti NMDA-R encephalitis in the first trimester**

- 4 previously reported cases diagnosed during pregnancy


4. Barry, Helen; Hardiman, Orla; Healy, Daniel G.; Keogan, Mary; Moroney, Joan; Molnar, Peter P. et al. (2011): Anti-NMDA receptor encephalitis: an important differential diagnosis in psychosis. *Br J Psychiatry* 199; 5-8-509.
Anti–N-methyl-D-aspartate Receptor Encephalitis During Pregnancy

Monisha A. Kumar, MD; Ankit Jain, BS; Valerie E. Dechant, MD; Tsukasa Saito, MD; Timothy Rafael, MD; Hitoshi Aizawa, MD, PhD; Kevin C. Dysart, MD; Takayuki Katayama, MD, PhD; Yasuo Ito, MD; Nobuo Araki, MD; Tatsuya Abe, MD; Rita Balice-Gordon, PhD; Josep Dalmau, MD, PhD

Objective: To report 3 patients who developed anti–N-methyl-D-aspartate receptor encephalitis during pregnancy.

Design: Case reports.

Setting: University hospitals.

Patients: Three young women developed at 14, 8, and 17 weeks of gestation acute change of behavior, prominent psychiatric symptoms, progressive decrease of consciousness, seizures, dyskinesias, and autonomic dysfunction.

Main Outcome Measures: Clinical, radiological, and immunological findings.

Results: The 3 patients had cerebrospinal fluid pleocytosis, normal magnetic resonance imaging, and electroencephalogram showing slow activity. All had higher antibody titers in cerebrospinal fluid than in serum and 2 had ovarian teratomas that were removed. The pregnancy was terminated in 1 patient with recurrent bilateral teratomas. All patients had substantial neurological recoveries, and the 2 newborns were normal. Results of extensive antibody testing in 1 of the babies were negative.

Conclusion: The current study shows that anti-NMDAR encephalitis during pregnancy can have a good outcome for the mother and newborn.

Arch Neurol. 2010;67(7):884-887.
Tremor Vs Myoclonus

- Involuntary or subconscious rhythmic oscillatory movement of a body part
- Regularity essential
- All tremors cease during sleep (except myorhythmia & palatal myoclonus/tremor)
- Younger pt – Wilson’s disease, DRD
- Older pt – parkinsonism Holmes tremor, dystonic tremor, hemiballismus

- Shock-like (jerky) irregular involuntary movements arising from the CNS
- Often due to brief bursts of muscle activity - positive myoclonus
- Can be due to sudden short inhibitions of ongoing tonic muscle activity – negative myoclonus
Case IV - Falling, “tremors and slow”

75 yo man with stooped posture, unsteadiness & slowness for 2 years, recent falls and sudden transient worsening, long history of bipolar disorder
But Dopamine Amine Transport (DaT) scan normal – not parkinsonism

Lamotrigine increased 1 week before the deterioration and subsequently decreased with improvement

Medication:
- Diazepam 5mg bd
- Zopiclone 7.5mg nocte
- Lamotrigine 50mg bd
- Valproate 1000mg bd
- Donepezil 5mg nocte
- Modafinil 100mg daily
- Paracetamol500/codeine30mg daily
- Naproxen EC 500mg bd
- ASA 75mg
- Atorvastatin 20mg daily
- Bisoprolol 2.5mg daily
- Fesoterodine 4mg daily
- Pantoprazole 20mg
- Ideos one bd
- Vidisic tube eye and emulgel gel
- Voltarol emulgel gel 1%
Case V

Complains of tremor

History of vertigo Rx Prochlorperazine
Tardive Syndromes

Abnormal movements that occur within 6 months of exposure to a dopamine blocking agent & persist for at least 1 month after cessation of the drug

- **Tardive Dyskinesia** (Commonest movement disorder seen in Psychiatry)
- **Tardive Parkinsonism**
- **Tardive Dystonia**
- **Tardive Akathesia**

Curacao Island - 1 psychiatric facility
39.7% parkinsonism
13.4% tardive dystonia
9.3% akathisia
Case VI

54 yo  history of alcohol abuse (neuropathy), depression, psychosis & history of assault, 2 mths of falling and tilt to left. Rx: chlorpromazine 200mg, zuclopenthixol depot 300mg monthly, citalopram 60mg daily, mirtazepine 30mg nocte, flurazepam 30mg nocte, diazepam 10mg tds, clonazepam 0.5 bd, gabapentin 400mg tds

Abrupt onset post gall bladder surgery
Figure 1: Normal DaT image in our patient with drug-induced Pisa syndrome. Striatal uptake of radioligand is normal and demonstrates no presynaptic dopaminergic deficit. (Specific ratios- right caudate:2.12; left caudate: 2.2; right putamen: 1.82; left putamen: 1.84)
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<th>Parameter</th>
<th>Tardive Dystonia</th>
<th>Tardive Dyskinesia</th>
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<tr>
<td>1. Prevalence</td>
<td>Lower (1-2%)</td>
<td>Higher (15-33%)</td>
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<tr>
<td>2. Subjective discomfort + awareness of symptoms</td>
<td>Marked</td>
<td>Minimal or none</td>
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<td>3. Distribution</td>
<td>mainly face, neck and trunk</td>
<td>mainly face and mouth (oral-buccal-facial dyskinesia)</td>
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<tr>
<td>4. Reversibility</td>
<td>generally irreversible</td>
<td>Reversible in initial stages</td>
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Tardive Syndromes

- Preferable to use an atypical neuroleptic if possible
- Withdrawal of drug (tapered if possible)
- 1/3 remission if off neuroleptics for 2 years (less for tardive dystonia and akathisia)
- TBZ or reserpine often help TD and akathisia, less so tardive dystonia
- Others: neuroleptics, anticholinergic for dystonia, benzodiazepines, botulinum toxin, stereotactic neurosurgery
Case VII: First Presentation - February 2010

• Behavioural change since September 2009
  – More likely to be irritable or agitated
  – Less interest in doing housework
  – Less patient with the family and friends

• Fatigue

• Not managing at work
  – Difficulty with simple calculations
  – ‘Silly mistakes’
Past medical history

• Thyroid disease
  – hyperthyroid then hypothyroid, on replacement
• Hypercholesteroleemia
• Non-specific joint pain 2008
• Non-smoker
• 4-6 units of alcohol per week
• Strong family history of autoimmune disease
  – 2 sibs with pernicious anaemia
  – Sister RA
  – Nephew is hypothyroid
Progression….

- Cholecystectomy Nov 2009 (laparoscopic)
- Imbalance noted soon afterwards
- General slowing in performing ADLs
- Reduced memory and concentration
- Blurring of vision reported at times to family
- Hallucinations, visual more than auditory
Psychosis

• Frequently with reference to a baby she had ‘lost’
• Did have an ectopic pregnancy in her 20s
• Had told family she was ‘pregnant with 8 babies’
• Reported seeing and talking to her deceased parents
• Delusional beliefs relating to ex-husband
  – ‘getting married next week’
  – ‘we have the honeymoon arranged for June’
• Paranoid ideation in relation to hospital staff
More recent features......

• Compulsive eating
• Constant use of mobile phone at inappropriate times
• Erratic spending when out on leave ‘with no regard to affordability’
• Frequently repeating conversations and having little memory of family visits of the previous day
Normal investigations

- Renal profile
- Liver profile
- Bone profile
- FBC
- TFTs (on eltroxin)
- ESR
- CRP
- Coag
- B12
- Methylmalonic acid
- Lipids
- Lactate
- Serum and urinary porphyrins
- Homocysteine
- Haematinics
- VDRL, HIV serology
- Lyme serology
- SPEP
- C3, C4
Imaging

• PET CT thorax, abdomen and pelvis
  – Increased uptake in left groin
  – Benign spindle cell lesion on biopsy

• Brain PET
  – No significant abnormality

• MRI brain- 19/2/10 and 1/3/10 in another hospital– microvascular changes noted
Autoimmune and CSF investigations

- Paraneoplastic Abs all normal
- Anti NMDA and Anti VGKC negative
- ANA weakly positive, homogenous pattern
- CSF
  - cells, protein, glucose normal
  - OCBs not present
  - S-100b 0.91 (>0.41 ng/ml)
  - 14-3-3 negative
- Anti thyroglobulin Ab = 3219U/ml (N<100)
- Anti microsomal Ab = 383U/ml (N<100)
Dx: Hashimoto Encephalopathy?

- Admitted for iv methylprednisolone
- 5 days, 1g IV daily with oral taper
- No improvement
- Possible exacerbation of psychotic behaviour
- On-going decline in FAB and MMSE despite reduction in anti-thyroid antibody titres.
Cognitive Decline 26\textsuperscript{th} March to 2\textsuperscript{nd} June

<table>
<thead>
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<th>Date</th>
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<th>Anti thyroid microsomal (U/ml)</th>
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<td>3219</td>
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<tr>
<td>7/5/10</td>
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? Cortical ribbon hyperintensity

Control Scan
Human Prion Disease

• 3 human forms
  – Sporadic (85%)
  – Genetic (15%): up to 60% will have no fam hx
  – Acquired (<1%)

• 1 to 1.5 cases per million population per year

• sCJD
  – Mean survival of 4-8 months
  – Peak age 55 to 75 years, mean 61 years
  – Wide pathological and clinical spectrum
MRI in the diagnosis of CJD

• Pulvinar sign
  – Seen in variant CJD
  – Bilateral high signal relative to other deep grey matter nuclei and cortical grey matter
  – Sometimes associated with medial thalamic hyperintensity
  – Seen in > 70% of variant CJD cases

• Basal ganglia hyperintensity with or without cortical ribbon hyperintensity more typical of sCJD
  – Cortical signal > basal ganglia > thalamus
  – DWI more sensitive than FLAIR or T2

• 7.5% of 162 sporadic patients in one series displayed bilateral thalamic hyperintensities in a vCJD pattern
The Pulvinar Sign in Variant Creutzfeldt-Jakob Disease, March 2004, Summers et al. 61 (3): 446
Sporadic CJD - Diagnostic Criteria

WHO 1998

Progressive dementia with any 2 of:
- Myoclonus
- Pyramidal/extrapyramidal
- Visual/cerebellar
- Akinetic mutism

AND
- Typical EEG or 14-3-3 if <2 year duration
- No other condition to explain

Proposed by MRI-CJD Consortium*

Clinical
- Dementia
- Cerebellar or visual
- Pyramidal/extrapyramidal
- Akinetic mutism

Tests
- Abnormal EEG
- 14-3-3 if < 2 years
- High signal in caudate & putamen or 2 cortical regions

*Updated clinical diagnostic criteria for sporadic CJD, Zerr et al Brain 2009: 132; 2659–2668
Further amendments to criteria?

- Proposed by San Francisco Aging & Memory Centre
  - Greater weighing to DWI to reduce false positives?
  - Remove 14-3-3 as it is insensitive and not prion specific
  - Frontal cortical ribbon changes should be included
  - Include higher cortical signs in acceptable clinical features (aphasia, apraxia etc)
Case VIII

Young woman who fell from a horse

Left leg problems Post RTA
Psychogenic Movement Disorders

- Can be very disabling
- Requires great deal of effort by neurologist and psychiatrist to manage these patients
- Diagnosis made by neurologist bearing in mind the often bizarre nature of organic movements disorders
Psychogenic Movement Disorders

- Abrupt onset but static course or spontaneous remission
- History of minor trauma
- Only paroxysmal worsening
- Multiple somatizations
- Associated other psychiatric disease
- Bizarre movement disorders
- Paroxysmal attacks
- Variability over time

- Improvement with distraction
- Increases with attention
- Movement disorder may temporarily correct itself with voluntary movement on the opposite side
- Extreme slowness
- False weakness
- False sensory disturbances
- Atypical pain
- Abnormal affect
Case IX
Tremor & Metabolic Disorders

- Any patient with a movement disorder (esp new-onset tremor) under age of 50 years consider Wilson disease
- B12 deficiency – blood film, B12, urine organic acids (homocystine)
- Hyperthyroidism – TFTs
- Enhanced physiologic tremor - catecholamine (pheochromocytoma, stress, anxiety, fever, amphetamine)
- Hypoglycaemia, renal and hepatic dysfunction

Kayser-Fleischer ring
Wilson’s Disease

- Hepatic (30%), neurological (older pt) and psychiatric (20%) personality or mood change, anxiety, psychosis late), school performance decreasing
- Neurological initially in 40-60% of pts
- Tremor commonest –"wing-beating", rest, postural, action
- Dystonia in 40%, gait, dysarthria, ataxia, parkinsonism
- “Sardonic smile”

Kindly provided by Dr S Bressman
Wilson’s disease

- Recessive 13q14.3 - ATB7B gene: Cu-ATPase protein
- Failed biliary excretion of Cu
- Gene testing not useful
- Slit lamp examination, ceruloplasmin, 24h urine copper
- MRI brain
- +/- Liver biopsy
- Copper chelation to increase excretion (Trientine or penicillamine) and/or reduce copper absorption (zinc)
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<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madapar disp 62.5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinemet plus</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sinemet CR</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Entacapone 200mg</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Quetiapine 25mg</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Citalopram 25mg</td>
<td>1</td>
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</table>

75yo 20 yrs of rest & action tremor right hand, REM sleep disorder
Fragile X tremor-ataxia syndrome (FXTAS)

- X-linked recessive, premutation in FMR1 gene - CGG repeat 50-200 (Xq27.3) – normal is ~30 repeats
- FMRP is involved in synaptic development
- ET-like tremor, ataxia and mild cognitive impairment with frontal dysexecutive dysfunction, parkinsonism (DAT normal), dysautonomia, neuropathy & cerebral atrophy
- Rare cause of MSA-like condition

**Figure 2** Clinical and pathogenic consequences of expanded CGG repeats in the *FMR1* gene. In the left portion of the figure, the various expansion ranges are indicated. The CGG repeat (yellow) is located within the 5' untranslated portion of the gene (purple; i.e. the expanded CGG repeat is not incorporated into protein). For full-mutation alleles (>200 CGG repeats), the promoter and CGG repeat regions are usually methylated (red spots), which leads in turn to gene silencing. Absence of the mRNA and fragile X mental retardation 1 protein (FMRP) gives rise to fragile X syndrome. By contrast, premutation alleles (35-200 CGG repeats) are associated with substantial increases in fragile X mental retardation 1 gene (*FMR1*) mRNA; the excess RNA itself results in inclusion formation through excess binding of a number of nuclear proteins (red spheres), dysregulation of the nuclear lamina A/C architecture, and the clinical manifestations of fragile X-associated tremor/ataxia syndrome. With premutation alleles, FMRP levels are almost normal or only slightly reduced, and are not thought to contribute to fragile X-associated tremor/ataxia syndrome. Abbreviation: FXTAS, fragile X-associated tremor/ataxia syndrome.
Table 1  Clinical diagnostic criteria for FXTAS (Adapted from Jacquemont et al 2003)

<table>
<thead>
<tr>
<th>Molecular</th>
<th>CGG repeat 55–200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>Intention tremor</td>
</tr>
<tr>
<td></td>
<td>Gait ataxia</td>
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<tr>
<td>Minor</td>
<td>Parkinsonism</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe short term memory deficiency</td>
</tr>
<tr>
<td></td>
<td>Executive function deficit</td>
</tr>
<tr>
<td>Radiological</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>MRI white matter lesions involving middle cerebellar peduncles</td>
</tr>
<tr>
<td>Minor</td>
<td>MRI white matter lesions involving cerebral white matter</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe generalized brain atrophy</td>
</tr>
</tbody>
</table>

Diagnostic categories

<table>
<thead>
<tr>
<th>Definite</th>
<th>Probable</th>
<th>Possible</th>
</tr>
</thead>
<tbody>
<tr>
<td>One major clinical, and either one major radiological, or Presence of intranuclear inclusions (Hagerman and Hagerman 2004)</td>
<td>Two major clinical; or One minor clinical, and One major radiological</td>
<td>One major clinical, and One minor radiological</td>
</tr>
</tbody>
</table>

Abbreviations: FXTAS, fragile X-associated tremor/ataxia syndrome; CGG, cytosine, guanine and guanine; MRI, magnetic resonance imaging.

Figure 1  MRI of the patient at the age of 72 years. (A) Axial T2-weighted image demonstrating symmetric, increased signal within the middle cerebellar peduncles. (B) Axial fluid-attenuated inversion recovery (FLAIR) image revealing increased signal within the periventricular cerebral white matter. (C) Sagittal T1 image demonstrating mild atrophy of the caudal pons, mild cerebral volume loss and thinning of the corpus callosum. Images courtesy of J. Brunberg.

Figure 3  Ubiquitin-positive intranuclear inclusions (black arrowhead) within a centrally located neuronal cell body and two adjacent astroglial nuclei from a patient who died with fragile X-associated tremor/ataxia syndrome. Note that the nucleolus (white arrowhead) is visible as a separate structure within the neuronal nucleus. (Original image x400 magnification.) Image courtesy of C. Greco.
Tourette’s Syndrome

- A neurologic disorder manifested by motor and vocal tics that usually start during childhood and often are accompanied by behavioural problems such as obsessive-compulsive disorder, lack of impulse control, and attention deficit disorder
Tics

• Relatively brief and intermittent movements (motor tics or vocal tics)
• Characterised by suggestibility, exacerbated by stress, excitement, boredom, fatigue, heat and may increase during post-stress relaxation
• Motor and vocal tics may persist during sleep
• Usually start during childhood
• Often accompanied by behavioural problem e.g., OCD, lack of impulse control, ADHD
Tics

- Preceded by feeling (premonitory) or sensory urge in over 80% that is relieved by carrying out the movement (“unvoluntary”)
- Can be suppressed (“involuntary”), but inner tension builds and is only relieved by an increased burst of more tics, the intentional component of the movement helps to differentiate other hyperkinetic disorders
- May have to repeat a particular movement to relieve the uncomfortable urge until it “fells good” or “just right”
Tics

- Motor tics: simple or complex, rapid (clonic tics) or slower causing sustained abnormal posture (dystonic posture) or isometric contraction (tonic tics)
- Eye movements are common and are not a feature of chorea or myoclonus
- Phonic tics can be simple or complex
- Blocking tics are sudden transient cessation of all motor activity without alteration of consciousness
Simple Motor Tics

- Simple: abrupt, sudden isolated movement involving only one group of muscles causing a brief jerk-like movement or a single sound e.g., blinking, nose twitch, head jerk, blepharospasm, oculogyric movements, bruxism, sustained mouth opening, torticollis, shoulder rotation, tensing abdominal or limb muscles
Complex Motor Tics

- Complex: coordinated patterns of sequential movements resembling normal motor acts, or gestures, which are inappropriately intense and timed and appear in different parts of the body e.g., non-purposeful head shaking, trunk bending, or purposeful touching, throwing, hitting, jumping, kicking; also gesturing such as “giving the finger”, copropraxia, echopraxia
Simple and Complex Vocal Tics

• Simple e.g., throat-clearing, sniffing, grunting, squeaking, screaming, coughing, blowing, sucking sounds

• Complex include linguistically meaningful utterances and verbalisations e.g., shouting obscenities or profanities (coprolalia), repetition of another’s words or phrases (echolalia), and repetition of one’s own utterances particularly the last syllable, word or phase (palilalia)
Definite Tourette’s syndrome
(Tourette Syndrome Classification Study Group 1993)

• Both multiple motor & one or more vocal tics have to be present at some time during the illness
• Tics must occur many times a day, nearly every day, or intermittently throughout a period of more than one yr
• Anatomic location, number, frequency, type, complexity, or severity of tics must change over time
Definite Tourette’s syndrome (contd)
(Tourette Syndrome Classification Study Group 1993)

- Onset must be before age 21
- Involuntary movements and noises cannot be explained by other medical conditions
- Motor and/or vocal tics must be witnessed by a reliable examiner or be recorded by videotape at some stage during the illness
Tourette’s Syndrome

• Transient tic disorder of childhood, identical to Tourette’s syndrome except it lasts less than one year, ~24% school children

• Chronic multiple tic disorder similar to tourette’s syndrome but patient has only motor or vocal tics lasting at least one yr

• Chronic single tic disorder is the same as above but patient has only a single motor or vocal tic
Pathogenesis of Tourette’s Syndrome

- Loss of the asymmetry of basal ganglia, reduced volume of the caudate
- Dysregulation in presynaptic dopamine function
- Developmental disorder resulting in dopaminergic hyperinnervation of the ventral striatum (functionally linked to the limbic system)
- Antineuronal antibodies e.g., PANDAS
Treatment of Tourette’s Syndrome

- Dopamine receptor blockers, good for tics
- Dopamine depleters, good for tics
- CNS stimulants, good for ADHD
- Noradrenergic drugs, good for impulse control and ADHD
- Serotonergic drugs, good for OCD
Treatment of Tourette’s Syndrome

Tics

- Dopamine receptor blockers: fluphenazine, pimozide, haloperidol, thiothixene, trifluoperazine, molindone, sulpiride, flunarizine, risperidone, olanzapine, quetiapine, clozapine, nicotine,
- Noradrenergic drugs: clonidine
- Dopamine depleters: tetrabenazine
- Others: naltrexone, clonazepam, pergolide, transdermal nicotine patch, botulinum toxin
Treatment of Tourette’s Syndrome

Obsessive Compulsive Disorder

• Serotonergic drugs: imipramine, clomipramine, fluoxetine, sertraline, trazodone, paroxetine, fluvoxamine, venlafaxine

• Others: carbamazepine, buspirone, clonazepam, lithium

• Functional neurosurgery e.g., cingulotomy, limbic leucotomy, anterior infrathalamic
Treatment of Tourette’s Syndrome

ADHD

- CNS stimulants: methyphenidate, pemoline, dextroamphetamine
- Noradrenergic drugs: clonidine, guanfacine
- Others: imipramine, nortriptyline, desipramine, selegiline, bupropion,