Long term cognitive outcomes 10 years after first episode schizophrenia

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The natural history of neurocognition in schizophrenia is unclear, with great uncertainty over whether the common baseline, characterised by a range of functional and neurocognitive deficits reported in subjects with, and at risk of, schizophrenia can provide any prediction as to patient outlook and outcome. Several recent follow-up studies have tracked 'change' in neurocognition over time (Censits et al, 1997; Heaton et al, 2001; Hughes et al, 2002). Studies restricted to first episode cases (Nopoulos et al, 1994; Gold et al 1999; Townsend et al, 2002) have yielded equivocal findings, with some authors reporting no overall pattern of change (see Rund's meta-analysis: Rund, 1998) and others reporting modest and/or selective improvement over time (Hoff et al, 1999; Townsend et al, 2002). Unfortunately, first-episode studies have, for the most part, been limited by the relatively short duration of follow-up (often less than 24 months) and/or significant sample attrition.

Cross-sectional studies, in which samples of patients who have been ill for different periods of time are compared, offer an alternative methodology, and have yielded evidence of differential neurocognitive outcome. Several studies have, for example, found evidence of specific impaired function in the realms of (verbal) memory or spatial skills which is most pronounced in individuals who have been ill for the longest periods of time (Saykin et al, 1994; Harvey, 1999; McGurk et al, 2000). However, by their very nature, cross-sectional studies cannot illustrate change over time, and, in any case, they are invariably confounded by the effects of age, medication, health service contacts and other extraneous variables. Thus, in view of the inherent frailties of the cross-sectional approach, researchers generally agree that long-term first-episode studies of epidemiologically-derived samples of patients provide the most effective means of studying the evolution of neurocognitive function in schizophrenia. Ideally, patients should be assessed early in their illness, and then again, repeatedly if possible, over an extended period of time; spanning perhaps several years or even decades.

The Manchester first-episode psychosis study meets some (though not all) of these demanding criteria. We have followed consecutive cases of first episode psychosis (mainly schizophrenia) over a 10–12 year period following index admission in an attempt to establish epidemiological and natural history parameters for the condition (Stirling et al, 2003). From a geographical catchment area comprising over 307,000 individuals, 112 subjects were identified as first admission cases with psychosis over a 24- month period between 1987 and 1989. Some two thirds of our cohort was male, with a mean age of 26.3 years.

At baseline, a number of assessments were made of patient cognitive and intellectual function, together with appraisal of symptoms, behaviours and signs that would provide an overview of patient status, well-being and mental health. In addition to the Schedule for the Assessment of Negative Symptoms (SANS), Present State Examination (PSE) and Research Diagnostic Criteria (RDC), patients were evaluated using the pre-morbid adjustment scale (PAS), questioned about their substance use habits and duration of positive symptoms, and assessed for neurological soft signs.

During index admission, but at a time when psychological functioning was deemed to have improved sufficiently to permit effective neurocognitive assessment, 37 subjects completed a test battery comprising four sub-scales from Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1986); [object assembly: OA, picture completion: PC, block design: BD, and picture arrangement: PA], the Warrington word and face recognition memory tests (Warrington, 1984),

the memory-for-design test (Graham & Kendall, 1960), verbal fluency (Benton et al, 1983) and the modified Wisconsin Card Sorting Test (WCST) (Nelson, 1976).

Mean follow-up of patients occurred 10 years and 7 months after index admission, with 111 (of 112) subjects traced, of which 11 had died. Within the follow-up cohort, after ten years the numbers of subjects with a diagnosis of schizophrenia (DSM-IV lifetime criteria) had risen to 69, while 7 subjects were classed as having schizoaffective disorder, 25 subjects had bipolar disorder and a further 10 subjects had another form of psychosis.

Surviving cohort members were appraised either through a comprehensive follow-up interview and assessment comprising Schedule for Affective Disorders Schizophrenia – Lifetime version (SADS-L) outcomes, SAPS and SANS (i.e., current positive and negative symptoms), Global Assessment of Functioning (GAF) overall symptom rating, severity and disability and repeat neurocognition (n=70), or by means of case note review and information provided by general practitioners (n=30). Two summary outcome measures; behavioural functioning and service contact, were derived from factor analysis of selected behavioural, functional and symptomatic scores garnered at follow-up interview.

Some 49 of the 70 subjects who underwent comprehensive follow-up assessments had a diagnosis of schizophrenia or schizoaffective disorder, and the following results are based on this sub-set of the cohort. In general terms, neurocognitive functioning, though often compromised at first admission did not predict functional outcome 10–12 years later. On the other hand, poor neurocognitive functioning at follow-up was associated with poor behavioural function and prevalence of enduring negative symptoms. Notably, follow-up WCST performance was associated with poor behavioural function ($p<0.005$), marked negative and positive symptoms ($p=0.01$ and $p<0.01$, respectively), and low GAF symptom score ($p=0.04$). Level of service contact was not associated with any onset or follow-up assessment, but was associated with the absence of an effective support network and/or living alone.

24 patients with a life-time diagnosis of schizophrenia completed the full neurocognitive battery at both first admission and follow-up. Test-retest comparison indicated significant neurocognitive deterioration from baseline for WAIS OA ($p<0.05$), WAIS PC ($p<0.001$) and memory-for-designs ($p<0.02$). No significant differences were noted for the other two WAIS tests, verbal fluency, modified Wisconsin test, or recognition memory for words or faces. In fact, recognition memory and verbal fluency improved (nonsignificantly) during follow-up.

The study also examined patients' WHO Life Chart in the 24 months before the follow-up assessment. This is a tool which provides insights into independent living, ability to work, in-patient time and persistence of symptoms; a poor outcome in terms of these parameters was predicted by a deterioration in WAIS PC ($p=0.03$) and Median Fixation Duration (MFD) ($p=0.03$), and a failure to improve verbal fluency ($p=0.02$).

Overall, results from this long-term follow-up of patients presenting with schizophrenia and related symptoms suggest that executive function (assessed by WCST and VF) is already impaired in a significant proportion (>50%) of first episode cases. However, this does not appear to progress over time after diagnosis and may, in some cases, improve. By contrast, it appears that visuo-spatial performance may be intact at symptom onset but decline progressively after disease diagnosis (as indicated by deterioration for OA, PC and MFD). A poor functional outcome could, therefore, be predicted by decline in visuo-spatial function and by a patient's failure to restore executive functioning. On the other hand, we note that such an outcome is relatively uncommon with only 3 of 49 individuals receiving a GAF rating for symptoms and disabilities at follow-up of 1 (severe), and 15 receiving a rating of 2 (moderate). Indeed, the 'modal' outcome rating in patients 10 years after initial diagnosis with schizophrenia or schizoaffective psychosis was 4 (recovered/residual features only) in 23 of 49 individuals, with a further 8 participants receiving a GAF rating of 3 (mild). Clearly, these data point to a range of possible outcomes with

only a minority of patients conforming to the so-called ‘deficit schizophrenia’ profile associated with widespread or pronounced neurocognitive decline (Carpenter et al, 1999).

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