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New-onset psychiatric disorders in individuals with autism

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ABSTRACT A follow-up study to at least the age of 21 years of 135 individuals with an autism spectrum disorder diagnosed in childhood and an IQ of over 30 was conducted. The study is distinctive in its large size, low attrition rate and use of systematic interviews to obtain clinical information. Questionnaires completed by caregivers asked about the development of new psychiatric disorders. For the 39 individuals with a possible new disorder, a detailed psychiatric assessment was undertaken through parental interview. Of all participants, 16 percent developed a definite new psychiatric disorder. A further 6 percent developed a possible new disorder. Five individuals developed an obsessive-compulsive disorder and/or catatonia; eight an affective disorder with marked obsessional features; three complex affective disorders; four more straightforward affective disorders; one a bipolar disorder; and one an acute anxiety state complicated by alcohol excess. There was no case of schizophrenia.

KEYWORDS *affective disorder; autism; catatonia; obsessive-compulsive disorder; schizophrenia*

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Introduction

There are numerous reports that autism spectrum disorders (ASDs) may be associated with other psychiatric syndromes. Associations have been found with common syndromes such as depressive conditions (Ghaziuddin et al., 2002; Lainhart and Folstein, 1994; Perry et al., 2001; Stewart et al., 2006), or anxiety features (Gillott et al., 2001), or post-traumatic stress symptoms

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(Cook et al., 1993), as well as with rarer syndromes that might be especially common in individuals with autism. Thus, there has been a focus on obsessive-compulsive disorder (Gross-Isseroff et al., 2001; McDougle et al., 1980; 1995; Russell et al., 2005), catatonia (Hare and Malone, 2004; Realmuto and August, 1991; Wing and Shah, 2000) and Gilles de la Tourette syndrome (Baron-Cohen et al., 1999). Sturm et al. (2004) commented, too, on the frequency with which autism was associated with ADHD phenomena.

Opinions have differed on the frequency with which these associated features occur in ASD. Thus Rumsey et al. (1985) noted that symptoms of other conditions were common but co-occurring *diagnoses* were rare. Conversely, Szatmari et al. (1989) considered comorbid disorders to be common. The existing literature also suggests that when co-occurrence arises the presentation of the associated disorder is often atypical.

The problem with much of the existing literature relating to clinical populations is that the pattern of reported associations will be influenced by referral practices (so that referrals made because of associated problems have not usually been excluded); that autism often involves features such as specific phobias, overactivity and obsessions (so that it is uncertain when these should be regarded as involving a separate condition); that there are considerable difficulties in differentiating stereotypies and tics, and stereotypies and obsessive-compulsive phenomena (Ghaziuddin et al., 1992); and that impaired communication makes the assessment of feeling and thought processes problematic (a particular difficulty with respect to the diagnosis of depression in non-verbal individuals). All of these problems are most strikingly present during the period of childhood and especially at the time of first referral. A further constraint is that few studies have followed up individuals diagnosed in childhood into adulthood, and thus have not be able to study the pattern of disorder in adult life, particularly those disorders such as bipolar disorder and schizophrenia which tend to have a more typical adult onset. To date only Volkmar and Cohen (1991) in their study of 163 individuals aged 15 to 41 years have been able to cover much of the risk period for schizophrenia – finding only one case (0.6%). The findings were limited, however, by reliance only on case records. Nevertheless, the lack of an increased rate of schizophrenia in individuals with autism has been evident in other studies, too (Chung et al., 1990; Ghaziuddin et al., 1992).

The present study was planned to examine the emergence of new-onset psychiatric disorders in adolescence or adult life that were not present at the time that autism was first manifest in childhood. By design, it did not deal with contemporaneous comorbidity in childhood. The study had six key features: (1) a sample referred only for the diagnosis and treatment of

autism; (2) diagnosis based on standardized interview and observational measures; (3) a systematic follow-up into adult life with a low attrition rate; (4) the use of an investigator-based standardized interview that gave rise to detailed descriptions of actual behaviour; (5) the availability of systematic psychometric assessment; and (6) the availability of systematic data on the occurrence of epileptic seizures.

Sample

In order to obtain as valid as possible an assessment of the development of new-onset psychiatric disorders in individuals with autism, the starting point comprised all individuals seen at a Maudsley Hospital specialist outpatient clinic for children with possible autism between the years of 1950 and 1985 inclusive. The inclusion criteria included referral before the age of 16 years for possible autism (and not for some secondary or other psychiatric problem), a non-verbal IQ of over 30 (in order to reduce the problems of diagnostic uncertainty), the lack of a specific medical disorder (such as tuberous sclerosis) that might be implicated in the causation of the autism, no major sensory deficit or significant physical disability, no institutional upbringing, and not a twin or other multiple birth (because an independent study of twins was being undertaken in parallel). During the period of referral, there were few patients from ethnic minorities and, because their inclusion would result in subsamples too small to analyse, they were excluded. Finally, a definite clinical diagnosis of autism must have been made, and in almost all cases this was confirmed using the Autism Diagnostic Interview (Le Couteur et al., 1989) and the Autism Diagnostic Observation Schedule (Lord et al., 1989). Most of the sample had been previously followed up and studied in some detail (see Howlin et al., 2004) but the present sample included a few additional individuals missed in the previous follow-up (and omitted a few who could not be traced). The Howlin et al. (2004) article did not cover the development of new psychiatric disorders because they were assessed later in the study reported here. For present purposes, in order to provide coverage that extended into adult life, the sample was restricted to individuals who would have reached at least the age of 21 years at the time of follow-up. Excluding the two individuals who had died, this left a potential sample of 164.

Of these, 16 could not be traced or had declined to participate in the earlier follow-up, this being still the case for this follow-up. In addition, there were a further 13 who were lost from this follow-up, making a total non-participation number of 29, a participation rate of 81.5 percent in relation to the original target sample of 164. The sample of 135 that was studied had a mean age at follow-up of 34.9 years, the range extending

from 21 to 57 (with over two-thirds over the age of 30). Of the sample, 104 were male and 31 female, the ratio of 3.4:1 being in keeping with that usually found for individuals with autism.

Procedure and measures

The first step comprised sending a screening questionnaire to the person most likely to know most about the individual's current functioning and life history. In the great majority of cases this was the parents but, in a few cases in which the parents had died or were seriously ill, it was a sibling who was known to make regular contact with the individual with autism. In the few cases in which the person was in long-term institutional care involving little contact with the family, the questionnaire was sent to care staff. In the case of one high-functioning individual for whom there was no suitable informant, the questionnaire was sent to the individual himself.

The questionnaire covered a range of issues but asked particularly if there had been the development of any apparently new disorders, or escalation of more long-standing problems. In cases where there was uncertainty about what was described, this was clarified by means of a telephone call. The questionnaire responses were supplemented with information from previous research assessments and from clinical files.

In all cases for which the information suggested a possible new-onset psychiatric disorder, the informant who knew the person best was interviewed in detail using the Schedule for Assessment of Psychiatric Problems Associated with Autism (SAPPA), an investigator-based informant interview (see Bradley and Bolton, 2006, for details and Raznahan et al., 2006, for its application in a sample of adults with tuberous sclerosis) designed to obtain descriptions of behaviour relevant for the making of psychiatric diagnosis, according to ICD-10 research diagnostic criteria (World Health Organization, 1992). The style of interview is based on the well-established Child and Adolescent Psychiatric Assessment (CAPA: Angold et al., 1995). It was modified, however, to make it more suitable for use for individuals who varied greatly in their level of social functioning and of cognitive impairment. Diagnoses were based on consensus codings made by two raters (either JH and MM, or JH and MR). This more detailed psychiatric assessment was undertaken for 39 individuals.

Most of the participants had had multiple cognitive assessments over the years. It was decided to deal with verbal and performance scores separately and to use the earliest assessment for which full data were available in these domains. In all cases preference was given to the scores on the age-relevant Wechsler scale, when several tests were available. When scores on a Wechsler scale were not available, the best test available in each domain

was chosen from a list arranged in order of preference (the order varying by age). For individuals who had failed to score above the floor on any test, randomized scores (between zero and the floor of the best test attempted) were used, so as to minimize bias due to a greater number of missing values at lower levels of functioning. However, no data were available on the performance domain for 1.6 percent of participants and on the verbal domain for 20 percent.

On the performance measures, 19 scored below 50, 37 in the 50–69 range and 76 above 70 (the range extending from 33 to 133). The comparable figures for verbal measures were 42, 27 and 36. The mean IQs in both domains were about 10 points lower in females (69 versus 77 on performance IQ and 54 versus 62 on verbal IQ).

The study was approved by the joint ethics committee of the Institute of Psychiatry and what was then the Bethlem/Maudsley Hospital (now the South London and Maudsley Trust).

Results

Descriptive data

Out of the sample of 135, only 14 were living independently. Altogether, 21 (16%) of the sample population were in regular employment, although in some cases this was through a 'supported employment' scheme. Of the 14 who lived independently, all were in regular employment, one was married, one had been married (but was divorced) and a third had a regular girlfriend. However, several still received support from relatives or professionals.

About a quarter of the sample lived with their parents and three-fifths were in some form of hostel or residential placement for autistic individuals. Three percent were in a long-stay hospital.

A fifth of the sample had experienced one or more epileptic attacks (this was confirmed by means of a detailed separate interview, together with information from case notes). About two-thirds of the attacks had their onset in adolescence or adult life.

New psychiatric disorders

Of the 135 participants, 21 (16%) had a definite new-onset psychiatric disorder that had arisen at some time after and independently of the initial referral. There were also another eight individuals (6%) with a dubious or uncertain new psychiatric disorder. The new-onset disorders fall into two main groups: obsessive-compulsive disorders (some with catatonia), and affective disorders (often associated with obsessive-compulsive phenomena).

One woman also had a severe eating disorder; one man had a typical bipolar disorder requiring several inpatient stays; and one other experienced an episode of an acute anxiety state accompanied by confusion and brief paranoid ideas thought to be related to excess alcohol and sleep deprivation. There were no cases of schizophrenia.

Before the new-onset disorders themselves are examined, the findings on correlates of these disorders need to be considered. Those individuals with new-onset disorders (these were separately considered in terms of definite disorders only and the total group of both definite and possible new-onset disorders) were compared with the remainder of the sample. No statistically significant differences (tested for using the exact test) were found with respect to gender, IQ (either verbal or performance), diagnosis/history of epilepsy, type of placement (i.e. independent living, supported accommodation, long-stay hospital) and employment status. Similarly, within the group with a history of epilepsy there was no association between the timing of the onset of new disorder and the timing of the onset of epilepsy.

The only possible precipitating factor for the onset of new disorder was a major change in either residence or caregivers. In the absence of a life history charting all such changes (which we did not obtain), the association has to remain a clinical impression, rather than an objective finding. In a few cases, there was also a history of other major negative life events shortly before onset. The man with a bipolar disorder had his first episode of hypomania following the death of his father and his second a few years later on the anniversary of his death, However, the thought content in the episode did not involve the death, and the other episodes had no such temporal connection. Many of the individuals had experienced the loss of one or both parents by death and some had had parental loss through divorce. In the majority of instances, this had not been associated with the development of a psychiatric disorder and there was considerable individual variation in whether there was obviously expressed grief. In summary, as would be expected in any group of individuals, seriously stressful life events often occurred without clinically significant disorder, but they did sometimes seem to play a precipitating role in the onset of a new psychiatric disorder.

Obsessive-compulsive and catatonic syndromes Appendix 1 provides details of four individuals with a disorder mainly characterized by obsessive-compulsive phenomena or catatonia or both. In each case, although there had been stereotyped, repetitive behaviour in childhood, this lessened in early adolescence and the new disorder constituted a definite break from the previous pattern, with a relatively sudden onset, marked social impairment, the development of marked rituals, severe distress over the obsessional

thoughts (which differed markedly in content from previous thoughts) and some resistance to the compulsions. All four individuals required psychiatric treatment, in three cases on an inpatient basis. In two cases, the disorders resolved with treatment (in one case completely so) but in the other two there was only a partial recovery and the obsessive-compulsive phenomena persisted to a considerable degree. In each case, the recognition of the development of a new psychiatric disorder led to a beneficial change in therapeutic approach. The fifth case in Appendix 1 did not have a clear-cut new disorder but there was a prominent symptom of standing transfixed at a particular spot in a fashion that suggested it was catatonic in form. All of these disorders seemed to have a relatively specific association with autism even though they constituted a clear break from the pre-existing autism.

Affective disorders with obsessional features Appendix 2 describes the development of affective disorders associated with marked obsessional features, but without a clear differentiation from autistic features. The first three cases began after an obvious and marked stressful life event but this did not seem to be so with the next five. In each case, the episode had an onset of a kind that would be found with any new affective disorder and in most instances there was recovery from the episode, although individuals 8 and 9 both had chronic or frequently recurrent affective problems. With this group of individuals, it seems reasonable to regard the disorders as separate from the autism, but with symptoms that were possibly shaped by the presence of autism.

Complex affective disorders Appendix 3 provides descriptions of three individuals who developed complex disorders, all of which involved clear affective components, but with a diverse range of other new problems. Thus, case 13 involved a clear-cut eating disorder but also marked obsessive routines, suicidal attempts, aggression and reckless sexual behaviour. Functioning was severely impaired and treatment involved several admissions. The nature of this complex disorder is not clear but it seems to reflect aspects of a major affective disorder, autism and abnormal personality traits. The same applies to case 15.

More typical depressive disorders Appendix 4 comprises four cases of somewhat more typical depressive disorders (although case 18 included bulimia). Despite the less pervasive behavioural disturbance, the diagnosis of each new disorder was somewhat problematic because of the communication difficulties associated with the autism.

Other definite disorders Appendix 5 includes one case of typical bipolar disorder that seemed to be relatively independent of autism and one very acute case of anxiety complicated by alcohol excess and lack of sleep, again relatively independent of autism.

Other possible new psychiatric disorders The final appendix comprises a mixed bag of possible disorders. In each case affective disturbance had been thought to have played a role but the inference was uncertain.

Remaining individuals

To be included as a new psychiatric disorder, there had to be some kind of condition that represented more than a worsening of previously present autistic features. That meant that there were several individuals whose behaviour became markedly worse associated with increasingly impaired function and requirement for new interventions but who were not included as having new-onset disorders. For example, one woman had several periods of worsening aggression resulting in the use of a range of psychotropic drugs. A man developed severe self-injury that provided a major challenge in management. There were others, at all levels of intelligence, who had no new clear-cut episodes of disturbed behaviour but whose autism required regular professional intervention/attention (albeit at a frequency that was less than in childhood).

By contrast, there were many individuals whose functioning in adult life provided little or no additional cause for concern. The majority of these continued to have impaired social reciprocity and stereotyped interest patterns but, despite this, lived relatively independent lives, holding a job and organizing their own holidays, even though they continued to need some support and guidance. In addition, there was a very small number who functioned normally or near normally. Thus, one man was married and living with his wife in a flat that they were buying together. He worked as a civil servant, was a responsible member of his community church, and worked well with children in a leadership and teaching role. Another man obtained a first-class honours degree, followed by a master's degree. He has a steady girlfriend, good social relationships and seems to live a completely normal life.

Conclusions

What is most striking about the findings from this long-term follow-up into adult life is the immense variation in outcome – spanning the complete range from normal functioning to severe handicap, and from no new psychiatric disorders to severe chronic or recurrent psychiatric impairment. A previous follow-up had shown that, to an important extent, the overall

level of social functioning in adult life was a function of the initial level of non-verbal intelligence and of the presence/absence of useful communicative language in childhood (Howlin et al., 2004).

Perhaps surprisingly, however, our findings showed no association between the predictors of developmental outcome in autism and the occurrence of new-onset psychiatric disorders Well-functioning individuals of normal non-verbal intelligence as well as severely impaired individuals living in residential settings of one kind or another were affected. This finding is sufficient, on its own, to raise doubts over the extent to which the new-onset disorders constituted an intrinsic feature of an autistic liability. If they had been intrinsic, it would be expected that the same predictors of developmental outcome and social functioning in autistic individuals would apply to the emergence of new psychiatric disorders, but that was not the case.

The presence of obsessive-compulsive behaviour and of catatonia (which mainly seemed to stem from obsessive-compulsive symptoms) may be particularly characteristic of individuals with autism and deserves special consideration both because of the dramatic nature of this presentation and because of the interventions sometimes used in catatonia. It has been suggested by some clinical investigators that catatonia might constitute an indication for electroconvulsive therapy (ECT: Dhossche and Stanfill, 2004; Ghaziuddin et al., 2005; Zaw et al., 1999). If the impression that catatonia develops as a result of obsessive-compulsive phenomena is correct, this would not seem a strong indication. It should be added that catatonia lacks a clear definition and, if it is to be diagnosed using a broad definition as Wing and Shah (2000) suggested, there would be a danger of moving too readily to heroic interventions of unproven value. Rather, the emergence of new obsessive-compulsive phenomena in adult life would seem to suggest the value of trying the pharmacological and/or psychological approaches that have been found to be effective in cases of obsessive-compulsive disorders unassociated with autism.

Given that the most common disorders were affective in type, usually with an admixture of anxiety and depression, a key diagnostic issue concerns their recognition. Although most verbal individuals with autism are not good at describing their emotions or their emotional cognitions, they can usually provide some account of negative emotions, even if they find difficulty differentiating between anxiety and depression. Moreover, parents are generally quite good at recognizing changes in the emotions of their son/daughter with autism. In those with a definite depressive disorder, vegetative symptoms were usual and systematic questioning of the family member or caregiver who knows the person best is likely to provide good relevant descriptions.

Greater difficulties arise in the case of individuals with autism who are non-verbal. As some of the cases illustrate, new behavioural disturbance often arose in association with the development of an anxiety or depressive disorder. Careful questioning of caregivers or other family members and careful observation of the individuals should serve to clarify the diagnosis in most cases, but again, as several of the cases illustrate, it may be difficult to be certain. Perry et al. (2001) used response to antidepressant medication as a validator of the diagnosis of a depressive disorder. That constitutes a rather uncertain strategy both because antidepressant medication has important actions beyond the relief of depression, and because not all depressive disorders respond to antidepressant medication. Nevertheless, if it seems at all likely that an adult individual with autism has developed a depressive disorder, a trial of antidepressant medication would seem to be indicated. If there is a strong anxiety component, one of the selective serotonin reuptake inhibitors that tends to relieve anxiety would be the preferred choice.

Given the difficulty experienced by many individuals in describing their feelings and cognitions, the focus should be on whether there has been a significant change in the person's emotional state (rather than focusing upon whether the individual fully meets accepted diagnostic criteria), whether there is clinically significant anxiety and/or depression, and whether the change in emotional state has been accompanied by an increased impairment in social functioning.

As in the general population, it was common for new-onset disorders to have been precipitated by negative life events or changes. In the case of the more impaired individuals, the stressor was particularly likely to involve a change of residence or a change of caregivers or some other change in familiar routines. In those with a normal non-verbal intelligence and functioning in the community, the stressors also sometimes involved loss of employment, or bereavement. Thus a key implication is that the clinical care needs to pay as much attention to the possible psychosocial precipitants as to the treatment of the symptoms. What is clear is that, although individuals with autism may sometimes develop new disorders that appear to be closely related to their autism, many new disorders seem to arise relatively independently (although the features are likely to be shaped by the autism) and need to be assessed and treated in their own right.

A limitation of our study is that our results are largely based on reports from caregivers or parents. Necessarily, these had to cover an extensive period and it is possible that informants might not remember milder episodes of short duration from which the individual recovered completely. In only a few cases were the individuals themselves systematically assessed. Because we wished to have a standardized interview that could be applied

across the entire sample, we took the decision to rely entirely on informant reports on the anticipation that it was unlikely that the same individual assessment could be used across a sample that varied so greatly in level of functioning. Similarly, because our focus was on the nature of new psychiatric disorders arising in individuals with autism, we did not assess a control group. The overall level of new disorders – at 16 percent, or 22 percent if dubious disorders are included – is probably roughly in line with population norms and, although no exact comparisons are possible, it is likely that the incidence is neither appreciably above nor below expectations. The main interest, therefore, is in the characteristics of new disorders as they arise in individuals with autism. The particular merit of these findings lies in their having been obtained through systematic diagnostic interviews in an unusually large sample followed prospectively from childhood, with a very low level of attrition.

Appendices

Definite cases are numbered 1–21, and dubious cases are lettered (a) to (h). Information in vignettes has to be limited in order to preserve confidentiality.

Appendix 1: obsessive-compulsive disorders and catatonia

1 In middle childhood many obsessions and circumscribed interests. Marked improvement in obsessional symptoms in early adolescence, and by age 13 almost none present. Development of new marked rituals age 19/20, associated with obsessive thoughts having a sexual content. Marked slowness but no catatonic symptoms as such. Substantial social impairment and admitted to inpatient unit for behavioural treatment. Marked improvement but obsessive-compulsive phenomena continued to a fluctuating degree up to the time last seen at age 50. Continued in regular employment, living independently, but a lot of problems managing his affairs for which received frequent help.

2 During childhood many stereotyped behaviours and routines but these did not constitute the main autistic features. During his early 20s, developed new very marked obsessional rituals that led to periods of obsessive indecision in which he could not proceed with activities. These could be interpreted as catatonic in type although very obvious obsessive thought content. Admitted to an inpatient unit for psychological treatment. After some months marked improvement but low-level obsessive-compulsive symptoms remained to a varying degree until last seen in his late 20s. Living in family home but held a job.

3 Markedly repetitive stereotyped obsessive behaviour with prominent routines as a child. Improved socially over the years and developed conversational skills, albeit with an odd quality. After special schooling, went on to a centre for learning disabled adults, with a workshop he attended. In early adult life developed a chronic physical condition requiring steroid treatment. At age 28 became full of obsessional rituals and at 31 (following a series of mentally stressful events) developed a fully fledged obsessive-compulsive disorder with marked catatonic symptoms. Periods of standing still for up to an hour or so, unable to move, with distressing indecision and multiple obsessional thoughts. Distressed by his symptoms, saying 'my thoughts are making me do things'; also some resistance to compulsions. Extreme slowness in eating. This phase lasted many months but improved with fluoxetine and cessation of steroids, and a fluctuating level of marked obsessive-compulsive behaviour persisted up to the time of follow-up in the early 40s, but without the same marked catatonic features.

4 At age 14, over the course of a few weeks developed marked catatonic symptoms. When seen in an outpatients clinic, remained in standing posture with arm held out after shaking hands for many minutes until it was realized that he had not moved, and was helped to sit down. Marked slowing of movements and severe difficulty in moving from whatever position he was placed in. Communication became more difficult and it was not possible accurately to assess the content of his thoughts. Clearly there were obsessive features but a generally depressed mood with anergy and slowing predominated. Admitted to hospital and rapidly improved without specific treatment. No further recurrence up to the time of follow-up at 29 years.

   (a) The disorder in this individual was classified only as a dubious disorder because there was no clear break from previous symptoms. Throughout adult life, while in long-term residential care, he had very marked obsessional routines and compulsions which intruded into all aspects of his life. At some time (the timing of onset being uncertain) he developed an apparently compulsive 'need' to stand on one particular spot for several minutes, being seemingly unable to move when asked. He tends to hit himself in the face when agitated and also often hits his hand on the wall (in both cases short of causing injury). His mood fluctuates with periods of marked restlessness, getting up at night and asking very repetitive questions. The psychiatrist in charge of his case has diagnosed bipolar affective disorder but the description obtained in both follow-ups (at ages 44 and 51) did not meet research criteria for that diagnosis.

The standing on one spot sounds catatonic in nature and it seems to derive from a mixture of severe obsessive symptomatology and affective disturbance. He has been treated with multiple neuroleptics for many years.

Appendix 2: affective disorders with marked obsessional features

5 Following losing his job (which was part of a special employment scheme), at age 22, became anxious, depressed and lacking in interest/pleasure. Tearful at times, sometimes waking with nightmares, outbursts of anger and destructiveness, marked anxiety and increase in previously occurring obsessive phenomena. Recurrence at age 29 with more marked obsessional features. Diagnosed as obsessive-compulsive disorder but no clear demarcation from pre-existing obsessional features.

6 Became depressed at age 27 when he was made redundant after 8 years in a regular job. Appeared depressed, sad, restless and lacking in interest, with mildly disrupted sleep and marked increase in pre-existing rituals (mainly involving counting and repeating actions). Saw a psychologist who diagnosed an obsessive-compulsive disorder.

7 Living independently with a regular job that he had held for 21 years. When he was 46, at the time his mother became ill (dying two years later), he became depressed, with an increase in the obsessional features that had been present since childhood.

8 Lives in family home and has a part-time job. Since the age of 22 has had stress-related phobias (with avoidance of travelling), associated especially in the winter months with depression, misery, poor concentration, anhedonia, marked anxiety/worrying and obsessive ruminations with paranoid ideation at times). Twice had treatment with antidepressants for 9–12 months, with some benefit. However, the dysthymia, anxiety and obsessions have persisted in a chronic, fluctuating fashion.

9 Developed a depressive disorder at age 13 that lasted some 5 years, with a recurrence at age 20. Both involved a diminution in speech, reduced movement, reduced spontaneity, marked misery and anxiety, loss of self-esteem, pessimism, pathological guilt, poor concentration, unpredictable behaviour and aggression. Also, the development of obsessional rituals that had not been present before. Seen by a psychiatrist who diagnosed depression. In addition, onset of bedwetting at age 21 when residential placement started to go badly.

10 At the age of 22 developed marked misery, lethargy, reduced spontaneity, slowing of movements and an increase in repetitive behaviour.

Diagnosed as having a major depressive disorder, which lasted some 2 years. Living in a psychiatric hospital.

11 Developed epilepsy at age 12. At age 15 episode of depression accompanied by obsessions and phobias and a worsening of a range of symptoms. Multiple similar episodes of a similar kind.

12 At 24 developed psychomotor agitation and retardation associated with both anxiety and depression, anhedonia, poor concentration and an increase in obsessive behaviour. Treated with both tranquillizers and antidepressants.

Appendix 3: complex affective disorders

13 At 16 developed anorexia and various preoccupations with food and with eating. At the same time became miserable and depressed, with loss of energy, psychomotor retardation, loss of self-esteem, pathological guilt, poor concentration, aggression and irritability. Treated with antidepressants and tranquillizers. Symptoms remitted but recurrence at age 20 following a severely stressful event. At age 24 developed marked obsessive checking routines. Also pre-existing preoccupation with a deceased popular singer. Recurrent psychiatric episodes with several suicidal attempts, arrests for violence (usually when drunk), once set fire to her bedroom, and showed reckless sexual behaviour. Multiple hospital admissions with mixture of antidepressant treatments and psychological interventions.

14 At age 43 developed marked anxiety associated with obsessional features; this lasted 4 months. Treated with lithium, antidepressants and sedatives. For 3 years in his mid 40s had depression, sleeplessness and restlessness each winter. At age 50, following changes in staff and of medication, developed marked mental and physical deterioration, stripping off his clothes, losing interest in food and losing weight, sleeping very poorly, decrease in activities, slowed movements, reduced responsiveness, misery, poor concentration, psychomotor agitation and clear-cut depression. Some aggression to other people associated with anxiety, restlessness and agitation. Admitted to hospital. Major affective disorder diagnosed.

15 Multiple episodes of pervasively disturbed behaviour from age 32 onwards, which her mother attributed to major changes in the regime at her residential placement. She seemed upset and sad and talked of wanting to kill herself (although mother unsure whether she understood what that meant). She engaged less, and showed less enjoyment, in her usual daily activities, seemed slowed down and less responsive. Also she was tense, anxious and worried and said negative things

about herself. She overate and was distressed by the resulting weight gain; there were temper tantrums in which she was destructive of property, and she pulled out her own hair.

Appendix 4: more typical affective disorders

16 At about the age of 20 developed marked generalized anxiety symptoms. She became tense and jumpy, particularly in unfamiliar situations, and expressed fears and worries, sometimes related to previous events that had upset her. For example, on one occasion, some of her clothes had been accidentally thrown away and said that she was afraid this would happen again. She became agitated and sometimes hit out at those around her, and could not be calmed. These features lasted about 6 months but responded well to a combination of psychotropic medication and behavioural treatment.

17 At the age of 10 developed a severe anxiety disorder from which he largely recovered after about a year. Following a move of the family home (where he lived) at the age of 21 had a severe episode lasting some 3 years that involved anxiety, misery, problems in eating and sleeping and refusal to leave the house (becoming panicky if he thought he might have to do so). He sweated excessively and put his hand to his chest as though his heart was thumping. Became markedly agitated and pale and warned that a dangerous criminal might be escaping from prison. He ate alone and found it difficult to swallow. Regarded as an anxiety disorder that was treated with a neuroleptic drug.

18 Since the age of 33 became agitated, depressed, anxious and tense, this lasting some 2 years up to the time of follow-up. Living in a residential unit for adults with autism. Disorder regarded as agitated depression and treated with antidepressants and neuroleptics. Living in a residential community.

19 Since the age of 22 had episodes of anergy, anhedonia, psychomotor retardation and general withdrawal. Treated with antidepressants. Regarded as a depressive disorder but difficult to judge in view of the level of handicap.

Appendix 5: other definite new-onset psychiatric disorders

20 Admission for severe hypomania at age 15 following his father's death. Further similar episode at age 29 at about the time of the anniversary of his father's death. Inpatient for 5 months and discharged on lithium. In neither episode was thought content related to the death. Further

episode at age 36 – again with hypomania, elevated mood, pressure of speech and major increase in energy, associated poor concentration. Throughout period of adult life lived independently and held a regular job. Further episode at age 48, with disturbed thought processes, flight of ideas and sleep disturbance. Admitted to inpatient unit. Lost to follow-up after that. All episodes diagnosed as a clear-cut bipolar disorder.

21 Living independently, buying his own home and in regular employment (albeit with ups and downs). Following various stresses that had been building up, went on holiday during which there was heavy drinking and lack of sleep. Hospitalized for one night when became acutely disturbed with marked anxiety and worrying, misery and tearfulness associated with paranoid ideas and 'confusion'. Responded rapidly to anxiolytic drugs and recovered completely after about 3 weeks on return from holiday. Regarded as an acute anxiety state, complicated by alcohol excess.

(b) Depressed for about 2 months in early adult life, at a time when another resident developed depression. Appeared fed up, miserable, uninterested in things, slowed down, lacking in enthusiasm and waking early. Probably a depressive disorder.

Appendix 6: other uncertain new-onset psychiatric disorders

(c) Became aggressive after a move of residential living at age 18. Three years before follow-up at age 29 began to make embarrassing lavatorial comments to people in shops and other public places. Also began to talk obsessively about a woman who was to have looked after her 20 years previously. Various odd behaviours, such as putting talcum powder on the stairs.

(d) At the age of 25 developed major behavioural problems associated with self-abuse, violence to others, smearing of faeces, urinating on the carpet, aggression to others, anxiety and misery. Treated with many different drugs. Regarded as having a depressive disorder but diagnosis very uncertain.

(e) Several episodes of increased behavioural difficulties associated with anxiety.

(f) Said to have had an anxiety disorder at age 22 and a major depressive disorder at 34 but these were predominantly manifest in more disturbed behaviour, although this was associated with emotional disturbance.

(g) In her mid 20s developed episodes of severe anxiety associated with markedly impulsive behaviour and agitation. Also swings to

low mood. The anxiety was considered to arise out of her autism and to be much influenced by the social situation. Nevertheless, the anxiety constituted a definite change of behaviour requiring medication.

(h) At her best between the ages of 13 and 16 years. Very marked behavioural disturbance around the age of 19 years. Re-referred at the age of 29 years because of very substantial emotional distress involving severe anxiety. Definite change in the previous 3 years but anxiety considered to have arisen out of her autism. Again re-referred at 39 years because of very disturbed behaviour involving aggression and a preoccupation with breaking other people's spectacles.

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