Update from the International Conference on Porphyrins and Porphyrias 2017: Bordeaux, France

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ICPP 2017
PRESENT
INTERNATIONAL CONGRESS
PORHYRINS AND PORPHYRIAS
P&P Patient Day
JUNE 25TH
P&P Scientific Congress
JUNE 25/28TH
PALAIS DE LA BOURSE
BORDEAUX
Alnylam
Clinuvel
ORPHAN EUROPE
RECORDATI GROUP
Abbott

PROGRAMME

- Sunday 25th June – Patient Day
- Monday 26th
- Tuesday 27th
- Wednesday 28th
- https://www.icpp2017.org

Sunday 25th June – Patient Day

- Together we are stronger
- World tour: Introducing each patient group
- Test tube to the population: Evaluation/supervision of drugs

- How academic research interacts with patient care
- Psychological assistance – The feeling of guilt

- Q&A Round Tables
  - Erythropoietic protoporphyria
  - Acute porphyrias
  - Cutaneous porphyrias- bullous

SCIENTIFIC PROGRAMME

- Mixture of plenary lectures, short talks and posters
- Mark the retirement of two French Clinician Scientists
  - Professor Jean-Charles Deybach
  - Professor Hubert de Verneuil
- Acute porphyrias
- Cutaneous porphyria
- Other

Acute porphyrias – diagnosis, genetics

- Prof R Desnick, New York: AIP update
  - Work confirms prevalence of pathogenic mutations in general population is approx. 1:1700. Penetrance is ~1%.
  - Suggests predisposing or protective modifying genes
  - Needs to be an international collaboration to identify and confirm pathogenic mutations.

- Prof Gouya, Paris. How do we explain the difference between clinical penetrance in the general population (~1%) versus families (~23%). Conclusion: that other genes were involved plus environmental factors as well.

- Dr Whatley, Cardiff. Identifying possible genetic factors associated with acute attacks. Identified several areas of the genome that might be involved. Several candidate genes for further study.

Acute porphyrias – Treatment

- (see Alnylam Givosiran talk)
- Prof Fontanellas – Spain; messenger RNA therapy to treat and prevent acute attacks in a mouse model of acute intermittent porphyria
  - mRNA for deficient enzyme
  - Coated in lipid nanoparticles
  - Intraveous injection
  - Lowers plasma and urine PBG and ALA
  - Demonstrates pre-clinical effectiveness

- Dr C Schmitt, France: Haem arginate/hematin treatment ? Impact on disease course
  - Increase in number of recurrent patients since licensed
  - Investigated explanted livers
  - Repeated haem may self induce it's own requirement
  - More cautious approach to using haem

Acute porphyrias – Treatment

- Dr Helen Bustad, Norway: Pharmacological chaperonins for the treatment of AIP
  - Small chemical molecules that can improve enzyme function
  - Screen large numbers of different compounds for effect
  - Choose those which have a “test tube” effect for further study in cell culture and mouse model

Acute porphyrias – late complications

- Dr Pallet, Paris. Kidney disease and porphyrias
  - Confirmed symptomatic acute porphyria (AIP) associated with slow decline in renal function
  - Some correlation with the specific mutation
  - Should we change our practice in UK?

- Prof. Wahlin, Stockholm. Liver cancer and liver fibrosis (scarring)
  - Affects noted mainly in AIP patients
  - Risk higher than general population
  - Screen above age of 50

Evening Visit to village of St Emilion

Erythropoietic porphyrias –CEP

- Prof Millet, Spain: Pharmacological chaperones as a treatment in CEP
  - Tested a library of chemical compounds that are known to improve protein functions
  - Model system created with common mutation (C73R)
  - Decreases accumulation of cell porphyrin in cell model
  - Testing in mouse model

- Prof John Phillips, Utah*:
  - Haem linked to iron availability may be able to limit the amount of ALA produced by limiting the availability of iron
  - When iron is limiting may be beneficial to prevent excess production of haem precursors.
  - J-M Blouin, Bordeaux. Showed effect in mice.
  - * Published case report in congenital erythropoietic porphyria patient confirms the effect

Erythropoietic porphyrias –CEP

- Francois Moreau-Gaudry, Bordeaux Metabolic correction of CEP with iPSCs
  - Obtain pluripotent stem cells from patient
  - Correct the genetic mistake by gene transfer (viral)
  - However now using new technology of targeted genome editing
  - Uses CRISPR/Cas9 (very topical)
  - Testing on mice at the moment
  - Still have risks that need to be ironed out (e.g. tumours)

Erythropoietic porphyrias – EPP

- Prof B Paw, Boston. Plenary on how iron and haem are managed in the red blood cell.
- Major contribution to our understanding of how haem is made and controlled in the bone marrow
  - New gene (CLPX) that causes erythropoietic protoporphyria .
  - Defective protein does not control ALAS and results in gain of function and increased protoporphyrin production (similar to XLEPP)
  - One family described

EPP- Research into treatments

- Dr F Halloy, Zurich. Oligonucleotide therapy for treatment of EPP.
  - Small artificial DNA molecules to correct the common mistake in ferrochelatase gene (the "low expression variant")
  - Experiments in cultured cells at the moment
  - Need to get the molecules into bone marrow cells
- P Cwiek, Zurich: Splicing modulation in mouse model of EPP
  - Gene therapy uses a viral vector to insert correcting DNA.
  - Mouse stem cells from bone marrow
- Prof L Gouya, Paris: Splice modulation treatment (not presented at conference)

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- Prof Millet, Spain: Pharmacological chaperones as a

Dinner at Chateau Giscours

Other presentations

- The role of longitudinal observational studies in understanding natural history of different porphyrias.
  - Complement clinical trials
  - Target knowledge gaps
  - Encourage international collaboration, widen ethnic diversity
  - Contribute to clinical guidelines
  - Improve understanding of psychosocial burden of disease – patients and families
- Studies
  - EPNET – the European Porphyria Registry
  - US Porphyria consortium
  - Explore: Natural history study

Other Presentations – QOL

- Ms H Naik, New York: EPP: Disease severity and quality of life.
  - Using new validated QOL questionnaire.
  - Allows focus on specific areas (pain, fatigue, physical function, depression)
  - Strong association wbetween severeity and certain domains.

- Ms H Naik, New York: Psychosocial issues in EPP; Parents, children and young adults perspective
  - Used 3 Focus groups: Documents age specific issues
  - Parents – guilt; Teenagers – difficulty adapting, family stress; Young adults –embarrassment at explaining.
  - More information, explanation, preparation from porphyria services

- J Andersen, Norway. QOL, health complaints and stress in AIP.
  - Mainly neurological health
  - Associated with increased stress and lower QOL

EPNET Association

- Formal (legal) association formed in May 2017
- Interim Steering Group for 12 months
- Objectives
  - Facilitate research
  - Optimise and harmonise diagnosis and treatment
  - Promotion and education via website
  - Improving diagnostic quality
  - Enhance training and education
- Self governing and financing

Summary

- New understanding of genetic factors in porphyria, but more to do:
  - Sharing on information on causative mutations
  - Identifying genetic influences affecting severity of porphyria

- Investigating new approaches to treatment of porphyria
  - Genetic: RNA interference, mRNA delivery, gene therapy
  - Small molecule therapies (chaperonins)
  - Primary and secondary care

- Improving collaboration and pooling resources
  - Regional (Europe, USA) and Internationally

- Improving diagnostic testing efficiency