

report on the society for the study of behavioural phenotypes conference – september 2013...

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This international but modest, friendly, well-organised meeting was held in the beautiful town of Stellenbosch, 50km outside Cape Town. It was a very stimulating multi-disciplinary event which updated the exciting developments in the neurobiology and genetics of behaviour. As the only psychiatrist from Australia attending, I would like to share the highlights..

Chris Oliver, neuropsychologist and director of the Cerebra Institute, Birmingham, presented on both the fundamentals of behavioural phenotypes and the management of behavioural problems in neurodevelopmental disorders and genetic syndromes. He noted that the term 'challenging behaviour' is now outmoded given the lack of specificity, and prefers to describe individual behaviours such as self-injury and its various subtypes. Operant conditioning and other psychological models of the aetiology of these behaviours fail to take into account the wide variety of patterns of behavioural disorders seen in different genetic syndromes. Examples include high rates of self-injury in Smith Magenis Syndrome (SMS) and Cornelia de Lange Syndrome (CdLS), but low rates of aggression, with a reverse pattern more typical of Angelmans syndrome. Aggression tends to be low in Williams and Down syndrome. The aggression seen in Angelmans appears to be particularly attention-seeking, consisting more of grabbing and pulling than of striking. Increased rates of autism spectrum disorder (ASD) seen in different syndromes are not explained by severity of intellectual disability (ID). In SMS the constant drive for parental contact combined with an inverted melatonin cycle creates particular distress for parents. There is a need to pursue genetic diagnosis where possible, in order to pursue more accurate understanding and behavioural management, although 50% of individuals with ID remain undiagnosed. In a second talk he noted the high prevalence of severe behavioural disorders in severe ID, ASD, and in some genetic disorders, and that there is an 84% persistence of behavioural problems over a 20-year period! He is interested in the role of pain, and e.g. in patients with CdLS. While reflux is the commonest cause of pain in this popu-

lation, there are many others. He highlighted the use of the FLACC Scale, standing for Face, Legs, Activity, Crying and Consolability for assessment of pain in non-verbal individuals (<http://bcmartin.yolasite.com/resources/FLACCSCALE.pdf>). He noted a variety of behavioural signs suggestive of reflux, such as excess salivation, bruxism, thirst, scratching of the throat and chest, bad breath, dental problems, and episodes of otitis media.

Carole Samango-Sprouse, Director, Neurodevelopmental Diagnostic Center for Young Children, Maryland, presented on Klinefelters disorder (47XXY), which occurs 1/500, with considerable under diagnosis. They can have subtle ASDs. There are androgen receptors in the frontal and temporal lobes. A double blind controlled trial of early androgen treatment showed significant improvements in performance at 3, 6 and 9 years.

Alex von Gontard from Hamburg presented on incontinence of urine and faeces in Angelman and Rett disorders, noting high rates in both, probably secondary to the severity of ID. He advocated ultrasound as the preferred investigation, which can show thickened bladder wall, increased residual volume and the presence of faecal impaction. Management can proceed along standard lines using an alarm, desmopressin, anticholinergics and laxatives.

VCFS (22q11 deletion syndrome) was a subject of a presentation by psychiatrist Dr. Evers from the Netherlands. He noted the high prevalence of ASD and ADHD in childhood, with cognitive decline in a subgroup in adolescence, especially those who subsequently develop psychosis. There is a 50% reduction in expression of the COMT gene, leading to less metabolism of and increased levels of dopamine and noradrenalin neurotransmitters. Bipolar disorder and schizophrenia are common.

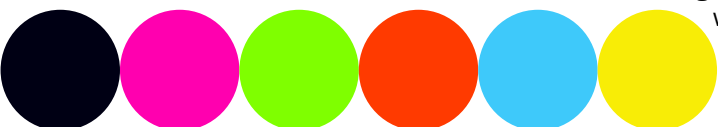
Jim Harris from Johns Hopkins University described brain structural abnormalities in Lesch Nyhan Syndrome, a syndrome first described in 1973. There is reduced cortical volume and thickness, especially in the medial orbito-frontal region and anterior cingulate gyrus, areas associated with emotional regulation and hyperactivity. Stereo-

typed, automatic behaviours are common, as is severe self-injury. Management is unsatisfactory, with hyperuricaemia responding to treatment with allopurinol, but without any improvement on behaviour.

Flora Tassone from UC Davis has found that there are significant numbers of copy number variations in Fragile X pre-mutation carriers, suggesting a 'two hit model of phenotypic variability'. This was a theme throughout the conference, namely that variability in the phenotype in a given syndrome may be explained by a second hit, leading to recommendations for array CGH testing even in individuals with defined genetic abnormalities such as DS and Fragile X. Individuals with the pre-mutation for Fragile X are prone to FXPOI and FXTAS but some are also prone to higher rates of autism, epilepsy, migraine and psychopathology. Individuals with the pre-mutation (55-200 CGG repeats) have an excess of micro RNA as a result of reduced binding to FMRP, which is in lower concentrations. This excess RNA leads to excessive production of neurotransmitters. 20% of a sample of 50 pre-mutation carriers harboured novel genomic events not observed in 8000 normal individuals.

“90% of children with FASD are in developing countries. South Africa has >10 % incidence...”

Catherine Lord from New York presented on syndromal and non-syndromal ASD. 20-40% of ASD is secondary to an identified genetic syndrome. She noted that there is still a major problem in defining the essence of autism, other than as a cluster of behaviour. DSM5 argued intensively about the diagnostic criteria for ASD. The diagnoses of Asperger's and PDDNos have been discarded. Communication difficulties have been collapsed into the social deficits, with a second criteria for repetitive behaviours or interests. Substantial impairment in expressive communication warrants a second diagnosis. The DSM5 subcommittee noted that from twelve sites, with the same data on autism screening questionnaires such as the ADOS, there was extremely wide variation between diagnoses, with some cen-



tres reporting high rates of Asperger's and others reporting none. The variability was due to the diagnostician rather than the patient population. There has been a major outcry from consumer groups about the abolition of the diagnosis of Asperger's disorder. Specifiers can be added, such as With Rett disorder, Fragile X, seizures etc. Onset must be in early childhood, not necessarily at less than 3 years, and individuals must continue to exhibit impairment. The new criteria favour sensitivity over specificity.

Day 2 started with an extended session on Foetal Alcohol Spectrum disorder (FASD). Western Cape in South Africa has the highest incidence in the world. 90% of children with FASD are in developing countries. South Africa has >10 % incidence, compared to Italy with 2%. It is a disease of the poor, with contributions from environmental adversity and malnutrition on top of alcohol exposure. The full syndrome represents the extreme end of the spectrum, when significant dysmorphic features are found. Identification of FASD children is therefore difficult. There are profound deficits in cognitive, motor and behavioural functions. Alcohol affects all stages of brain development, and the final picture is very heterogenous. Intellectual deficits are typically in the borderline to mild range. Behaviourally there is much overlap with ADHD. Social skills are poor. Dysmorphic features in FAS include thin upper lip, flat philtrum and flat mid-face. Affected individuals have a significantly increased risk of adult alcohol abuse. There is significant loss of white matter integrity on MRI scanning in affected infants; affected children fail to condition to eye blink; three-dimensional photography can successfully identify subtle dysmorphic features and identify affected children; and affected individuals performed significantly worse on the Reading the Mind in the Eyes tests, after controlling for IQ and executive function, suggesting a deficit in higher order Theory of Mind function. A

UK national clinic for individuals with FASD was established in 2009, offering a two-day comprehensive assessment of children and adults. Higher rates of ADHD and ASD were found. 3D photo recognition is central in identifying the characteristic dysmorphology. The majority of the attendees were adopted, and all of the adults had a forensic history.

André Strydom presented on The Londowns Consortium, a multidisciplinary investigation into cognition and Alzheimer's disease in Down syndrome (DS). 100% of individuals with DS have Alzheimer pathology at the age of 35, with 50% showing clinical dementia from the age of 50. It is unknown what protects the other 50%. Of 340 patients studied, the youngest with dementia was 32. Trisomy 21 produces an overdose of 300 normal genes.

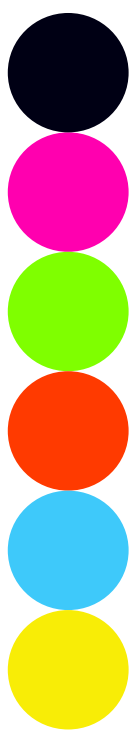
There were several presentations on Tuberos Sclerosis Complex (TSC). TOSCA, the TS registry to increase disease awareness, is an international retrospective and prospective disease registry, assessing manifestations, interventions and outcomes, with particular focus in Europe on a trial of everolimus, an mTOR inhibitor. This medication has been found to shrink both renal and brain tumours, so long as treatment is maintained. Work is underway on the impact on epilepsy, and perhaps shortly on neuropsychiatric manifestations. The goal is to enroll 2000 patients of the estimated 2 million sufferers worldwide. The TAND checklist, (TSC Associated Neuropsychiatric Disorders) is under development, modelled on a similar scale, the HAND which is used in individuals with HIV. IQ is normal in 50%, 20% have a mild to severe ID and 30% are in the profound range. Aggression is common. 50% have ASD and 30-50% ADHD. Epilepsy affects 75-90%. Only 18% TSC patients in the UK are ever assessed for TAND. This checklist will cover ten domains, takes around 10-15

minutes and annual review will be recommended. Early results of the current pilot project are promising. Challenging behaviours of self-injury and aggression in TSC were found to be strongly persistent over time. There is huge phenotypic variability in this condition. Rates of SIB across different studies vary from 10-40%, and aggression from 13-58%. Risk factors include severe ID, ASD, ADHD, male sex, and possibly pain secondary to brain and kidney tumours.

Petrus de Vries who hosted the meeting gave a very comprehensive presentation on the neuropsychiatry of TSC. 70% of cases are sporadic, with 30% autosomal dominant. Both the TSC 1 and TSC 2 genes, found in 90% of cases, can produce the condition, as a result of the TSC 1 and TSC 2 proteins binding together. This combined protein blocks the inhibition of production of mTOR, the concentration of which rises dramatically, creating widespread overgrowth, resulting in tumours and other manifestations. Rapamycin, a streptomycin-like antibiotic discovered on Easter Island, shrinks these lesions and has been licensed to treat the angiomyolipomata which occur in the kidney. It appears to be effective against SEGAs, (the subependymal giant cell astrocytomata) that occur in the brain. These often present late, and regular MRI surveillance is required. Excessive suppression of mTOR can cause problems of memory, but mTOR activity is currently unmeasurable.

Randi Hagerman gave a very comprehensive and stimulating talk on molecularly targeted treatments for genetic disorders. Rett syndrome has a frequency of 1/10,000 females. There is a reduction in MeCP2 which produces a GABA/glutamate imbalance, and reduced levels of BDNF and PSD95. BDNF stimulates neuronal connectivity. Memantine and dextromethorphan trials are underway. Insulin Growth Factor 1 stimulates the production of BDNF. Therapeutic trials are underway.





The Down Syndrome mouse is a close model. There is excess GABA, and GABAa antagonist trials are underway. Both Lithium and fluoxetine down-regulate mTOR and restores neurogenesis in adult mice with Down syndrome. Exercise stimulates neurogenesis. However a trial of memantine in DS failed and some patients got worse. Antioxidants can be helpful and melatonin is a potent antioxidant. She emphasised the importance of treating the epilepsy that is common in autism. ADHD in autism often responds better to clonidine than to stimulants, although the latter can be helpful. Sleep disorders can respond to melatonin. Both risperidone and aripiperazole are FDA approved for autism. Serotonin synthesis is reduced in autism, hence the role for SSRIs and buspirone. The Early Start Denver model of intensive intervention from the age of 2 has shown that subsequent EEGs on a face recognition task are normal. However no baseline measurements were obtained, so it is not yet known if this Early Start program normalises a previous abnormality. We need to add learning programs to drug therapy to capitalise on any subsequent improved potential.

mares in REM sleep, prominent in the later part of the night. In the early years there is far more REM than non-REM sleep, but only 20% of sleep in adults is REM. Obstructive sleep apnoea (OSA) reduces executive functioning, lowers mood and possibly IQ, impairs immune function and retards growth. Recurrent hypoxia has much more significant effects than chronic hypoxia, with recurrent re-oxidation causing oxidative stress and apoptosis. OSA is common in Downs, in VCFS post-pharyngoplasty and in Pierre Robin syndrome. However there is no reduction in IQ in this latter syndrome if obstructive sleep apnoea is treated early. Time in neonatal ICU delays the onset of melatonin rhythms. Multiple medical comorbidities adversely affect sleep. Many syndromes have specific problems, such as the morning melatonin peak in Smith Magenis syndrome, which can be treated with beta-blockers at times, with melatonin often unhelpful. Both morning light therapy and modafinil can help wake the patient. Individuals with autism have multiple sleep problems. Patients with Angelmans syndrome can benefit from melatonin, but some are slow metabolisers and require a low dose. Individuals with cerebral palsy can wake and startle as the result of increased muscle tone, which can be treated with a nighttime dose of baclofen or diazepam. Treatment with melatonin reduces sleep latency, but is not helpful with sleep consolidation. Movement and light, even low lights such as from a phone, can turn off melatonin. Melatonin lowers seizure threshold and can interfere with SSRIs and warfarin. She emphasised the importance of fine detail in understanding the daily routines, which often provides clues to effective behavioural management.

range of programs of early intervention for children with ASDs that show moderate and helpful improvement across the board but with wide individual variation. Improvement is only in those skills focused upon, with poor generalisation to other areas, and persistence of benefit is poor. Benefits are greater in those with a higher IQ and better language skills, and lessen where families are under significant stress. Most follow-up studies have been limited to 6-12 months. The major predictor of long-term outcome is baseline characteristics. The UK website 'Research Autism' summarises the evidence from current research. She noted that the mainstay of treatment for behavioural problems has focused on a reduction of attention for inappropriate behaviour and an increase in attention for positive and adaptive behaviours. But the literature is biased towards positive results and this is typically much easier in theory than in practice. Studying behavioural phenotypes is important and illustrates the extent to which accurate knowledge of the underlying aetiology can guide psychological, educational and medical interventions. She noted that there is an increased prevalence of autism with paternal age over 40, a possible contributor to the apparently increasing prevalence of autism in the community. The website <http://deevybee.blogspot.com> is a good source of rational analysis of the many claims for successful intervention made on the internet.

In Conclusion, the conference emphasised the increasing relevance of making a diagnosis of the aetiology of the ID and rapidly increasing relevance for targeted treatments across all domains of intervention - psychological, educational, general medical and specific molecularly targeted treatments. The next conference is in New York from 10-13th October 2014 and London in 2015.

The conference closed with Pat Howlin presenting on psychological and educational intervention for ASD. There is a

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Honey Heussler, Developmental Paediatrician from Brisbane, gave an overview of the management of sleep disorders in neurodevelopmental disorders. Poor sleep adversely affects intracellular signaling and mitochondrial function. Parasomnias occur in deep sleep, mostly early in the night, and night-