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EDITORIAL

Understanding comorbidity: from epidemiological designs and model-fitting approaches to systems biology as a new tool

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It is a common observation that persons with one particular psychiatric disorder often present with other disorders. This so-called co-occurrence, co-existence or comorbidity of disorders occurs at all ages, and cannot be explained away simply by sampling bias. Co-occurrence of disorders may lead to a higher rate of clinical referrals and use of services, and this could suggest inflated rates of co-occurrence. However, population-based studies confirm that many psychiatric disorders cluster in the same individual more than to be expected by chance [1–3]. Traditional explanatory models for this co-occurrence specify the following possibilities: artificial factors, such as overlapping diagnostic criteria or population stratification (the risk factors that influence the two disorders maybe more common in a part of the population); one disorder being a risk factor for the other; one disorder being a cause of the other; risk factors that are being shared between the two disorders; and both disorders being alternative expressions or different phases of the same overarching disorder [4]. Comorbidity has found to be associated with greater severity of illness, increased use of services and health care costs, lower response to treatment and an overall worse prognosis. Therefore, it is important to study the causes of comorbidity. This can have then a major impact on future research examining the two disorders, including research on classification, treatment, and etiology.

This issue contains a number of papers that focus on the co-occurrence of disorders. Polier et al. report on the significant comorbidity between conduct disorder problems and anxiety and depression in both a clinical and an epidemiological sample. Children with combined conduct and internalizing problems were more impaired and had more social problems than children with only conduct problems. In fact, the social problems of these children were more closely linked to increased levels of anxiety and depression than to conduct problems. The theoretical implication is that internalizing problems do not protect from developing high rates of conduct problems. In clinical practice, the disruptive effects of aggressive and antisocial behaviors rather than the less manifest internalizing problems easily get the attention of parents, teachers and health care professionals. Therefore, the practical consequence should be that more active screening is needed for the presence of internalizing problems among aggressive youngsters and that interventions for these internalizing problems should be offered proactively.

Not only more than one psychiatric disorder but also psychiatric and somatic disorders tend to cluster in the same individuals. This may be due to common risk factors, such as unhealthy lifestyle, adverse psychosocial circumstances, and personality characteristics as neuroticism [5]. These factors, however, cannot probably wholly explain that for example patients with schizophrenia have a baseline decreased insulin tolerance and increased risk for developing diabetes mellitus type 2, even before any exposure to treatment with antipsychotics [6]. Certainly, patients with such severe psychiatric disorders tend to be physically less active, may have less access to foods lower in calories and higher in nutrients and are more inclined to smoke. Smoking in turn can increase insulin resistance. In addition to these lifestyle factors, it is likely that common genetic or metabolic abnormalities underlie the vulnerability to develop both schizophrenia and diabetes mellitus and metabolic syndrome.

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These psychiatric–somatic comorbidities have been less well studied in children and adolescents. Kastner et al. discuss in this issue an example of somatic complications of psychiatric disease. About one-third of patients with anorexia nervosa had pericardial effusion on echocardiography that had no hemodynamic consequences and remitted in the majority of cases after normalisation of weight. Predictors of the pericardial effusion were a low body mass index and a low level of thyroid hormone T3. The authors do not recommend routine echocardiography in patients with anorexia but their findings should make clinicians even more cautious about handling the somatic status of these patients.

Erhart et al. were able to confirm that the association between ADHD and obesity reported in clinical samples is also found in population-based designs. Children with overweight in the general population were twice as likely to have significantly increased levels of ADHD symptoms compared to normal weight children. Vice versa, children with ADHD were twice as likely to have overweight. Their results are in agreement with at least two other studies in pediatric community samples, and with studies in adults with ADHD [7]. Erhart et al. discuss several explanations for their findings, such as increased impulsivity or delay aversion which may lead to uncontrolled eating behavior or even binge eating. Another possibility is that ADHD is related to increased risk for food addiction, next to addiction risk to various substances, through shared abnormalities in the dopaminergic and other biochemical systems of reward in the ventral striatum [8, 9]. We know for a longtime that acute intake of sweets and sugar is not a significant cause of symptoms of ADHD or cognitive dysfunctions in either low risk or high risk children [10, 11]. However, it could well be that increased long-term intake of high caloric foods sensitizes the dopaminergic systems in the ventral striatum and leads to food addiction. Obesity is a major factor in the development of numerous medical problems. Therefore, we should develop a more active stance toward identifying overweight in children with ADHD and integrate managing psychiatric symptoms and overweight and other aspects of somatic health in our care as usual.

Ekinci et al. did examine the phenomenon of autistic regression in a sample of children with autism spectrum disorders. Children with regression had much more often sleeping problems than those without regression, and those with regression type-2 (i.e., with regression of language and social behavior after already initially abnormal development) had higher rates of gastrointestinal complaints. They wisely refrain from speculating about the potential mechanisms underlying these links between psychiatric and gastrointestinal problems. The history about the relationship between autism spectrum disorders and gastrointestinal disease has been complicated by the Wakefield paper in Lancet [12]. This paper mixed up the issue with unsupported claims about a connection to mumps, measles and rubella (MMR) vaccination and had to be withdrawn after several years. Recent studies have confirmed the association between autism and gastrointestinal complaints [13], and a recent review offers several interesting hypotheses about this link, such as abnormal composition of gut microbiotica, abnormal cellular immunity, and increased food allergy [14].

It is now time to complement the traditional methods to study comorbidity as cross-sectional and longitudinal epidemiologic designs [15] and model-fitting approaches in genetically sensitive designs [16] with more rigorous biological system approaches [17]. These require to deconstruct existing psychiatric and somatic disease categories and start with bottom-up measures of key neural and body systems. These may include tests of cognitive control, reward sensitivity, and empathy, but also measure the status of the autonomous and endocrine stress systems, cellular and humoral immunology, cardiovascular reactivity, mitochondrial energy metabolism, and components of the gut–brain axis. These systems' functions should be studied at several different levels of analysis, i.e., genes, proteins, physiological activity, brain imaging, and reports of symptoms, to define the key constructs. Boosted by the results of cross-disorder genome-wide association studies, this may lead to organize psychiatric and somatic symptoms into new classes with more homogeneous pathophysiology and etiology. This would provide a more solid basis to develop new diagnostic and therapeutic approaches of these comorbid and complex problems.

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