

Aetiology Based Diagnosis and Treatment Selection in Intellectually Disabled People with Challenging Behaviours

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Abstract: Since both intellectual disability and challenging behaviour are entities encompassing heterogeneous clinical conditions and current taxonomies are of limited use in this field of psychiatry, diagnosing psychiatric symptoms in intellectually disabled patients is still very complex. In the diagnostic process of psychiatric symptoms and behavioural abnormalities, the first step should be genome profiling using the latest techniques in order to detect pathogenic CNVs or single gene mutations that are causative for the developmental delay. Their importance can be derived from the scientific observation that several genetic syndromes are associated with a specific behavioural, psychiatric, neuropsychological or neurological symptom profile, relevant for both choice of treatment and prognosis. Second, it has to be stressed that psychiatric disorders, especially from the depression and anxiety spectrum, frequently manifest with atypical symptoms that may hamper adequate pharmacological treatment. With respect to challenging behaviours in general, it should be emphasized that these are essentially dependent on contextual variables for which no rational pharmacological treatment is available and behavioural interventions are primarily warranted. Prescription of psychotropics has been demonstrated to be marginally effective only and to induce regularly unwanted side effects or even an increase of abnormal behaviours. It is therefore recommended to measure always the plasma concentration of psychotropics and antiepileptics and to perform, preferably prior to the start of treatment, genotyping of relevant cytochrome isoenzymes.

It is concluded that, apart from the a priori genetic analysis, careful investigation of the here described data sources is needed to formulate a diagnostic hypothesis and treatment proposal.

Keywords: Psychiatric diagnosis, DSM, genetic etiology, psychotropics, pharmacogenetics, behaviour, behavioural phenotype.

INTRODUCTION

For psychiatry, genetic disorders form an intriguing challenge since they present a unique opportunity to study symptoms or symptom profiles in relation to a known aetiology and sometimes pathophysiology. As shown over the past decades, the search for candidate genes and copy number variations has increased the understanding of putative pathophysiological mechanisms underlying psychiatric disorders such as schizophrenia [1, 2], bipolar disorders [3], attention deficit disorder [4] and autism [5].

For all psychiatric disorders, categorical psychiatric taxonomies like the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association are routinely used for diagnosing which, however, often results in several 'diagnoses' at the same time. This phenomenon is called comorbidity. As stated for

decades by several authors, such a nosological approach leads to diagnostic inflation with harmful side effects such as proliferation of new diagnoses and magnifying of comorbidity [6-8]. Moreover, the DSM system that was originally intended to create a common language may generate an epistemology of blindness that hinders the evolution of well founded diagnoses [9]. Finally, it should be emphasized that current psychiatric taxonomies are primarily tailored by consensus, not by empirics, and based on the presumption that a common pathophysiology underlies psychiatric categories.

As formulated by Lyketsos and colleagues, (neuro) psychiatry should operate *bottom-up* 'beginning with the emergence of pathology in the brain and attempting to understand the emerging of clinical syndromes out of this pathology' [10]. Such a bottom-up approach also needs a theoretical framework because, without theory, categories tend to increase as is illustrated by their growing number in subsequent DSM-versions [11, 12]. Clinical syndromes that arise from such a bottom-up orientation are not congruent with DSM categories but

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are reflections of a certain probability to develop a variety of psychiatric and neurocognitive symptoms [13].

The triviality of a top-down approach is best illustrated by the 'disorder' called mental retardation or intellectual disability (ID) that is not a disease or a disability but rather an essential phenomenon in a heterogeneous group of clinical conditions, ranging from genetic disorders to infectious diseases [14, 15]. In case of genetic disorders, the chance to define a phenotype is proportional to the prevalence of the disorder and the research efforts on its phenomenology and pathophysiology [13]. The same holds for emerging pharmacological treatment modalities that will be increasingly targeted not at DSM diagnoses but at functional impairments related to genetics and genomics crossing nosological boundaries [16, 17].

In the following, first, main ingredients will be outlined for an appropriate diagnostic process of neurocognitive and behavioural abnormalities as well as psychiatric symptoms in intellectually disabled patients. Second, a few examples of genetic syndromes with their variable levels of ID and their specific neuropsychiatric symptom profile, course and putative treatment regimens will be given. Finally, some future vistas will be discussed.

PHASING THE DIAGNOSTIC PROCESS

Clarification

In the majority of cases, challenging behaviours are the primary reason for psychiatric consultation [18, 19]. To start with, results of recent psychological data, both cognitive and social emotional, as well as information about developmental and family history have to be collected. Since, with the exception of mood and anxiety disorders, the prevalence of psychiatric disorders in patients with ID is comparable to that in the general population [20, 21], instantaneous psychiatric labelling should be avoided. Instead, the diagnostic process should first continue with a functional analysis of the behaviour using detailed interviewing of primary care givers, preferably supported by video registration of the patient's behavioural repertoire. The latter can also be used to record phenotypical characteristics, especially dysmorphic features.

Subsequently, from the behavioural repertoire, essential elements can be discerned and specified by using e.g. the Aberrant Behaviour Checklist (ABC) [22,

23], the Diagnostic Assessment for the Severely Handicapped (DASH) [24, 25] and the Psychiatric Assessment Schedule for Adults with a Developmental Disability (PAS-ADD) [26, 27]. From these, cognitive and behavioural aspects of psychiatric disorders can be tentatively grouped into the symptomatic domains of motor activity, motivation, affect as well as thinking and perception [28].

The here described initial diagnostic phase translates the original referral question into a more circumscribed plan of investigative actions.

Additional Inquiries and Hypotheses

Here, the first step has to be the diagnostic genome profiling with recent techniques since submicroscopic rearrangements are a common cause of ID [29, 30]. In the past two decades, traditional karyotyping and molecular cytogenetic techniques such as fluorescence-in-situ-hybridization (FISH) and multiplex ligation-dependent probe amplification (MLPA), both with limited level of detection, have been replaced by array-based comparative genomic hybridization (array CGH) [31, 32]. Genome wide array analysis may reveal etiologically relevant copy number variations (CNVs) while diagnostic exome sequencing aims to detect single gene mutations [33, 34].

Second, detailed information about developmental trajectory and family history has to be collected. These data may reveal a relapsing or deteriorating course as well as family load with psychiatric diseases, in particular (bipolar) affective disorders. The case history should also include information on the use of medication by the mother during pregnancy e.g. antiepileptics that may lead to ID with accompanying behavioural problems and somatic comorbidities [35]. In general, a substantial percentage of patients with ID are suffering from epilepsy for which treatment with antiepileptics is given. Special forms of epilepsy also exist, as is the case with gelastic seizures in hypothalamic hamartomas and the specific behavioural disturbances which these entail such as excessive laughing and crying as well as aggressive outbursts [36]. The use of antiepileptics may also give rise to behavioural and psychiatric symptoms e.g. psychosis-inducing properties of levetiracetam and topiramate as well as confusional states induced by benzodiazepines [37]. Furthermore, it should be stressed that epileptic seizures are frequently associated with psychoses, both post- and interictal, and mood disorders [38] and that there exists an array of potential risk factors for

ictally related psychoses, such as early age at epilepsy onset, history of prolonged febrile convulsions, and intellectual disability [39].

Moreover, since virtually no information exists about the bioavailability of psychotropics in patients with ID, measurement of plasma concentrations and identification of genetic polymorphisms of cytochromes P450 is strongly recommended [40, 41], especially in case of antiepileptic co-medication. Finally, it should be stressed that, in ID patients, a great variety of physical, medical and contextual conditions may present with behavioural problems only [42, 43].

With respect to the manifestation of psychiatric symptoms in ID patients, one should constantly be aware of atypical phenomena, in that e.g. depression frequently presents with a disturbed regulation of aggression and that episodic alterations of mood and behaviour which do not meet the criteria for bipolar disorder or cyclothymia, occur regularly [44] and should therefore be termed unstable mood disorder [45].

For the purpose of diagnostic hypothesis formulation, it should be underlined that ID and other brain disorders obviously affect the development of interpersonal contact and social as well as language skills, with lower levels of intellectual functioning generally associated with higher incidence of interpersonal contact problems. In ID populations, autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are often wrongly classified since these 'diagnoses' are typically based on DSM-criteria without providing information regarding aetiology [46, 47].

Clinical Decision Making

Based on all available data from the former phases complemented by information from most recent literature, a psychiatric diagnosis may be formulated in one of the following forms: (a) classic psychiatric disorder with or without an atypical symptom profile [21]; (b) syndrome-specific psychiatric disorder e.g. bipolar disorder in Prader-Willi syndrome [48]; (c) psychiatric disorder related to underlying somatic/neurological suffering e.g. cognitive-affective syndrome in Charlevoix-Saguenay ataxia [49]; (d) disinhibited behaviours due to environmental factors; or (e) drug-related behavioural disorders. In case a genetic syndrome is associated with a specific cognitive, neurological or psychiatric profile, the term psychopathological or, more specific, neuropsychological,

neurological or (neuro) psychiatric phenotype, can best be used. Once a diagnosis has been made, mostly, a targeted and personalized treatment design can be formulated.

PSYCHOPATHOLOGICAL PHENOTYPES: SOME EXAMPLES

22q11.2 Microdeletion (22q11.2DS; OMIM:192430)

This is the most common microdeletion syndrome formerly called Velo-Cardio-Facial Syndrome, with a highly variable phenotype. Its behavioural phenotype, including the psychopathological features and endocrine dysfunctions, especially hypoparathyroidism, was originally described by the speech therapist Robert Shprintzen [50]. Over subsequent years it became apparent that 22q11DS is highly associated with symptoms from the schizophrenia, bipolar, anxiety and autistic spectrum [51, 52]. With respect to the neuropsychological phenotype, it has been shown that deficits in problem solving and planning as well as in abstract and social thinking are most prominent [53]. It has to be stressed, however, that psychiatric symptoms from the affective, obsessive-compulsive and psychotic domains originate from the discrepant intellectual profile and impaired visuoperceptual abilities with a diminished comprehension of abstract and symbolic language [54]. Although Schneider and co-workers recently mentioned the persistence of negative psychotic symptoms in 22q11DS [55], it should be underlined that these phenomena may also stem from the neurocognitive dysfunctions.

Apart from the above mentioned neuropsychiatric and neuropsychological sequelae, it has become obvious that the 22q11.2 microdeletion syndrome, from approximately the age of forty, shows, in a minority of cases, a deteriorating course with Parkinsonian symptoms [56, 57].

Concerning the treatment regimen, a distinction should be made between pharmacological and non-pharmacological strategies. First, of course, endocrine dysfunctions have to be corrected since they may mimic psychotic features. Second, it has been repeatedly demonstrated that psychotic symptoms in 22q11.2DS do not respond to classical antipsychotics, including risperidone, whereas results from case descriptions suggest that some atypical antipsychotics may be effective in reducing psychotic symptoms (Table 1). In case of Parkinsonian symptoms, some alleviation may be achieved upon treatment with L-

Table 1: Atypical Psychosis in Patients with del22q11: Putative Treatment Strategies

Case report	Sex/Age (y;m)	Antipsychotic Daily Dose	Co-Medication	Results	Remarks
Gladston & Clarke (2005) [122]	male/32	clozapine 300mg	sodium valproate 1200mg	Marked reduction of psychotic symptoms	Constipation and hypersalivation; myoclonic epilepsy without history of epilepsy
Briegel (2007) [123]	male/12;10	clozapine 450mg	none	Significant reduction of psychotic symptoms	No improvement and severe extrapyramidal side-effects on haloperidol; clozapine stopped because of seizures
Krahn et al. (1998) [124]	male/30	clozapine 125mg (?)	phenytoin 200mg	Medically stable condition	No effect of and extrapyramidal side effects on fluphenazine;
Yacoub & Aybar (2007) [125]	female/25	clozapine 75mg	sodium valproate 750mg	Full recovery of psychosis	Initially seizures; no effect of olanzapine, aripiprazole, ziprasidone and perphenazine
Gagliano & Masi (2009) [126]	female/7;1	aripiprazole 15mg plus clozapine 150mg	none	Dramatic improvement of psychotic symptoms	Nonresponsive to risperidone and aripiprazole monotherapy
Sporn et al. (2004) (four cases) [127]	unknown	clozapine or olanzapine or quetiapine	none	Good clinical response	Epileptiform EEG changes/seizures in three patients
Müller & Fellgiebel (2008) [128]	female/41	quetiapine 300-400mg	none	Free of psychotic symptoms	No side-effects
Lin et al. (2010) [129]	female/16	aripiprazole 10-25mg	calcium 1500mg plus calciferol 0,25µg	Free of psychotic symptoms	Hypoparathyroidism; no side-effects
Carandang & Scholten (2007) [130]	male/17	metirosine 1000mg*	none	Significant functional improvement	No response on aripiprazole

Note. * Competitive inhibitor of the enzyme tyrosinehydroxylase.

dopa [57]. Most important, however, is a contextual psychological treatment that guarantees a safe, well known and structured environment, where possible directed at the impaired capacity to estimate intentions, emotions and behaviours of others [58, 59].

Distal 22q11 Microdeletionsyndrome (OMIM: 611867)

Here, the microdeletion is located distal to the common ~ 3Mb deletion as seen in 22q11DS. In contrast to the classical 22q11.2 microdeletion syndrome, facial dysmorphisms, cognitive and behavioural problems as well as psychiatric symptoms are typically less pronounced. With respect to somatic comorbidity, a wide range of congenital heart defects have been described extending the cardiac phenotypical range [60]. When the 22q11 distal deletion includes the *SMARCB1* gene, an increased risk is present on the development of malignant rhabdoid tumor [61]. In some patients with distal 22q11 microdeletion syndrome, symptoms from the anxiety cluster have been reported that may be pathophysiologically connected to the absence of the

MAPK1 gene which is accompanied by a disordered neurobiological stress homeostasis. Treatment with an antidepressant such as citalopram may then lead to full remission of anxiety symptoms [62].

17q21.31 Microdeletion Syndrome (Koolen-De Vries Syndrome; OMIM:610443)

This microdeletion syndrome was first described genotypically by Koolen and colleagues and thought to be caused by an interstitial deletion in 17q21.31, comprising the *MAPT* gene. Subsequently, they reported the somatic abnormalities of which facial dysmorphisms, central nervous system anomalies, and congenital heart and/or kidney defects are most prominent [63]. Nowadays, the *KANSL1* gene (17q31.31) has been demonstrated to be causative for the phenotype [64]. Given its monogenic aetiology, the syndrome was re-termed as Koolen-De Vries syndrome. With respect to the behavioural phenotype, in addition to intellectual disability, an amiable, friendly disposition was described [65]. Cognitive phenotyping of a small number of patients disclosed hypersociability accompanied by high levels of frustration tolerance to

form the core of the neuropsychological phenotype [66]. Such a profile is to some extent comparable to that observed in Angelman syndrome and Williams syndrome and therefore, Koolen-De Vries syndrome should be included in their differential diagnosis.

9q Subtelomere Deletion Syndrome (Kleefstra Syndrome; OMIM:610253)

Kleefstra syndrome, originally termed 9q subtelomeric deletion syndrome, is in the majority of cases caused by a microdeletion in chromosomal region 9q34.3 [67] and in some by a mutation in the euchromatin histone methyltransferase 1 (*EHMT1*) gene [68, 69]. In all cases, however, loss of function of the *EHMT1* gene is the causative factor. Its core phenotype comprises developmental delay/intellectual disability, hypotonia and distinct facial dysmorphisms, and may be associated with congenital heart and/or renal defects and epilepsy [70]. The behavioural phenotype of Kleefstra syndrome constitutes particular sleep disturbances, characterized by frequent awakenings and daytime sleepiness, and marked loss of activity [71]. With respect to course, it has been demonstrated that the severity of behavioural and motor deficiencies such as fixed flexure of arms and hands, increases over time and debuts after adolescence, pointing at a neurodegenerative pattern [72]. Over time, reduced motor activity, markedly restricted social interactions and minimal to absent behavioural initiative and emotional responsivity become most prominent, a cluster of symptoms that meets the criteria for the syndrome of apathy. This constellation of motor and emotional features may easily be misdiagnosed as either mood disorder [73] or catatonia [74]. It is understandable, therefore, that treatment with antidepressants or benzodiazepines cannot be effective.

Beta-Propeller Protein Associated Neurodegeneration (BPAN; OMIM:300894)

Neurodegeneration with brain iron accumulation (NBIA) comprises an array of progressive brain disorders presenting with neurological and psychiatric symptoms, sometimes accompanied by intellectual impairment and behavioural problems. Originally, the neuropathologists Hallervorden and Spatz described in 1922 a typical phenotype characterized neurologically by movement disorders and pathologically by iron accumulation in the basal ganglia [75]. Since the late sixties of the past century, several progressive movement disorders with iron excess in different parts of the basal ganglia have been described that, with the

introduction of brain magnetic resonance imaging techniques, could be further differentiated and can clinically be subdivided into two major groups: early onset / rapid deterioration, and late onset / slow deterioration [76].

NBIA has to be suspected when brain MRI findings point at abnormal iron accumulation in the basal ganglia, particularly globus pallidus or substantia nigra, in combination with dystonia and Parkinsonism. Until recently, seven genetic types of NBIA could be identified, of which six are inherited in an autosomal recessive and one in an autosomal dominant way.

Recently, Kruer and co-workers [77] described a novel NBIA showing an additional specific neuroimaging pattern in the substantia nigra together with global cerebral atrophy. Clinically, this NBIA is different than the other types and does not fit within the aforementioned subdivision into two groups. Here, the disease starts with early childhood intellectual impairment that remains static during several decades after which progressive cognitive decline occurs and neurological symptoms emerge, especially dystonia and Parkinsonism, and therefore termed Static Encephalopathy of childhood with Neurodegeneration in Adulthood (SENDA). Shortly thereafter, it became clear that this condition is caused by *de novo* heterozygous mutations in the WD repeat-containing protein 45 (*WDR45*) gene (OMIM:300526) located in Xp11.23 [78]. Given the specific properties of the protein encoded by *WDR45*, the name Beta-propeller Protein Associated Neurodegeneration (BPAN) was suggested to be most appropriate [79, 80]. Nowadays, it has been demonstrated that the clinical phenotype of this X-linked dominant NBIA disorder is in its early phase characterized by developmental delay and intellectual disability, and frequently associated with epileptic seizures. The second phase, generally starting in the second or third decade, is clinically dominated by progressive cognitive and motor deterioration with prominent dystonia and Parkinsonian symptoms, ultimately leading to dementia [81].

Since in the beginning of the second phase, symptoms from the apathetic/autistic and anxiety/mood spectrum may be present, these can be wrongly diagnosed as a depressive disorder instead of contingent upon the symptom profile in patients with early stages of Parkinson's disease. Therefore, antidepressants will not be effective. Treatment with Levodopa/carbidopa in patients with BPAN may result in temporal or partial effects on motor function [79, 82].

Lysosomal Disease

Although metabolic disorders generally debut at early age, some of these may start in late adolescence or early adulthood. In case of lysosomal disease such as Niemann-Pick type C (mutation *NPC1* gene; 18q11.2 [OMIM:257220] or *NPC2* gene; 14q24.3 [OMIM:607625]) a late onset presentation may, apart from pre-existing (mild) developmental delay, manifest firstly with a schizophrenia-like psychosis with or without catatonic symptoms [83, 84]. Another example is mucopolysaccharidosis type IIIB (MPSIIIB; Sanfilippo B; OMIM: 252920) that is caused by a mutation in the *NAGLU* gene (17q21.1; OMIM: 609701) resulting in a deficiency of N-acetyl- α -D-glucosaminidase. MPSIIIB is characterized by later onset developmental delay followed by slow progressive dementia starting from the fourth decade [85, 86]. These two lysosomal diseases do not present with specific dysmorphisms and can therefore be easily misdiagnosed as either late onset schizophrenia or early onset Alzheimer's dementia.

DISCUSSION AND CONCLUSIONS

In this paper, the difficulties in the diagnostic process and the choice for rational treatment strategies in intellectually disabled patients with challenging behaviours and/or neuropsychiatric symptoms are presented. Because of the regular co-occurrence of psychiatric and/or neurological symptoms in this group of patients, some examples of genetic syndromes are given that are characterized by a psychopathological and/or neurological phenotype.

As mentioned previously, psychiatric symptoms may originate in the context of a traditional psychiatric disorder that presents frequently with an atypical symptomatology like disinhibited behaviours and/or self-injuries, or as part of a so called psychopathological phenotype. Moreover, a psychiatric disorder may be related to an underlying somatic/neurological disease. In addition, both challenging behaviours and psychiatric symptoms may be drug-related (e.g. antiepileptics and psychotropics). Finally, disinhibited behaviours frequently arise as a result of environmental factors.

As known for several decades, both depressive diseases and anxiety disorders frequently manifest with either pronounced irritability, perseverative/compulsive behaviours and motoric signs, or an exacerbation of challenging behaviours, and are therefore often

symptomatically treated with antipsychotics instead of with antidepressants [87-89]. Concerning antidepressant medications, it has been shown that these compounds, particularly SSRIs, reduce symptoms in only half of the patients [90]. When depressive symptoms occur in the context of a so called unstable mood disorder or a bipolar affective disorder, treatment with antiepileptics, preferably valproic acid is the method of choice [45, 91].

By using categorical diagnostic systems, repetitive/stereotyped and/or disinhibited behaviours may easily meet the criteria for autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD). Although some beneficial effects of atypical antipsychotics, especially risperidone and aripiprazole, on autistic symptoms (i.e., irritability and repetition) have been reported [92, 93], systematic reviews could not substantiate this claim for either risperidone or aripiprazole [94, 95]. This holds, a fortiori, for ADHD [96]. As reported recently, for the treatment of ADHD in intellectually disabled patients in whom anxiety disorders or severe tics are frequently also present, the selective noradrenaline reuptake inhibitor amoxetine should be preferred [97].

In case of challenging behaviours in general, prescription of neuroleptics, particularly second generation antipsychotics, has been demonstrated to be only marginally effective [98, 99]. It should be stressed that such treatments are regularly accompanied by unwanted side effects especially significant weight gain and the development over time of dislipidemia and/or diabetes mellitus, subsumed under the term metabolic syndrome [100,101].

With respect to psychopathological phenotypes, it has become obvious that certain genetic syndromes can be characterized by their specific psychiatric or neuropsychological profile like e.g. 22q11.2 micro-deletion syndrome and Koolen-De Vries syndrome. In those cases, routine pharmacological treatments are generally ineffective. For some syndromes, such as Prader-Willi syndrome, a circumscribed subset of recurrent affective/psychotic symptoms may occur, especially when the aetiology is a maternal uniparental disomy. These patients develop, starting in their late adolescence, a subacute polymorphous psychosis with a symptom profile that meets the criteria for cycloid psychosis [102-106]. In some cases, an increase of psychomotor symptoms dominates the psychotic-syndrome resembling catatonia [107]. After several relapses with generally full recovery, course and

symptomatology overlap that of a bipolar affective disorder and the psychosis should therefore be treated primarily with mood stabilizing agents e.g. Lithium or valproic acid [54, 108].

As can be inferred from the aforementioned, the contribution of psychopharmacological agents to the reduction of ID-related behavioural problems and psychiatric symptoms is relatively poor. This is affirmed by the results of the only placebo controlled study with haloperidol and risperidone showing the largest effect on challenging behaviours of placebo [109]. Furthermore, controlled discontinuation of antipsychotics prescribed for behavioural symptoms over multiple years has demonstrated improved behavioural functioning and amelioration of metabolic parameters [110-112]. In fact, challenging behaviours may even be the first and only manifestation of motor or autonomic side effects of psychotropics e.g. acathisia [42].

Given the frequent polymedication in ID patients and the absence of reliable data on plasma concentration-effect relationship of psychotropics in this group of patients, it is highly recommended to measure the plasma concentration of antipsychotics, antidepressants and antiepileptics and, if applicable, their active or toxic metabolites. As mentioned before, the latter is of special importance since the clinical impact is influenced by the genetically determined capacity of the cytochrome P450 (CYP) isoenzyme system, in particular CYPs 2D6, 2C9 and 2C19. It should be noticed that CYP 2D6 and CYP 2C19 are responsible for metabolizing a range of antipsychotics and antidepressants, and polymorphism for these enzymes may result in ultra rapid or poor biotransformation which, in turn, defines effect and toxicity [40, 113, 114]. CYP-genotyping prior to the prescription of psychotropics especially in case of co-medication with antiepileptics has therefore always to be considered.

Since challenging behaviours are essentially dependent on environmental variables and no rational psychopharmacological treatment is available for such behaviours, again, functional re-analysis of the behavioural history is needed in order to define appropriate psychological and/or behavioural interventions. To this end, several treatment programs based on operant learning and cognitive models with documented efficacy can be employed such as differential reinforcement strategies (e.g. to reduce inappropriate vocalisations), low level problem solving, assertiveness and goal management training [115-118]. In certain genetic disorders like Noonan

syndrome and Turner syndrome, specific impairments in affective information processing and social interaction can be identified and may be modulated by means of targeted social-cognitive training [119-121].

In conclusion, from the here presented data, it has become obvious that a careful investigation and analysis of abnormal behaviours in patients with ID is essential for establishing an appropriate diagnostic process leading to a diagnostic hypothesis with a subsequent, individually targeted, treatment program including regular evaluation of effectiveness and potential side effects. This holds particularly for some genetic syndromes that may be accompanied with a specific set of behavioural, psychiatric or neurological symptoms that may be of major clinical relevance for prognosis. Albeit that psychotropics may be effective in the treatment of psychiatric symptoms and useful for alleviating challenging behaviours in patients with intellectual disabilities, behavioural interventions have to be employed where possible, and effectiveness as well as side effects of psychopharmacological interventions should be monitored regularly.

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