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LETTER TO THE EDITORS

Disease-relevant autoantibodies in first episode schizophrenia

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Dear Sirs,

Schizophrenia is a common, heterogenous and complex disorder with unknown aetiology [1]. There is established evidence for *N*-methyl-D-aspartate receptor (NMDAR) hypofunction [2] as a central component of the functional dysconnectivity that is the most accepted model for symptoms [3], and increasing evidence for potassium channel dysfunction [4]. Moreover, autoimmune mechanisms have been proposed, perhaps in subgroups of patients [5, 6]. In the last few years, antibodies to neuronal cell surface antigens have been identified in cases of autoimmune encephalitis that respond to immunotherapy [7, 8]. Over two-thirds of patients with NMDAR antibody encephalitis, and some with potassium channel antibody-associated limbic encephalitis, have prominent psychiatric symptoms, or may present to psychiatric services in the first instance [7, 9, 10]. The psychiatric symptoms are those seen in schizophrenia including delusions, hallucinations, and catatonic movement disorder. There is good evidence for specificity and pathogenicity of these antibodies, with absence in large numbers of healthy individuals and those with other neurological diseases [9, 11, 12]. However, there have been no cases of NMDAR or potassium channel antibodies identified in patients with purely psychiatric disorders. We hypothesized that these antibodies would be present in a proportion of patients with early schizophrenia, in the absence of overt seizures, movement disorders, or other neurological signs.

Serum was obtained prospectively from a cohort ($n = 46$) of patients at first presentation of psychosis to an epidemiologically principled early intervention for psychosis service (http://www.cameo.nhs.uk), which provides 3 years of treatment and follow up when possible. We retrospectively measured NMDAR antibodies using a cell based assay and subjective visual scoring system [9]. We identified antibodies to components of potassium channel complexes (VGKCs) by radioimmunoassay [8]. The sera were tested blind to diagnostic status. Patients with positive results were retrospectively interviewed and extensively investigated. Full clinical details are given in the Table and supplementary information.

Patients 1 and 2 had NMDAR antibodies, [patient 1: score 2, (range 0–4, normal 0–0.5, Fig. 1); patient 2: score 1]. Patient 1 was unwell for 6 months before recovering; he was well and antibody negative at 3 years. Patient 2 has had a protracted course; antibodies remained repeatedly positive at 24–35 months follow up, but were then negative at 36 months. Patient 3 had VGKC antibodies (1,435 pM; normal <100), was unwell for 6 months before recovering, but has subsequently relapsed after 1 year and has now

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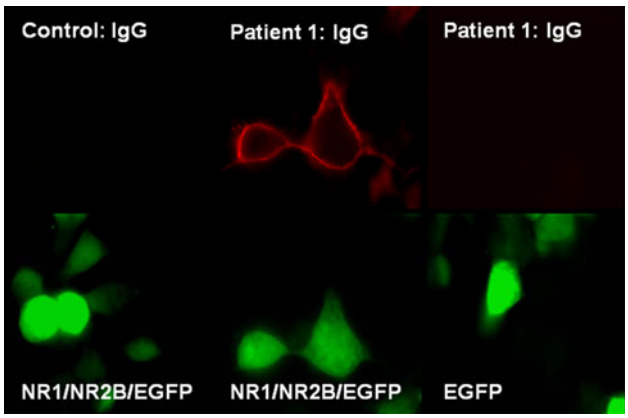

Fig. 1 HEK cells co-transfected with NR1, NR2B and EGFP cDNA or transfected with EGFP cDNA alone. Serum of patient 1 bound to the surface of unpermeabilised cells transfected with NMDARs, but not EGFP alone. Healthy controls (Control) showed no binding

been lost to follow up. There were no clinical features to differentiate these cases from other cases of psychosis in Cameo (Table 1), even in retrospect, and the autoantibody positive cases fulfilled criteria for DSM-IV schizophrenia. No patient had physical neurological symptoms or signs.

A further patient, patient 4, with first episode psychosis identified after the prospective cohort, had NMDAR antibodies (score 1.5). He was unwell for 4 months, partially responsive and then relapsing despite treatment with antipsychotics. To reduce the levels of NMDAR antibodies he received plasmapheresis and made a significant clinical improvement 3 weeks later, improving further with prednisolone. He remains clinically and functionally improved at 7 month follow up, on no antipsychotic medication. This is the first case description, to our knowledge, of a patient with NMDAR antibodies and a purely psychiatric presentation responding to immunotherapy.

These preliminary data show that some patients with schizophrenia have potentially pathogenic autoantibodies to relevant membrane proteins. Three of the patients had NMDAR antibodies, which have been shown to reduce NMDAR clusters in vivo [12], which mirrors that seen in models of schizophrenia [13]. All of our antibody positive cases (6.5% of 46) fulfilled DSMIV criteria for schizophrenia and the patients were tested early in the course of their illness. None of the chronic schizophrenia controls in our large case series had NMDAR antibodies [9], but this could be because NMDAR and VGKC antibodies spontaneously drop with time ([14]; SRI, AV unpublished data); this suggests a critical early period of illness for detection and treatment. We did not measure antibody in CSF, and future prospective systematic studies of antibody in paired serum and CSF will be informative.

The 46 patients in the Cameo cohort were given DSM-IV diagnoses a year after intake to the service. Of these,

Table 1 Demographic and clinical data for antibody positive cases

Patient	Antibody, titre	Sex	Age	Illness duration at intake/assay (days)	Positive psychotic symptoms	Negative psychotic symptoms	Cognitive deficits	Time to recovery, time to relapse, (months)	Total follow up (months)
1.	NMDAR score 2	M	21	4	Grandiose and paranoid delusions, delusions of control	Anergia, poor motivation	Verbal fluency	6, n/a	36
2.	NMDAR score 1	M	28	730	Auditory verbal hallucinations. Paranoid delusions, delusions of control	No	No	Chronic	36
3.	VGKC 1435 pM	F	22	14	Paranoid delusions, thought disorder	Poor self care and motivation, anergia	Working memory	6, 12	12
4.	NMDAR score 1.5	M	19	88	Auditory verbal hallucinations, thought disorder, paranoid grandiose delusions	Poor motivation, social withdrawal, incongruent affect	Recall and verbal fluency	5 (partial), n/a	7
Antibody negative Cameo cases $n = 43$	n/a	M:F 4:1	22 (17–35)	145 (2–270)	Auditory hallucinations, paranoid grandiose delusions	Social withdrawal	Not known	Chronic 23% Relapse 58% No relapse 19%	36

63% had a diagnosis of schizophrenia. Other psychotic diagnoses were psychosis not otherwise specified (15%), bipolar affective disorder (13%), schizoaffective disorder (4%), major depression with psychosis (2%) and delusional disorder (2%). It is therefore possible that the proportion of cases with diagnoses of schizophrenia that have specific antibodies is higher than the proportion described here. However, there is significant diagnostic instability in patients with early psychosis, due to the threshold of chronicity required for a diagnosis of schizophrenia. There is also increasing evidence of shared heritability between the psychotic disorders and consequently a move away from the use of categorical diagnoses in those with psychotic disorders.

There is a need for a systematic screen of available neuronal surface antigens in first episode psychosis and schizophrenia to characterise the true prevalence of these antibodies among different population groups, with implications for diagnosis, prognosis and treatment.

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