PhD Project Aisha Augustin

Objective assessment of muscle rigidity in exploring aetio-pathogenesis of Parkinson's disease

BACKGROUND

The PhD student's project is within a team with the overall aim to develop a unified statistical model, an 'aetio-pathogenic construct', for the complex of Parkinson's disease, overlap dementias and depression, and functional bowel disease (the 'PD-complex'). Path-defining longitudinal observational and interventional studies are used to probe the pathophysiology.

There is growing evidence that neuro-inflammation in PD is driven by systemic immuno-inflammatory processes. It is not just the adverse effect of microglial scavenging of degenerating neurons and reaction to aberrant protein deposition. We are homing in on potential microbial driving forces and their immune-inflammatory mediators.[1,2] Dysbiosis in the gastrointestinal tract is likely to be the predominant driver.[3,4] Intervention against forces and mediators would offer novel ways to modify the disease course.

In a randomised placebo-controlled trial, biopsy-proven *H. pylori* eradication had differential effects on objective measures of PD facets: improvement in hypokinesia and worsening rigidity over the year post-eradication, both plateauing over the next year.[3] Overall, there was clinically-relevant improvement. In the team's surveillance work, antimicrobials for indications other than *Helicobacter* had no effect on hypokinesia, but successive courses were associated with cumulative increase in rigidity.[4] This might fit with a low gene count in the intestinal microbiota, or reduced microbial diversity, being associated with an increased risk of inflammatory comorbidities.[5] However, overgrowth of particular taxa or an invading pathogen might be the culprit.

INTRODUCTORY WORK.

The student, as an honorary clinical assistant at the Maudsley, has already embraced the work, to the stage of submitting an abstract on clinical audit (see below) for an International Learned Society Meeting:-

"Osmotic laxatives are associated with lower rigidity in idiopathic parkinsonism.

Aisha Augustin et al.

Background. In idiopathic parkinsonism (IP), flexor rigidity is greater the higher the circulating natural-killer cell count, an effect modulated by CD4+ count.[2] These counts are higher with hydrogen-breath-test positivity for small-intestinal-bacterial-overgrowth. Two-thirds of IP-patients are positive at presentation.

Aims & Methods. Improving intestinal transit with laxatives might reduce rigidity by reducing overgrowth. Relationships of interventions for constipation to rigidity and overgrowth were explored. Surveillance yielded 1378 objective measures of arm rigidity in 74 IP-patients over 343 person years, with 437 2-h lactulose-hydrogen-breath-tests in 48. Maintenance osmotic laxative (macrogols) was exhibited in 50 (176 person years); bulk-forming laxative (ispaghula husk/methylcellulose/sterculia) in 52 (196); enterokinetic agent (prucalopride) in 25 (45); and guanylate cylase-C receptor agonist (linaclotide) in 8 (12).

Results.

Osmotic laxative was the only intervention associated with a change in rigidity. Flexor rigidity increased (by 6.8 (4.3, 9.4) % per year, p=0.001) where not exhibited, stabilised where exhibited (1.4 (95% CI -0.9, 3.8) % per year, p=0.2). Bulk-forming laxative had no additional effect on rigidity (p=0.5). Similarly, the ratio, flexor to extensor rigidity, indicating tendency to simian posture, increased (3.2

(0.7, 5.7) % per year, p=0.01) where osmotic laxative was not exhibited, stabilised where exhibited (-1.6 (-3.9, 0.8) % per year, p=0.2). Bulk-forming laxative had no additional effect on the ratio (p=0.6). Only bulk-forming laxative was associated with change in breath-hydrogen. Peak hydrogen was lower by 11 (1, 20) ppm (p=0.03) where exhibited, with no differential effect of time (p=0.9). (Odds ratio for a positive breath-test where exhibited compared with where not: 0.55). Osmotic laxative had no additional effect on peak hydrogen (p=0.3).

Conclusions.

Osmotic laxative may reduce rigidity by reducing inflammation, directly, or by removing an inhibitory effect on anti-parkinsonian medication. Any effect of overgrowth on rigidity may relate to organisms not flagged by hydrogen-breath-test.

PRIMARY AIM OF PROJECT

The aim is to:-

- validate methodology for objective assessment of 'rigidity' in PD
- define subject groups 'down-the-way' towards PD in this respect
- survey effects of clinical interventions for PD and constipation on rigidity
- input into the design of a study of the role of the intestinal microbiota in PD

OUTLINE

VALIDATING METHODOLOGY FOR OBJECTIVE ASSESSMENT. Rigidity is one of the cardinal signs of Parkinson's disease, it is usually estimated by an observer gripping the patient's hand whilst moving the forearm as if it were pivoted at the elbow joint. The perceived resistance as the hand is moved is noted, and where quantification is required for research, a descriptive five-point United Parkinson's Disease Rating Scale (UPDRS) used.

An immediate problem with the UPDRS is lack of distinction between flexor and extensor rigidity, in a disease where the excess flexor rigidity over extensor determines the flexed (simian) posture. Validating the objective assessment requires a wider approach than simply using the 5-point overview as a gold standard. Cross-referencing to measures of other disease facets is essential to evaluating the potential contribution of the rigidity measurement.

The next phase will involve introduction of a new 'muscle tone monitor device', in which the forearm is not to supported from beneath but suspended from above (i.e. as if the forearm were the bob of a pendulum), such that lateral forces to move the forearm would be virtually independent of weight.

DEFINING SUBJECT GROUPS 'DOWN-THE-WAY'. Comparison of the 'rigidity' measurement between patients with clinically definite idiopathic parkinsonism and a well-defined healthy control group will be the foundation for defining:-

- cut-point at which the diagnosis is made
- a pre-presentation state.

It will be considered whether spouses of PD sufferers,[1] and patients with irritable bowel syndrome with constipation, lie in a spectrum from healthy control to clinically-definite idiopathic parkinsonism.

SURVEYING EFFECTS OF CLINICAL INTERVENTIONS. Further surveillance work will include exploring the association of rigidity with

- interventions with classes of anti-parkinsonian medication.
- Conventional and recently licensed (a specific 5-HT_4 agonist enterokinetic agent and a guanylate cyclase-C receptor agonist) treatments for constipation.
- interactions between interventions.

DESIGN OF A STUDY OF THE ROLE OF INTESTINAL MICROBIOTA. The study will include cross-sectional and intervention studies relating the gastrointestinal microbiota and potential immune-inflammatory mediators to facets of parkinsonism. A series of preliminary experiments involving the Student is envisaged.