

The Clinical Diagnosis of ADRs

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Annual Course 2013

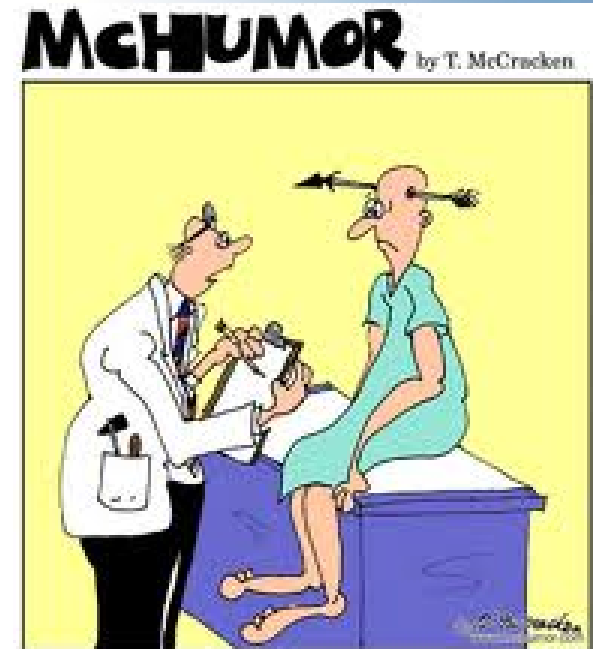


Outline

- What is a medical diagnosis?
- How is it reached?
- The certainty of diagnosis
- ADR or "natural illness"?
- Selected conditions often associated with the use of medicines

Medical diagnosis

- **Medical diagnosis:**
 1. is the process of attempting to determine or identify a possible disease
 2. the opinion reached by this process



"Off hand, I'd say you're suffering from an arrow through your head, but just to play it safe, I'm ordering a bunch of tests."

Differential Diagnosis

- Many candidate conditions -> elimination process -> diagnosis of exclusion



Key elements

- Recognizing patterns
- Comparing observation with experience
- Setting priorities
- Investigating
- Accepting and communicating that a final opinion cannot always be reached

Diagnostic certainty

- 83 yr old lady feels dizzy and falls
- Unable to get up, pain in hip and leg
- At admission:
 - Patient in pain, unwell, unable to lift left leg which shows a rotation to the left
- Suspected diagnosis?



Diagnosis

- Fractured neck of left femur due to trauma



Diagnostic certainty

- 25 yr old, middle european man with recurring abdominal pain
- No temporal pattern
- No stool abnormalities
- No fever
- No history of travel
- All investigations (physical examination, x-ray, ultrasound, stool cultures etc. etc) bland

So?



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ADRs...

- ... are drug induced disease: they present the same way as natural disease does and show a similar course
 - > the questions asked and diagnostic procedures will be the same

Skin

- Most frequently targeted organ
- Drug "eruptions" -> mostly benign
- Severe reaction may be fatal

Exanthemous Drug Eruption

- Common ($\geq 1\%$)
- Higher risk with allopurinol, antiepileptics, antibiotics (sulpha, cephalosporins, aminopenicillins)
- Time to onset 4-14 d (also after discontinuation)
- Trunk -> extremities
- Conservative treatment

Exanthematous Drug Eruption



SJS and TEN

- Stevens Johnson Syndrome and Toxic Epidermal Necrolysis are
 - Rare (TEN 0.4-1.2/mio py; SJS 1-6/mio py)
 - Life-threatening (mortality 10% SJS and >30% TEN)
 - Drug induced skin reactions (70%)
 - Blistering and skin detachment (SJS 10% body surface, TEN >30% body surface)
 - Mucosal involvement
 - High fever
 - Hepatic, intestinal and pulmonary involvement possible

Roujeau et Stern 1994

Most commonly associated drugs

- Sulphonamides
- Anticonvulsants
- Allopurinol
- Oxicam and pyrazolone NSAIDs

SJS/TEN

- Time to onset <4 weeks
 - 7 to 21d when first exposed, faster if rechallenge
- Symptomatic treatment
 - Fluid/electrolyte balance
 - Nutritional support
 - Nursing care

TEN



SJS/TEN – mucosal involvement



EyeRoundls.org

Relevant elements in reporting dermatological ADRs

- Description, distribution, number of lesions
- Mucosal involvement
- Duration of eruption
- Associated symptoms
 - Fever
 - Itching
 - Lymph node enlargement
 - Hepatic involvement
 - Blood count (eosinophilia)

Reference

Roujeau JC et al

*Medication use and the risk of Stevens
Johnson Syndrome or Toxic Epidermal
Necrolysis*

New Engl J Med 333: 1600-7 (December 14th 1995)

Haematological ADRs

- Myelosuppression
 - One or all cell lines
 - Production and /or maturation of cells
- Shortened peripheral cell survival
- Effects on clotting (plasma factors)

Myelosuppression

- Cytotoxic Type A effects
 - Predictable based on pharmacology
 - Dose dependent
 - Common
 - ...
- Idiosyncratic effects
 - Not predictable
 - Dose independent
 - rare

Individual susceptibility

- Individual differences in absorption and metabolism can affect Type A reactions
- Genetic predisposition for some Type B reactions
 - Chloramphenicol
 - Clozapine
 - 6-Mercaptopurine
 - Methotrexate
 - ...

Aplastic Anaemia

- Hypocellular bone marrow
- Pancytopenia (all cell lines affected)
 - Haemoglobin < 100g/l
 - Neutrophil granulocytes <1.5 x 10⁹/l
 - Platelets <100 x 10⁹/l
- Associated with medicines, radiation, exposure to chemicals, infections, autoimmune disorders, ?

Died of AA



Examples

- Anticonvulsants
 - Phenytoin, carbamazepin
- Antimicrobials
 - Chloramphenicol, sushonamides, zidovudine, amodiaquine, mebendazole....
- Antirheumatics
 - Indomethacin, phenylbutazone, piroxicam, penicillamin...
- Other
 - Captopril, lisinopril, acetazolamide, alpha-interferon....

Agranulocytosis

- Severe neutropenia (neutrophils <0.5 G/I)
- Drug induced agranulocytosis is immune mediated and involves myelosuppression as well as peripheral cell destruction
- Medicines involved as for AA, particularly well known are clozapine and antithyroid drugs
- Febrile neutropenia can be life threatening

Clozapine

- Antipsychotic indicated for therapy resistant schizophrenia approved in the 1960ies.
- No EPS as with other antipsychotics
- Intense monitoring program with regular white cell counts prescribed according to risk pattern: highest in the first 3 months of therapy (1:700)

Antithyroid drugs

- Carbimazole, propylthiouracil and methimazole
- Incidence highest in the first 3 months (3/100'000/year)

Hepatotoxicity

- Potential complication of every medicine
- Principal cause of termination of clinical trials (approx 30%)
- Leading cause of market withdrawal of approved drugs between 1975 and 2005 (Friedman et al 1999)

Classification

- Hepatocellular liver injury
 - $ALT \geq 2 \text{ ULN}$ alone OR $ALT/AP \geq 5$
- Cholestatic liver injury
 - $AP \geq 2 \text{ ULN}$ alone OR $ALT/AP \leq 2$
- Mixed liver injury
 - ALT/AP between 2 and 5

CIOMS 1999

Evaluation

- Chronology
- Specificity of pattern
- Exclusion of alternate explanations within the same pattern
- CIOMS-RUCAM scale
- Maria+Victorino scale (underscoring!)
- Liver biopsy and histology

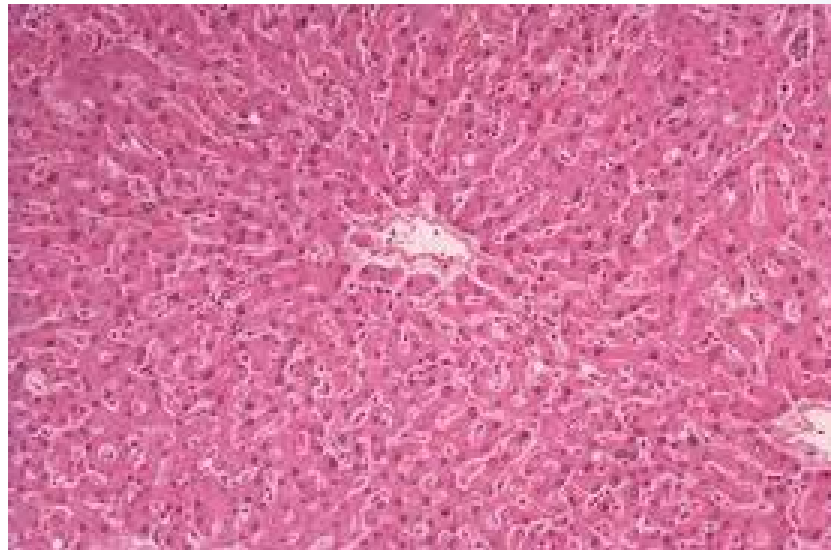
Mechanisms

- Metabolic
 - Metabolism into chemically reactive intermediates -> large amounts cannot be neutralized -> liver injury
- Immunological
 - Involvement of other organs, slower onset with acceleration if rechallenged
 - Immune response targeted at primary drug or metabolite (-> mixed aetiology)

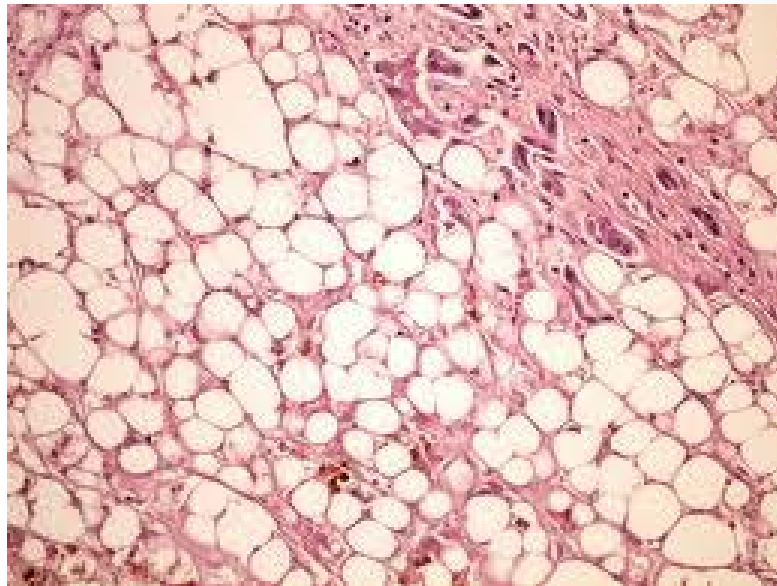
Hepatic Steatosis (fatty liver)

- If mitochondrial oxydation process is impaired -> fatty acids accumulate in the liver
 - Ex tetracyclines, amiodarone, perhexiline....

Normal liver



Steatosis







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