

Review Article

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First-episode psychotic disorders in the wake of the COVID-19 pandemic: a descriptive review of casereports

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Abstract

Objective: Since the onset of COVID-19 pandemic, many case reports and case series dealt with new-onset psychotic disorders in patients either infected with SARS-CoV-2 or thematically linked to the pandemic, but without an infection. Our aim was to provide a comprehensive collection of these reports to illustrate the nature of these psychoses. **Methods:** We conducted a literature search in MEDLINE, Embase, PsycINFO, using search terms regarding first-episode psychotic disorders in the context of corona. **Results:** 96 case reports or case series covering 146 patients (62 without and 84 with SARS-CoV-2 infection) were found. Compared to patients without infection, patients with infection showed significantly more often visual hallucinations (28.6% vs 8.1%), confusion (36.9% vs 11.3%), an acute onset of illness (88.5% vs 59.6%) and less often depression (13.1% vs 35.5%) and a delusional content related to the pandemic (29.5% vs 78.3%). Both groups had an equally favourable outcome with a duration of psychosis ≤ 2 weeks in half and full remission in two-thirds of patients. In patients with infection, signs of inflammation were reported in 78.3% and increased CRP in 58.6%. While reports on patients with infection are continuously published, no report about patients without infection was found after July 2020. **Conclusion:** Cases without infection were considered reactive and originated all from the first wave of the corona pandemic. In cases with infection, inflammation was considered as the main pathogenetic factor but was not found in all patients. Diagnosis was impeded by the overlap of psychosis with delirium.

Summation

- COVID-related first episode psychoses without SARS-CoV-2 infection are most probably stress-related and occurred only during the first wave of the pandemic.
- First episode psychoses accompanying SARS-CoV-2 infection are of much more ambiguous origin. Inflammation seems to be important, yet in many patients only low-grade inflammation was found.
- Short-term outcome in both groups of psychoses is very good. There are arguments for a favorable long-term prognosis, but until now data of follow up are lacking.

Consideration

- Since this paper relies on case reports, the findings might be distorted by various aspects of reporting bias
- Etiological considerations concerning these psychoses are hampered by the poor understanding of the pathophysiology of psychosis in general
- More systematic investigations in the pathophysiology, epidemiology, and outcome of these psychoses are warranted

Introduction

The SARS-CoV-2 pandemic has led to an unprecedented medical, social and economic crisis. While COVID-19 was considered first to affect predominantly the respiratory tract, it soon became obvious that it is a multisystem illness (Dinakaran *et al.*, 2020; Steardo *et al.*, 2020; Yamamoto *et al.*, 2020). SARS-CoV-2 is considered to be ‘neurotropic’ as it can enter the central

nervous system (CNS) and very early during the pandemic reports on neurologic and psychiatric manifestations started appearing (Mao *et al.*, 2020; Varatharaj *et al.*, 2020). The neuropsychiatric dimension of COVID-19 extended not only to people infected by the virus but as well to the general public. While the whole society suffered from the fears, restrictions and losses which came by the pandemic, those infected by the virus had to cope additionally with the effects of the virus on the body and the brain.

New-onset psychosis is one of the possible neuropsychiatric sequelae. Since the beginning of the pandemic, concerns were expressed about an increase of psychotic disorders (Troyer *et al.*, 2020; Watson *et al.*, 2021) and the term 'COVID-psychosis' became popular, especially in the lay press. As early as January 2020, observations on occurrence of first-episode psychoses in conjunction with COVID-19 were made (Hu *et al.*, 2021) and since then numerous case reports have appeared. In this respect, there are two types of psychoses found in the literature. On the one hand, psychoses originated in otherwise healthy persons without being infected and on the other hand in those suffering from an acute infection with SARS-CoV-2. The first ones are not mere first-episode manifestations of schizophrenia in times of COVID-19, but in most instances distinct from schizophrenia due to symptoms, course, and outcome. These psychoses are mostly considered to be related to stress caused by the pandemic and are thematically intimately linked to issues of the pandemic. Of course, the question remains whether this demarcation from schizophrenia is really valid and sustainable in the long run.

There is no reason to assume that patients infected with SARS-CoV-2 do not suffer from stress and will not be prone for the same kind of psychosis. Yet in these patients, additional biological pathomechanisms must be considered. There are many arguments linking psychosis with infections and inflammation. Since the occurrence of schizophrenia-like psychoses during the pandemic of Spanish flu in 1918/19 (Menninger, 1919) especially viral infections are considered a possible origin of psychosis (Torrey & Peterson, 1976; Yolken & Torrey, 2008). Inflammation and auto-immunological processes might serve as decisive links between infection and development of psychotic symptoms (Kępińska *et al.*, 2020; Watson *et al.*, 2021). In a substantial proportion of schizophrenic patients, elevated markers of inflammation have been found, and the 'vulnerability-stress-inflammation' model of schizophrenia was proposed (Müller *et al.*, 2015; Müller, 2018). The importance of immune processes is furthermore underlined by the Psychiatric Genomics Consortium finding of a variety of risk genes for schizophrenia regulating immune functions (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Yet, up to now all these data connecting psychosis, viral infection and inflammation are just small pieces in the intriguing puzzle of the biological basis of psychosis which is still far from forming a coherent picture.

The combination of direct invasion into the brain, (hyper)inflammation and autoimmune processes is considered to be the cause for neurologic and neuropsychiatric sequelae for SARS-CoV-2 infection, too (Stearo *et al.*, 2020; Tancheva *et al.*, 2020). Psychosis is especially linked to coronaviruses as already the former epidemics of coronaviruses SARS and MERS were suspected to increase psychotic disorders (Brown *et al.*, 2020). Beyond this, also the less pathogenic corona strains HKU1 and NL63 (causing mild flu-like disorders) have been linked to schizophrenia as antibodies against these were found more often in schizophrenic patients than in controls (Severance *et al.*, 2011). For COVID-19, the situation is further complicated by an additional risk factor as some medications broadly used for treatment

(especially corticosteroids and hydroxychloroquine) carry a risk for psychosis, too.

The aim of this observational study is to provide a comprehensive collection of reports of first-episode psychoses occurring during the pandemic, in persons with and without infection. A similar collection of cases with and without infection was performed by Watson *et al.* (2021) early during the pandemic. While psychoses with infection were covered by some smaller reviews (Parra *et al.*, 2020; Tariku & Hajure, 2020) and a large systematic review (Smith *et al.*, 2021), reviews for patients without infection lack until now. Thus, in this paper we want to fill this niche and review cases of first-episode psychoses during the pandemic in persons with as well as without COVID-19 infection. We will put special emphasis on the clinical presentation of the psychoses in the two groups of patients, its treatment and outcome, and the difficulties to diagnose these patients appropriately, a problem which applies especially for the patients with infection. We will present key clinical features in a descriptive comparison to illustrate similarities and differences.

Methods

We conducted our review following the SANRA-criteria for quality assessment of narrative review articles (Baethge *et al.*, 2019). The literature search was conducted in PubMed, Embase and PsycINFO, using the search terms [(COVID-19 OR SARS-CoV-2 OR corona) AND (psychosis OR psychotic OR mania OR manic OR bipolar OR hallucination OR delusion or paranoi* OR cataton*)] searching for reports on first-episode psychotic disorders in the context of corona infection. The search covers publications until December 12th, 2021. Additionally, the bibliography of relevant papers was reviewed.

Inclusion and exclusion criteria

We selected all case reports or case series presenting these features: 1) first-episode psychosis; 2) other psychiatric disorders accompanied by prominent hallucinations or delusions (e.g. affective states with 'psychotic symptoms'); 3) patients had to be either infected with SARS-CoV-2, proven by polymerase chain reaction (PCR) or antibody tests or patients whose first-episode psychosis was timely and thematically linked to the pandemic, but who tested negative for SARS-CoV-2; 4) patients with delirium were only included if there was a time span during which they were considered not to be delirious but psychotic. Excluded were 1) persons <18 years (for a review covering children and adolescents see Javed & Shad, 2021); 2) patients with prior episodes presenting any psychotic symptoms; 3) patients with postpartum psychosis; 4) patients with 'pure' catatonia, without delusions or hallucinations (as e.g. published by (Amouri *et al.*, 2020; Mulder *et al.*, 2020)), due to the ambiguous aetiology of catatonia 5) cases of 'pure' mania without psychotic symptoms 6) cases with 'pure' delirium.

Extracted items

Personal data

Country of origin of the report, date of occurrence of psychosis, age, sex, previous psychiatric history, family history of psychosis.

Illness-related data

Psychopathology, COVID-19 as content of delusions, reason for admission to inpatient treatment (due to psychosis; due to COVID-19; due to both; due to other causes), acute onset (duration of untreated psychosis ≤ 7 days), presence of inflammation,

C-reactive protein (CRP), cerebro-spinal fluid (CSF), CT or MRT scans (only changes with a potential relevance for COVID), duration of psychosis (≤ 1 week; > 1 to ≤ 2 weeks; > 2 to ≤ 4 weeks; 1 to ≤ 2 months; > 2 months), severity of COVID-19 (no = no somatic symptoms; mild = outpatient treatment for COVID-19; severe = inpatient treatment except for treatment in intensive care unit (ICU) for COVID-19; very severe = treatment for COVID-19 in ICU), relation between diagnosis of infection/beginning of COVID-19 and onset of psychosis (patients with psychosis, but without somatic symptoms of COVID-19; psychosis before start of somatic symptoms; psychosis concomitant with somatic symptoms; psychosis when somatic symptoms had abated), diagnosis as provided by the authors ("psychosis (px)" was filled in if the authors provided no specific diagnosis or discussed differential diagnoses without making a decision).

Treatment and outcome

Duration of inpatient treatment, treatment with antipsychotics (AP) (dosage at discharge converted to risperidone equivalents based on the data of Leucht *et al.* (2014)), treatment with drugs at risk for psychosis (chloroquine (CQ); hydroxychloroquine (HCQ); glucocorticoids (CS); treatment with other agents, if the authors considered it as putative causal), outcome (full remission; improvement; not improved), treatment response (fast response to treatment was documented if reported by the authors or remission occurred within 1 week).

Statistics

To characterise the two groups of patients, we performed descriptive statistics reporting mean, median and standard deviation for continuous variables and percentages for nominal variables. For comparing the two groups via hypothesis testing, we used chi-square tests with continuity correction for nominal and Mann-Whitney U-tests for continuous variables (Table 4).

Results

The search retrieved 4.035 hits (PubMed 762, Embase 1505, PsycINFO 1768). After exclusion of duplicates and irrelevant papers, 96 publications covering 146 patients could be found. Thirty-one papers comprising 62 patients dealt with patients developing psychosis without being infected with SARS-CoV-2, 67 papers covering 84 patients reported on patients with SARS-CoV-2 infection. Table 1 shows the distribution of the papers' countries of origin. Cases were reported from all continents, with almost half (46.5%) of them originating from Europe and about a quarter (22.9%) from the USA.

One paper presenting 10 cases (Parra *et al.*, 2020) was included as far as the aggregate presentation of data allowed. There is one multicentre study (Valdés-Florido *et al.*, 2021) which recruited systematically patients with brief psychotic disorders according to DSM-5 during the climax of the national lockdown in Spain (March 14th to May 14th 2020), whose patients are not included in this paper for lack of comparability and data.

Patients without infection

All cases of patients presenting first onset psychosis without being infected with SARS-CoV-2 originated from January to July 2020. Table 2 presents the individual data of the patients, Table 4 presents the aggregate findings. Patients without infection were 43.3 years old as a mean (41.5 as median) and equally distributed

Table 1. Geographic origin of 62 cases of psychosis without SARS-CoV-2 infection and 84 cases with infection

	Cases without SARS-CoV-2 infection	Cases with SARS-CoV2 infection
Europe	37	30
Spain	13	15
Italy	11	2
UK	9	6
USA	6	27
South America	3	6
Asia	10	19
Africa	5	2
Australia	1	0
Summ	62	84

concerning sex. Psychopathology was characterised by delusions which were typically centred on COVID-related themes in more than three-quarters (78.3%) of patients. Common issues were the conviction of being infected (despite negative test results), the fear to spread the virus and such being responsible for the death of others or the urge to fulfil divine commands to save the world from the virus. Religious contents were found in 29% of patients. Hallucinations (mostly acoustic), disorganisation, and agitation were present in about 40 to 50% of patients, anxiety and depression in about a third of patients. Twenty (35.7%) patients had a history of previous psychiatric illness, half of them anxiety disorders.

Most patients were admitted to hospital for psychosis and treated as inpatients, only 6 (9.7%) (Martin, 2020; Mehra *et al.*, 2020; Oloniniyi *et al.*, 2021) were treated as outpatients. Inpatient treatment ranged between 1 and 42 days, with a mean of 11.2 (median 8) days. Duration of psychosis was ≤ 2 weeks in more than 70% of patients. Most patients were treated with antipsychotics (AP), the mean dose equivalent was 3.3 mg risperidone. For four patients, no AP were used (Martin, 2020; Ambar Akkaoui *et al.*, 2021). Six patients discontinued the medication with APs within 1 month (D'Agostino *et al.*, 2020; Loehde & Novakovic, 2021; Oloniniyi *et al.*, 2021; Shakya & Upadhaya, 2021), of whom one suffered a relapse after 1 month (Loehde & Novakovic, 2021).

Outcome with full remission occurred in two-thirds of patients, and almost as many reports describe a fast response to antipsychotic treatment. Only the paper of Deshpande & Livingstone (2021) presents three patients with slow response to treatment and long inpatient stays. These patients were selected for reporting among others because of their advanced age and to illustrate the deleterious effects of social isolation on elder persons normally living an active life. There are more reports of this kind (de Oliveira, 2021; Lynch & Bastiampillai, 2021). There is no information about the further fate of patients except for two, who were reported to be well after about half a year (de Oliveira, 2021; Marouda *et al.*, 2021).

Two-thirds of patients were diagnosed with either 'brief psychotic disorder' (BPD) according to DSM-5 or 'acute and transient psychotic disorder' (ATPD) according to ICD-10. This includes five patients diagnosed with 'brief reactive psychosis' and five patients with 'cycloid psychosis', a type of brief psychosis most closely related to ICD-10 ATPD, polymorphic subtype (Giné

Table 2. Reports on patients with COVID-19-related psychosis without SARS-CoV-2 infection

Author	Country	N, Cases	Age	Sex	Inpat. (d)	Durat. px	Outcome	Diagnosis	Treatment, AP	Fast response	Psych. hist.	Psych hist./COVID-related delusions; special features
Ambar Akkaoui et al. (2021)	FRA	1	57	F	NA	NA	1	Induced px	0		F4	Subsyndromal anxiety/ self-treatment with HCQ
Anmella et al. (2020)	ESP	1	42	F	2	1	2	BRP	1.3	Yes		HCW; del. of catastrophe
Apurva et al. (2021)	IND	1	25	M	NA	5	2	Delusional disorder	6.5		F4	Hypochondriasis/ del. of being infected
Belvederi Murri et al. (2021)	ITA	1	19	F	NA	4	1	Schizophrenia	7.25			Subtle symptoms already some months before
Brahmi et al. (2021)	TUN	1	29	M	NA	NA	2	Px	4		F7	Intellectual disability; tuberous sclerosis, epilepsy/del. of being responsible for pandemic
Cerejeira et al. (2021)	ESP	1	27	F	NA	1	1	ATPD	2	Yes		
Chandra et al. (2020)	IND	1	34	F	7	2	1	ATPD	4	Yes	F4	Anxious personality/ del. of getting infected as punishment
Ciria Villar & D�a Sah�n (2020)	ESP	1	42	F	NA	NA	2	ATPD	NA	Yes	F4	HCW
Costardi et al. (2021)	BRA	1	48	M	outp	NA	NA	BPD	NA	Yes		Del. of wanting to die to save the world
D'Agostino et al. (2020)	ITA	1	73	M	25	3	1	ATPD	3			Del. of being infected
		2	61	M	14	3	1	ATPD	3.75			Del. to be infected, of end of world
		3	47	F	9	2	1	ATPD	1.25	Yes		Water intoxication
		4	55	M	18	3	1	ATPD	4	Yes		Del. of being infected
		5	23	F	6	1	1	ATPD	2			
		6	61	F	11	2	1	ATPD	1.5	Yes		Del. of punishment by God for not attending funerals during lockdown
de Oliveira (2021)	BRA	1	70	F	no	2	1	Px	1	Yes		
Deshpande & Livingstone (2021)	GBR	1	71	F	21	3	1	BPD	2.67			Anxiety
		2	62	F	1	5	3	Px	2		F4	Anxiety
		3	71	F	42	5	3	Px	4		F4	Del to get test results from god
Dhir et al. (2020)	USA	1	56	M	NA	NA	1	Induced px	0			Self-treatment with acetyl-L-carnitine; del. of being prosecuted for self-treatment
Doufik et al. (2021)	MAR	1	28	M	14	4	1	Schizophreniform px	3	Yes		Del. of being the origin if COVID
		2	24	M	9	NA	3	ATPD	5	Yes	F1	Cannabis use/ Del. of being sent by God to inform people how to deal with COVID

Table 2. (Continued)

Finatti <i>et al.</i> (2020)	ITA	1	30	M	NA	1	1	BPD	3	Yes	Delusion that quarantine is a show	
		2	40	F	NA	1	1	BPD	5	Yes		
		3	40	M	10	2	1	Px	2.67	Yes		
Giné Servén <i>et al.</i> (2021)	ESP	1	33	M	3	1	1	CP	4	Yes	F3	Depression/del. of infection
		2	39	F	5	2	1	CP	4	Yes	F3	Depression/ del. of catastrophe
		3	37	M	7	2	1	CP	5.25	Yes	F4	OCD
		4	56	M	3	1	1	CP	4	Yes	F3	Depression
		5	45	F	7	3	2	CP	6.67	Yes	F3	Depression/ del. of catastrophe
Huarcaya-Victoria <i>et al.</i> (2020a)	PER	1	38	F	14	1	1	BPD	2	Yes	Del. of being infected	
Kusen <i>et al.</i> (2021)	IRL	1	24	M	15	4	1	Px	4		F4, F8	Anxiety; autism spectrum disorder /del. of 'being trapped in a virus mind game'
Lazzari <i>et al.</i> (2020a, b, c)	GBR	1	50	M	7	2	2	ATPD	NA	Yes	Del. of Coronavirus being government's strategy to control society; planning to kill family to reduce suffering	
		2	57	F	7	2	1	ATPD	NA	Yes	Del. that Coronavirus is a conspiracy	
		3	64	F	7	2	1	ATPD	2.8	Yes	Del. of Coronavirus being connected with the devil	
		4	38	M	7	2	1	ATPD	1.3	Yes		
		5	44	F	7	2	1	ATPD	2.7	Yes	F4	Anxiety
		6	59	F	7	2	1	ATPD	5.25	Yes	F3	Depression/Del of living like Jesus and saving people
Loehde & Novakovic (2021)	DNK	1	37	F	NA	NA	1	ATPD	NA	Yes	Antipsychotic terminated after 1 month, recurrence after 3 months	
Lynch & Bastiampillai (2021)	AUS	1	78	F	4	4	1	Px depression with catatonia	1.3		Treatment with ECT; Del. of guilt for pandemic	
Marín <i>et al.</i> (2021)	ESP	1	29	M	7	2	1	Induced BPD	2.7		F1	Cannabis withdrawal syndrome
Marouda <i>et al.</i> (2021)	GRE	1	34	M	13	NA	NA	BPD	5.25	Yes	Del. of pandemic being a fight of good versus evil with him having a special mission	
Martin (2020)	USA	1	45	F	outp	2	1	BPD	0	Yes	HCW; del. of being infected	
		2	45	F	NA	NA	NA	BPD	NA	Yes	F3, F4	Depression, anxiety; HCW
		3	45	F	outp	NA	NA	BPD	0		F4	Anxiety; HCW; del. of being infected
Mehra <i>et al.</i> (2020)	IND	1	60	F	outp	NA	NA	MDE with px sy	1.3		F3	Depression; del. of being infected
Oloniyyi <i>et al.</i> (2021)	NGA	1	41	F	outp	2	1	ATPD	2.5	Yes	Del. to have a mandate from God to end the pandemic	
		2	40	F	outp	2	1	ATPD	2.5	Yes	Del. of being responsible to find a cure for COVID-19	

(Continued)

Table 2. (Continued)

Author	Country	N, Cases	Age	Sex	Inpat. (d)	Durat. px	Outcome	Diagnosis	Treatment, AP	Fast response	Psych. hist.	Psych. hist./COVID-related delusions; special features
Rivas <i>et al.</i> (2020)	ESP	1	60	M	1	2	2	BRP	2.7	Yes		HCW; del of imminent death due to COVID-19
Sarli <i>et al.</i> (2020)	ITA	1	59	M	15	3	2	MDE	2			Del. of ruin, suicide being the only solution
Shakya & Upadhaya (2021)	NEP	1	20	M	7	1	NA	Induced px	2	Yes	F1	<i>Polytoxicomania</i> / cannabis-induced px
Shanbour <i>et al.</i> (2020)	USA	1	23	M	NA	NA	2	Px	NA			Del of being God's messenger of impending apocalypse
		2	30	F	NA	NA	2	xPx	NA			Del. of pseudocyesis, caused by the virus
Sunbul <i>et al.</i> (2021)	IND	1	34	M	20	3	1	BPD	2.7			Living alone, lost job through pandemic; del. of being infected
		2	53	M	NA	3	1	BPD	NA			Living alone, lost job through pandemic; del. of being infected
		3	31	M	17	3	1	BPD	NA			Living alone, lost job through pandemic; del. of having found a cure for COVID-19 and being therefore prosecuted
Tuna <i>et al.</i> (2020)	TUR	1	34	M	14	3	2	ATPD	5.25			Del. of being the source of COVID-19
Valdés-Flrido <i>et al.</i> (2020)	ESP	1	33	M	2	1	1	BRP	2.7	Yes		
		2	32	F	14	2	1	BRP	4		F4	<i>Adjustment disorder</i> ; del. that a friend has died from COVID-19
		3	45	M	3	1	1	BRP	1.5	Yes		Del. of the Illuminati being behind the pandemic
Zhang <i>et al.</i> (2020)	CHN	1	20	M	12	2	2	ATPD	5.33	Yes		Del. of being infected
Zulkifli (2020)	MYS	1	31	M	3	2	1	BPD	NA	Yes		Del of world's end

Column headings: Country: Code according to ISO 3166 Alpha-3; Inpat. (d): inpatient treatment (days); Duration px: duration of psychosis (1: ≤1 week; 2: >1–2 weeks; 3: >2–4 weeks; 4: 1–2 months; 5: >2 months); Outcome (1: full remission, 2: improvement, 3: no improvement); Treatment AP (treatment with antipsychotics at discharge, risperidone equivalents); Fast response (to treatment: as stated by the authors or within ≤ 1 week); Psych. hist.: history of previous psychiatric illness according to categories of ICD-10 (diagnosis is set in *italics*); COVID-related delusions are described if present.

Abbreviations: ATPD: acute and transient psychotic disorder; BPD: brief psychotic disorder; BRP: brief reactive psychosis; CP: cycloid psychosis; Del.: delusion; ECT: electroconvulsive therapy; F: female; F1 mental and behavioural disorders due to psychoactive substance use; F3 mood [affective] disorders, F4 neurotic, stress-related and somatoform disorders, F7 mental retardation; F8 disorders of psychological development; HCQ: hydroxychloroquine; HCW: health care worker; M: male; MDE: major depressive episode; NA: data not available; Outp: treatment as outpatient; Px: psychosis; sy: symptoms

Table 3. Reports on patients with SARS-CoV-2 infection

Author	Country	Age	Sex	COVID severity	Somatic sy/px	Inpat. (d)	Durat. px	Out-come	Diagnosis	Treatment (risperidone equivalents)	Fast response	Psych. hist.	Psychiatric history/special features
Alba <i>et al.</i> (2021)	ESP	40	M	2	4	NA	1	1	Secondary px	1	Yes		Lack of concern, px after recovery from COVID
Al-Busaidi <i>et al.</i> (2021)	OMN	46	M	3	4	NA	2	1	ATPD	1.3			
Alvarez-Cisneros <i>et al.</i> (2021)	MEX	43	M	1	1	NA	NA	NA	Manic px	NA			Px as only symptom of infection
Ariza-Varón <i>et al.</i> (2021)	COL	48	F	2	3	NA	2	1	Px, encephalitis	NA	Yes		Improvement with glucocorticoids
Austgen <i>et al.</i> (2021)	USA	52	F	2	4	47	4	1	Px depression catatonia	NA			Antipsychotics, glucocorticoids not effective, improvement with ECT
Atris <i>et al.</i> (2021)	OMN	46	M	2	3	Outp	NA	2	Px, Diff dx delirium	1.3			Pat on hemodialysis
Baral <i>et al.</i> (2021)	USA	53	M	2	4	5	2	1	BPD	0	Yes		Px 5 weeks after infection; single injection of haloperidol; px caused by social stigma?
Benjelloun <i>et al.</i> (2020)	MAR	46	M	3	3	NA	1	1	Chloroquine induced px	0	Yes		Amisulpride 100mg for 1 week. Stop of chloquine
Bernard-Valnet <i>et al.</i> (2020)	CHE	64	F	1	4	NA	1	2	Meningoencephalitis	0	Yes		Tonic-clonic seizure, meningoencephalitis; para-infectious?
Borovina <i>et al.</i> (2021)	CRO	74	F	2	3	12	2	1	PDGMC	6	Yes		Fast resolution of px sy. Died for unknown reasons
Boulos <i>et al.</i> (2020)	USA	56	M	3	4	18	3	2	Substance-induced px	5			Two doses of HCQ 1 week before onset of px as cause for px?
Caan <i>et al.</i> (2020)	UK	43	M	3	4	10	3	2	Catatonia	0			pxcatatonia; treatment with lorazepam
Chacko <i>et al.</i> (2020)	USA	73	M	2	3	NA	3	1	Px	0.7			mutism; suicid attempt; ECT
Clouden (2020)	USA	46	F	3	4	NA	5	1	Persistent delirium	3		F4	PTSD /hallucinosi for 15 weeks
Correa-Palacio <i>et al.</i> (2020)	ESP	43	M	3	4	30	4	1	Affective px	11.3		F1	Substance abuse (cocaine), abstinent for 2 weeks
Costardi <i>et al.</i> (2021)	BRA	45	F	NA	NA	NA	NA	NA	BPD	NA			
DeLisi (2021)	USA	34	M	1	1	NA	5	2	Schizophreniform disorder	4			Provisional diagnosis

(Continued)

Table 3. (Continued)

Author	Country	Age	Sex	COVID severity	Somatic sy/px	Inpat. (d)	Durat. px	Out-come	Diagnosis	Treatment (risperidone equivalents)	Fast response	Psych. hist.	Psychiatric history/special features
Desai <i>et al.</i> (2021)	USA	55	F	3	4	14	3	1	Px	2			Presumed causes: COVID, GC and stress.
Duyan & Ozturan (2021)	TUR	31	F	2	4	5	1	1	Substance-induced px	3.3	Yes		Px due to favipiravir?
Elfil <i>et al.</i> (2021)	USA	20	F	1	4	NA	NA	NA	Covid-19 induced px	0			Px catatonia. Treatment with lorazepam
Elkhalel <i>et al.</i> (2020)	QAT	23	M	4	3	15	3		CLOCC	0			prominent hallucinations delirium; died
Faisal <i>et al.</i> (2021)	IDN	48	M	3	4	16	2	1	BPD	NA		F1	History of cocaine use; urine test negative
Ferrando <i>et al.</i> (2020)	USA	30	M	1	1	4	1	2	Px	0,3	Yes		'lack of preoccupation'
		34	F	1	1	NA	NA	NA	Px	1		F4	<i>Panic disorder</i> / 'lack of preoccupation'
		33	M	1	1	NA	NA	NA	Px	1.3		F1	<i>Opioid use, on methadone</i> / 'lack of preoccupation'
Gillett & Jordan (2020)	GBR	37	M	2	4	32	2	2	Px	NA			HCW; Suicidally injured; Diff dx delirium
Grover <i>et al.</i> (2021)	IND	31	M	3	3	NA	NA	2	Steroid-induced px	2.7			Suicide attempt; px while on CS
Haddad <i>et al.</i> (2020)	QAT	30	M	2	4	31	1	1	BPD	2	Yes		Very anxious; stop of meds after 4 weeks; Well at follow-up after 3 months
Haddad <i>et al.</i> (2021)	QAT	38	F	2	3	5	2	1	Delirious mania	4	Yes		No stress; stop of meds after 4 months
Huarcaya-Victoria <i>et al.</i> (2020b)	PER	23	F	2	5	9	2	1	Px	4			
		38	F	1	1	10	2	1	Px	5.3		F3	<i>Depressive episode</i>
		47	F	1	1	10	4	1	Px	4			
Ignatova <i>et al.</i> (2021)	BGR	43	M	3	4	NA	3	NA	ATPD	2.7			
Jaworowski <i>et al.</i> (2020)	ISR	NA	M	2	4	2	1	1	BRP	0	Yes		Px stress-related? Discharge without medication
		NA	M	1	3	2	1	1	BRP	0	Yes		Px stress-related? Discharge without medication
		NA	M	2	4	2	1	1	BRP	0	Yes	F1	<i>Cannabis withdrawal?</i> / Px stress-related? Discharge without medication
Jiménez-Fernández <i>et al.</i> (2021)	ESP	71	M	2	3	NA	2	1	Secondary mania	1	Yes		Stop of medication after 3 months; Well at follow-up after 1 year

Table 3. (Continued)

Jozuka <i>et al.</i> (2021)	JPN	55	F	2	3	67	1	NA	Encephalopathy	NA		Px sy as start of severe encephalopathy
Kaggwa <i>et al.</i> (2021)	UGA	52	M	2	4	14	3	1	Mania	6.7		Self-medication with cannabis
Kashaninasab <i>et al.</i> (2020)	IRN	25	M	2	3	NA	3	1	Bipol I disorder with px	11.6		Suicide attempt, treatment with ECT
Kazi <i>et al.</i> (2021)	USA	49	F	2	3	20	4	1	Px	6.7		Stop of meds after 2 months, after 8 months readmission with mania
		56	F	3	3	NA		4	Px	2.3		
Kazi & Hoque (2021)	USA	55	F	3	3	4	1	1	CS-induced px	2	Yes	Start of px 1 week after end of CS
Khatib <i>et al.</i> (2021)	QAT	52	M	4	4	21	3	1	Bipolar I disorder with px	3		Delirium when on CS + HCQ, recovered and discharged without sy. Start of px 2 days later
Kozato <i>et al.</i> (2021)	GBR	55	M	4	4	21	3	1	Px	4		Start of px some days after CS
Kumar <i>et al.</i> (2021)	IND	62	F	NA	4	Outp	5	1	Px	1		
Lanier <i>et al.</i> (2020)	USA	58	M	2	3	NA	2	2	Px	1.25	F1, F4	Polysubstance abuse, anxiety; hepatic encephalopathy
Lim <i>et al.</i> (2020)	GBR	55	F	3	4	20	4	2	Px	NA		Delirium px, Capgras syndrome
Lorenzo-Villalba <i>et al.</i> (2020)	FRA	33	F	2	3	14	3	1	Px	2.7		Discontinuation of AP at discharge
Łoś <i>et al.</i> (2021)	POL	39	M	3	3	NA	1	1	ATPD	2.7	Yes	
Losee & Hanson (2020)	USA	35	M	1	1	3	1	1	Delirium with px	2.7	Yes	Delirium px; epileptic seizure
Majadas <i>et al.</i> (2020)	ESP	63	M	3	4	14	2	2	PDGMC	6		Delirium px
Makivic <i>et al.</i> (2021)	AUT	46	M	3	3	3	1	1	Dissociative disorder	2		Pulmonary embolism, psychogenic seizures
Mawhinney <i>et al.</i> (2020)	GBR	41	M	3	3	14	3	2	Mania	2.7	F3	Depression / ICU for agitation
(McAlpine <i>et al.</i> , 2021)	USA	30	M	2	3	5	3	1	Autoimmune px	0		Rapid cure with iv immunoglobuline
Mirza <i>et al.</i> (2020)	USA	53	M	3	3	NA	2	2	PDGMC	NA		Command suicidal hallucinations
Mollà Roig (2021)	ESP	43	M	1	1	2	2	1	BRP	2.7	Yes	Stop of AP 2 weeks after discharge; no recurrence until 4 months

(Continued)

Table 3. (Continued)

Author	Country	Age	Sex	COVID severity	Somatic sy/px	Inpat. (d)	Durat. px	Out-come	Diagnosis	Treatment (risperidone equivalents)	Fast response	Psych. hist.	Psychiatric history/special features
Noone et al. (2020)	USA	49	M	3	4	25	3	2	Px	2.67			
	USA	34	F	2	3	17	4	2	Px	2			
Panariello et al. (2020a)	ITA	23	M	3	3	NA	NA	2	Anti-NMDA receptor encephalitis	0		F1	Substance use disorder
Park et al. (2021)	USA	56	M	2	3	NA	1	NA	BPD	0	Yes		Discharge after 1 day without AP; 10 days later readmission with mania
Parker et al. (2021)	USA	57	M	1	4	35	4	1	Px, Diff dx delirium	6		F0	Profound cognitive impairment
Parra et al. (2020)	ESP	54	M	4	3	NA	2	1	Px	1.8-2.3	Yes		Only aggregate data available
		54	M	4	3		2	1					
		54	M	4	3		2	1					
		54	M	4	3		2	1					
		54	M	4	3		2	1					
		54	M	3	3		2	1					
		54	F	3	3		2	1					
		54	F	3	3		2	1					
		54	F	3	3		2	1					
		54	F	1	1		2	1					
Reinfeld & Yacoub (2021)	USA	52	M	3	3	NA	4	1	Delirious mania	0			Px, suicidal ideation catatonia. Treatment with lorazepam without effect ECT
Russo et al. (2021)	ITA	60	F	1	1	NA	5	1	Mania with px features	8			
Santos et al. (2021)	PRT	61	M	2	2	15	4	1	Organic delusional disorder	3			Delusional jealousy
Sen et al. (2021)	TUR	33	F	3	3	10	1	2	Mania with px features	5.3	Yes		CLOCC resolution after 5 days
Smith et al. (2020)	USA	36	F	2	3	7	1	1	BPD	3	Yes		Self-discontinued AP after discharge without relapse
Spiegel et al. (2021)	USA	41	F	1	1	12	1	1	Px	1	Yes		Adrenal insufficiency compensated with GC
Talwar et al. (2021)	IND	46	M	3	3	NA	NA	1	BPD	NA			
Tuna et al. (2020)	TUR	52	F	2	2	NA	4	2	Schizophreniform px	5			Command hallucinations to attempt suicide; hallucinations started 1 month before COVID diagnosis

Table 3. (Continued)

Author (Year)	Country	Age	Sex	2	3	4	NA	NA	1	Acute px	NA	Start of px after end of quarantine
Umanah <i>et al.</i> (2021)	USA	26	F	2	3	4	NA	NA	1	Acute px	NA	Start of px after end of quarantine
Vepa <i>et al.</i> (2020)	GBR	40	M	3	3	3	NA	1	1	Px	0	Sedation with haloperidol without effect ICU for agitation. Remission after 2 days
Yesilkaya <i>et al.</i> (2021)	TUR	41	F	3	3	4	NA	NA	2	Px	5.3	Start of px 2 months after COVID. Cotard's syndrome, delusions COVID-related
Zain <i>et al.</i> (2021)	USA	69	F	2	2	3	14	4	2	Px with catatonia	0	Discharge without AP

Column headings: Country; Code according to ISO 3166 Alpha-3; COVID severity: 1: no somatic symptoms; 2: outpatient treatment for COVID-19; 3: inpatient treatment except for treatment in intensive care unit (ICU) for COVID-19; 4: treatment for COVID-19 in ICU; Somatic sy/px: 1: patients with psychosis, but without somatic symptoms of COVID-19; 2: psychosis before start of somatic symptoms; 3: psychosis concomitant with somatic symptoms; 4: psychosis when somatic symptoms had abated; Pat. (d) : inpatient treatment (days); Duration px; duration of psychosis (1: ≤ 1 week; 2: $> 1-2$ weeks; 3: $> 2-4$ weeks; 4: 1-2 months; 5: > 2 months); Outcome (1: full remission; 2: improvement; 3: no improvement; 4: no improvement); Treatment AP (treatment with antipsychotics at discharge, risperidone equivalents); Fast response (to treatment: as stated by the authors or ≤ 1 week); Psych. hist.: history of previous psychiatric illness according to categories of ICD-10 (diagnosis is set in *italics*). Abbreviations: AP: antipsychotics; ATPD: acute and transient psychotic disorder; BPD: brief reactive psychosis; CLOCC: cytotoxic lesion of corpus callosum; CP: cycloid psychosis; CS: corticosteroids; CQ: chloroquine; ECT: electroconvulsive therapy; F: female; F1: mental and behavioural disorders due to psychoactive substance use; F3 mood [affective] disorders; F4 neurotic, stress-related and somatoform disorders; F7 mental retardation; F8 disorders of psychological development; HCQ: hydroxychloroquine; HCW: health care worker; M: male; MDE: major depressive episode; NA: data not available; Outp: treatment as outpatient; pat.: patient; Px: psychosis; sy: symptoms.

Servén *et al.*, 2021). Some patients presented features complicating diagnosis: On two occasions (Dhir *et al.*, 2020; Ambar Akkaoui *et al.*, 2021), self-treatment with different drugs might have contributed to psychosis. Cannabis consumption with low intensity was reported in one case (Marouda *et al.*, 2021), with high intensity in two cases (Doufik *et al.*, 2021; Marin *et al.*, 2021). The authors of the latter paper attributed psychotic symptoms to cannabis withdrawal syndrome (due to lockdown and quarantine). Two patients received a schizophrenic spectrum diagnosis. Belvederi Murri *et al.* (2021) reported the case of a female student of Chinese origin living in Italy who became acutely psychotic during the first lockdown and in whom discreet psychotic symptoms had been present already 10 months before. The other patient was a male with a 1-month history of changed behaviour who responded quickly on treatment with AP (Doufik *et al.*, 2021). Eight times (12.8%) the diagnosis 'psychosis' was given without further specification.

Patients with infection

More than half of the cases (56.1%) dated from the beginning of the pandemic (January to June 2020), but there is an ongoing stream of publications. Table 3 presents the individual data of patients, Table 4 the aggregate findings and Table 5 the COVID-related data. Patients with infection were 46.5 years old as a mean (median 47.5 years). Males prevailed with 58.3%. The most prominent symptoms of psychosis were delusions (95.2%), agitation (60.7%), disorganisation (46.4%) and confusion (36.9%). Delusions thematically centred on the pandemic were found in 29.5%, with religious content in 25%. Almost two-thirds suffered from hallucinations, of whom 33 (39.2%) had acoustic hallucinations, 9 (10.7%) visual ones and 15 (17.9) both types. Ten patients (11.9%) had a history of previous psychiatric disorders, most commonly substance use disorders (six patients), of whom two had an active use of cannabis (Jaworowski *et al.*, 2020; Panariello *et al.*, 2020a) and one was substituted with methadone (Ferrando *et al.*, 2020).

The majority of patients (60.7%) came to hospital because of psychosis, while a quarter was admitted for COVID symptoms. Only four patients were treated for psychosis as outpatients. Most patients received APs. Patients not treated with APs suffered either from a defined organic brain disorder (Panariello *et al.*, 2020a; Alvarez-Cisneros *et al.*, 2021; Elfil *et al.*, 2021; McAlpine *et al.*, 2021), from catatonia (Caan *et al.*, 2020; Zain *et al.*, 2021) or were thought to have a psychosis due to an offending drug, which was then withdrawn. Three patients were treated with electroconvulsive therapy (ECT) (Chacko *et al.*, 2020; Vepa *et al.*, 2020; Austgen *et al.*, 2021). The mean dosage of antipsychotics at discharge was 3.4 mg risperidone equivalents. Sixteen patients (19%) did not receive antipsychotics at discharge or stopped it within the next month. Duration of psychosis was ≤ 2 weeks in 51.2% of patients, only in four (4.8%) the duration exceeded 2 months. Inpatient treatment ranged between 2 and 67 days with a mean of 15.1 days (median 14).

Outcome was full remission in 64.3%, and the rest was rated as improved. A fast improvement was observed in 33 (39.3%) patients. One patient showed a foudroyant course of COVID-19 and died (Elkhaled *et al.*, 2020), another patient's psychosis remitted, but she died some days later for unknown reasons (Borovina *et al.*, 2021).

In more than half of the patients, the somatic symptoms of COVID were either absent (16.7%) or that mild that no hospital

Table 4. Patients with and without SARS-CoV-2 infection: demographic and illness-related variables, psychopathology, treatment, and outcome. Statistic comparison between groups (chi-square tests with continuity correction, Mann–Whitney U-test)

	Without SARS-CoV-2 infection	With SARS-CoV-2 infection	Statistics
Number	62	84	
Age [years (SD/median)]	43.3 (14.9/41.5)	46.5 (12.1/47.5)	
Male [N (%)]	31 (50)	49 (58.3)	
Case originated January–June 2020	61 (98.4)	46 (56.1)	P = .000
Psychopathology			
Delusions [N (%)]	62 (100)	80 (95.2)	
Contentent COVID [N (%)]	47 (78.3)	18 (29.5)	P = .000
Content religious [N (%)]	18 (29)	21 (25)	
Hallucinations [N (%)]	28 (45.2)	53 (63.1)	P = .05
Visual	5 (8.1)	24 (28.6)	P = .004
Disorganisation [N (%)]	28 (45.2)	39 (46.4)	
Agitation [N (%)]	32 (51.6)	51 (60.7)	
Confusion [N (%)]	7 (11.3)	31 (36.9)	P = .001
Mania [N (%)]	7 (11.3)	22 (26.2)	P = .04
Depression [N (%)]	22 (35.5)	11 (13.1)	P = .003
Sucidality [N (%)]	16 (25.8)	17 (20.2)	
Anxiety [N (%)]	22 (35.5)	26 (31)	
Catatonia [N (%)]	4 (6.5)	9 (10.7)	
Previous psychiatric illness [N (%)]	22 (35.5)	15 (17.9)	P = .03
Family history of psychosis [N/N reported (%)]	5/34 (14.7)	4/33 (12.1)	
Duration of inpatient stay [days (SD/median)]	11.2 (9.2/8)	15.1 (13/14)	
Acute onset (≤7 days) [N/N reported (%)]	34/57 (59.6)	59/69 (88.5)	P = .002
Duration of psychosis			
–1 week [N (%)]	12 (19.4)	19 (22.6)	
–2 weeks [N (%)]	21 (33.9)	24 (28.6)	
–1 month [N (%)]	10 (16.1)	14 (16.7)	
–2 months [N (%)]	4 (6.5)	11 (13.1)	
>2 months [N (%)]	5 (4.8)	4 (4.8)	
Unknown [N (%)]	12 (19.4)	12 (14.3)	
Outcome			
Full remission [N (%)]	41 (66.1)	54 (64.3)	
Improved [N (%)]	13 (21)	20 (23.8)	
No remission [N (%)]	3 (4.8)	0	
Death [N (%)]	0	1 (1.2)	
Unknown [N (%)]	5 (8.1)	9 (10.7)	
Fast improvement [N (%)]	38 (61.3)	33 (39.3)	P = .01
Antipsychotic dosage (risperidone-equivalents)	3.3 (1.6)	3.4 (2.5)	

Abbreviations: SD: standard deviation.

treatment would have been necessary. Eight (9.5%) required treatment in an intensive care unit (ICU). Psychosis started in 35.7% of patients while somatic symptoms were present and in 32.1% after somatic symptoms had abated. On 2 occasions, psychosis manifested before somatic symptoms (Tuna *et al.*, 2020; Santos *et al.*, 2021). The time range from start of somatic symptoms to start

of psychosis was 0 to 60 days, with a mean of 13.4 (median 14). The aggregate paper of Parra *et al.* (2020) reported a mean time span of 'bigger than 14 days'.

The diagnoses varied considerably (see Table 3). Most often, a diagnosis of psychosis without further specification was made or differential diagnoses were discussed without a decision (N = 32,

Table 5. Patients with SARS-CoV-2 infection: illness, investigations, and treatment variables

Variable	Value
Number	84
COVID intensity	
No somatic symptoms [N (%)]	14 (16.7)
Light (outpatient treatment) [N (%)]	31 (36.9)
Severe (inpatient treatment) [N (%)]	29 (34.5)
Very severe (ICU treatment) [N (%)]	8 (9.5)
Unknown [N (%)]	2 (2.4)
Hospital admission for	
Psychosis [N (%)]	51 (60.7)
COVID-19 [N (%)]	21 (25)
Both [N (%)]	5 (6)
Other reasons [N (%)]	1 (1.2)
Not hospitalised [N (%)]	4 (4.8)
Onset of psychotic symptoms vs somatic sy of COVID-19	
No somatic symptoms [N (%)]	14 (16.7)
Px before somatic symptoms [N (%)]	2 (2.4)
Px during somatic symptoms [N (%)]	30 (35.7)
Px after somatic symptoms [N (%)]	27 (32.1)
Unknown [N (%)]	11 (13.1)
Mean time from onset of somatic sy to px [years; mean (SD/median)]	13.4 (12.9/10)
Inflammation [N/N investigated (%)]	47/60 (78.3)
CRP pathologic [N/N investigated (%)]	34/58 (58.6)
CSF pathologic [N/N investigated (%)]	6/25 (24)
CT/MR COVID-relevant pathologic [N/N investigated (%)]	5/65 (7.7)
Stressors [N/N investigated (%)]	27/55 (49.1)
Treatment prior to px with	
Corticosteroids [N (%)]	23 (27.4)
(Hydroxy)Chloroquine [N (%)]	18 (21.4)

Abbreviations: SD; standard deviation; px: psychosis.

38.1%). In 14 (16.7%) patients, ATPD/BPD were diagnosed, among these four cases of brief reactive psychosis (Jaworowski *et al.*, 2020; Mollà Roig, 2021). Mania with psychotic features was diagnosed in 10 patients (11.9%) and depression with psychotic features in one patient. Psychosis due to a general medical condition (PDGMC) was chosen in 12 (14.3%) patients, of whom 6 presented with a defined organic lesion of the brain: two cases with cytotoxic lesions of the corpus callosum (CLOCC), of whom one ended fatally (Elkhaled *et al.*, 2020), the other remitted fully within a few days (Sen *et al.*, 2021), further three cases with suspected meningoencephalitis (Bernard-Valnet *et al.*, 2020; Ariza-Varón *et al.*, 2021; McAlpine *et al.*, 2021), one case of encephalopathy (Jozuka *et al.*, 2021) and one case with NMDA autoantibody encephalitis (Panariello *et al.*, 2020b). Substance-induced psychotic disorder was diagnosed in six (8.3%) cases, CS (Grover *et al.*, 2021; Kazi & Hoque, 2021), CQ (Benjelloun

et al., 2020), HCQ (Boulos *et al.*, 2020), favipiravir (Duyan & Ozturan, 2021) and cannabis (Kaggwa *et al.*, 2021) being considered as offending substances. Beyond these cases, some more authors assumed strong evidence for psychosis being substance induced, without expressing it through diagnosis. This concerned CS (Desai *et al.*, 2021; Jiménez-Fernández *et al.*, 2021; Russo *et al.*, 2021), CS + HCQ (Correa-Palacio *et al.*, 2020) and azithromycin, which was thought to be responsible for catatonia (Caan *et al.*, 2020). Only twice the diagnosis of a schizophreniform disorder was made, in one patient with a prodromal phase 1 month before COVID-19 (Tuna *et al.*, 2020), the other for behavioural changes after infection with psychotic symptoms occurring 2 months later (DeLisi, 2021).

Analysis of CSF was performed in 25 patients, with pathologic results in 6 patients (Bernard-Valnet *et al.*, 2020; Noone *et al.*, 2020; Panariello *et al.*, 2020a; Parra *et al.*, 2020; Austgen *et al.*, 2021; McAlpine *et al.*, 2021). Detection of SARS-CoV-2 in the brain was never reported; in one patient (Noone *et al.*, 2020), antibodies against the virus were found in the CSF. Neuroimaging with CT or MRI was performed in 65 patients with pathologic results in 5 (7.7%). Presence of delirium as a clinical sign of compromised brain function was a frequent issue, even when cases of mere delirium were excluded. Yet there were patients who showed transition from delirium to psychosis (Caan *et al.*, 2020; Clouden, 2020; Lim *et al.*, 2020; Majadas *et al.*, 2020; Khatib *et al.*, 2021) and vice versa (Elkhaled *et al.*, 2020; Panariello *et al.*, 2020a; Jozuka *et al.*, 2021) or states alternating between delirium and psychosis (Bernard-Valnet *et al.*, 2020). Sometimes, delirium was reported as concomitant disorder or as a differential diagnosis to psychosis (Bernard-Valnet *et al.*, 2020; Gillett & Jordan, 2020; Losee & Hanson, 2020; Haddad *et al.*, 2021; Parker *et al.*, 2021; Reinfeld & Yacoub, 2021), and in more than a third of all patients, confusion was documented.

Blood tests were performed in almost every patient, yet not all reports were concise regarding the presence of inflammatory markers. Signs of inflammation were found in 47 (78.3%) of 60 evaluable patients. The most frequently reported parameter of inflammation was CRP, being above normal in 34/58 (58.6%) patients.

The possible effects of perceived stress were discussed in 27/55 (49.1%) of patients, yet only 7 times they were thought to be decisive (Haddad *et al.*, 2020; Jaworowski *et al.*, 2020; Parra *et al.*, 2020; Baral *et al.*, 2021; Mollà Roig, 2021). On the other hand, there were also reports which underlined the absence of any concern (Ferrando *et al.*, 2020; Majadas *et al.*, 2020; Alba *et al.*, 2021; Parker *et al.*, 2021).

Comparison of patients with and without SARS-CoV-2 infection (Table 4) revealed some significant differences regarding psychopathology. Patients with infection showed less often delusional contents thematically linked to COVID (29.5 vs 78.3%, $p = .000$) and less often depressive symptoms (13.1 vs 35.5%, $p = .003$), but more frequently hallucinations (63.1 vs 45.2%, $p = .05$), especially visual ones (28.6 vs 8.1%, $p = .004$), confusion (36.9 vs 11.3%, $p = .001$) and mania (26.2 vs 11.3%, $p = .04$). They had less often a personal history of other psychiatric illnesses (17.9 vs 35.5%, $p = .03$) and showed less often a fast improvement of psychosis (39.3 vs 61.3%, $p = .01$).

Discussion

Our literature search revealed 146 cases of first-episode psychoses, 62 without and 84 with SARS-CoV-2 infection, coming from all

parts of the world. Though this certainly represents only a tiny segment of occurring morbidity, it might serve to illustrate the characteristics of psychoses associated with COVID-19.

All patients without infection presented delusions and about half of them hallucinations and disorganisation. Delusions were thematically linked to COVID-19, with conviction to be infected or delusional fears of impending catastrophe, triggered by isolation, quarantine and economic problems. Especially in the first months of the pandemic, health care workers (HCW) were reported to be at heightened risk for physical and mental disorders (Salazar de Pablo *et al.*, 2020). Six (9.7%) of these patients belonged to this profession.

Course of illness was mostly favourable. More than 50% had a duration of psychosis of ≤ 2 weeks; full remission and rapid response to treatment was reported in more than 60% of cases. No improvement was only found in three patients: one chronic abuser of cannabis who left the hospital against advice after 9 days and the two patients of Deshpande & Livingstone (2021) already described. Most patients were treated with APs, some received only tranquilisers. Patients mostly were diagnosed as acute transient psychotic disorders (ATPD; F23 according to ICD-10) or brief psychotic disorder (BPD according to DSM-5).

The diagnosis ATPD/BPD is rare with an incidence of 4–6.7 cases per 100,000 persons/year (Castagnini & Foldager, 2013; Queirazza *et al.*, 2014; Fusar-Poli *et al.*, 2016) and so is research on this diagnosis. ATPD comprises 6 variations of brief psychotic disorders and allows a duration of up to 3 months, whereas psychosis in BPD must not be present longer than 1 month and provides three specifiers (with or without marked stressors, with postpartum onset). Though the diagnostic criteria of these two disorders differ in duration and specification of symptoms, the sociographic characteristics and outcome of the patients were found to be quite similar (Pillmann *et al.*, 2002; Fusar-Poli *et al.*, 2016). Prognosis of ATPD/BPD generally is considered to be much better than in schizophrenia (Marneros *et al.*, 2003), yet studies vary considerably concerning the proportion of patients who relapse. A meta-analytic study calculated the mean risk for relapse with 54% for ATPD and 53% for BPD over a period of 3 years (Castagnini & Fusar-Poli, 2017) and conversion to schizophrenia (median follow-up time 24 months) occurred in ATPD in 19% and in BPD in 15% (Fusar-Poli *et al.*, 2016).

Regarding age, our sample differed from other samples of ATPD/BPD in the literature, as in these (Marneros *et al.*, 2003; Castagnini & Foldager, 2013; Queirazza *et al.*, 2014), mean age of onset was reported to be 35–37 years, whereas our patients aged 43.3 years as a mean. The proportion of females in our sample (50%) lies on the lower side of the range reported by these studies spanning from 45.5% (Queirazza *et al.*, 2014) to 50% (Castagnini & Foldager, 2013) to 79% (Marneros *et al.*, 2003).

Factors heralding good prognosis of ATPD/BPD are female sex, higher age, a sudden onset of symptoms, short duration of symptoms and presence of stressful triggers (Pillmann *et al.*, 2002; Marneros *et al.*, 2003; Queirazza *et al.*, 2014; Rusaka & Rancāns, 2014; Stephen & Lui, 2021). The importance of stressful events preceding the psychosis has lost momentum since the diagnosis of brief reactive psychosis was discarded with the change from ICD-9 to ICD-10 and DSM-III-R to DSM-IV (Ungvari *et al.*, 2000). In actual schemes, presence of stressors can be coded only as a specifier. This might be justified as some case series found only a minority of patients in which preceding stressors could be found: 43% in a sample of Marneros *et al.* (2003) or only 12% in a sample of Pillmann *et al.* (2002). In contrast, stress seems of utmost

importance in our sample and is documented in all cases. This is also reflected by more than three-quarters of patients integrating COVID themes in delusional thinking. This fulfils a central criterion Jaspers proposed for reactive psychoses, that the content of the psychosis reflects the precipitating event (Jaspers, 1913; Ungvari & Mullen, 2000). Considering this, the cases here display a very 'reactive' sample of ATPD/BPD. In this vein fits the unexpected finding that all reports originated between January and July 2020, representing the occurrence of the first wave of COVID-19 in most countries. While case reports on psychotic patients infected with SARS-CoV-2 peaked in the first half-year of the pandemic but continued to appear until now, no single report of psychosis without infection was to be found after July 2020. It seems that only the threat and awe of the first wave of COVID-19 – a situation that in most parts of the world nobody has encountered before in his lifetime – was able to elicit these psychotic reactions. As people became accustomed to this threat, this type of psychosis apparently vanished, at least in the literature.

Taken all together, the good outcome of our patients in their index episode, the generally good prognosis of a diagnosis of ATPD/BPD, higher age, short duration of psychosis and the pathogenetic importance of extreme stress, a good outcome for these cases should be assumed in the long run too. Yet we should keep in mind that 'good' outcome of ATPD/BPD means 'better than in schizophrenia' and that the risk of relapse for ATPD/BPD was calculated to be about 50% within 3 years (Castagnini & Fusar-Poli, 2017) (albeit probably in samples with less 'reactivity'). Compared to patients with infection, these patients displayed more often a history of another psychiatric illness, especially anxiety disorders. This could hint to a greater psychosocial vulnerability of this group. In both groups, a family history of psychotic disorders was rare (with a low grade of reporting). Until now, no publication concerning follow-up information for these patients could be spotted.

Concerning psychosis among SARS-CoV-2 infected patients, we found 67 papers covering 84 patients. Comparing with the systematic review by Smith *et al.* (2021), which presents a somewhat smaller sample ($N = 48$) and is more restrictive concerning exclusion of cases overlapping with delirium, data on demographics and psychopathology are quite similar. Patients were somewhat older (46.5 years) than patients without infection, with a slight preponderance of males (58.3%). Most of them showed delusions, but a content concerning the pandemic was reported far less often as in the patients without infection. On the other hand, rates of confusion and hallucinations were higher, especially of visual hallucinations. This is an argument for an organic pathogenesis, as visual hallucinations are found there more frequently (Feinstein & Ron, 1998; American Psychiatric Association, 2013). Also, in delirium visual hallucinations are more prevalent than auditory ones (Webster & Holroyd, 2000) and the higher prevalence of confusion signals an overlap with delirium as well. Many authors reported problems delimiting delirium from psychosis. Delirium is the most prominent psychiatric symptom among hospitalised patients with COVID-19 (Manca *et al.*, 2020; Mukaetova-Ladinska & Kronenberg, 2020; Rogers *et al.*, 2020). The overlap of delirium with psychosis in the course of viral infections is not uncommon. Menninger reporting on the influenza pandemic of 1918/19 (Menninger, 1919) already found cases where delirium and psychosis were indistinguishable. Smith *et al.* (2021) also stated in their review that separation of delirium from psychosis is poorly accomplished and warrants further methodological efforts. As already shown, some cases changed between delirium and

psychosis. Symptoms of delirium seem to be distributed in a continuous rather than a categorical mode. While the occurrence of delirium (and also of neurologic symptoms) shows a clear correlation with severity of somatic symptoms of COVID-19 (Mao *et al.*, 2020; Mukaetova-Ladinska & Kronenberg, 2020; Tancheva *et al.*, 2020; Frontera *et al.*, 2021), no such correlation exists for psychosis, which occurred even in infections without clinical symptoms, yet in these significantly less often accompanied by confusion (7.1% vs 44.1% in the rest, $p = .02$, post hoc analysis).

Psychosis developing during presence of somatic symptoms of COVID-19 was the most common pattern, prevailing in more than a third of patients, followed by onset of psychosis after abating of somatic symptoms. The mean time lag between onset of somatic symptoms and onset of psychosis was 13.4 days (median 10) with a range from 0 to 60 days. This equates the mean time reported for neurologic complications of COVID-19, which is 12.8 days (range 0–56) (Podury *et al.*, 2021), suggesting that the similar mechanisms might be at work. Two patients showed an appearance of psychosis prior to somatic symptoms. Psychosis manifested 2 days (Santos *et al.*, 2021) and a month before somatic symptoms (Tuna *et al.*, 2020). These patients deserve attention because they highlight the possibility that psychosis can be the first manifestation of SARS-CoV-2 infection. They also illustrate the general difficulties to single out the timely relation between somatic symptoms of COVID and beginning of psychosis, either because patients do not have symptoms or do not complain about it, or authors do not report about it. The case described by Tuna *et al.* (2020) is potentially misplaced in this review but was included because it also highlights the diagnostic ambiguities accompanying these cases. A 52-year-old woman was admitted for trying to jump out of a balcony under the influence of command hallucinations. After admission, she was found out to have pneumonia and the PCR test was positive for COVID-19. Yet later, the patient reported that psychotic symptoms already started a month earlier. Therefore, either this patient had suffered a very protracted course of COVID-19 or psychosis had started before infection.

Possible pathogenetic mechanisms were discussed in all case reports. Effector categories are the virus itself, inflammation caused by the infection, side effects of treatment, psychosocial stress and mere coincidence of psychosis with infection. The last possibility was least discussed and mostly discarded. In general, authors considered the infection with SARS-CoV-2 as causative for the psychosis in some form or another. Most authors had little doubt that the virus itself was responsible for the psychosis, even if there was no single proof of the virus having entered the brain.

Investigations of the CSF were done only in a minority of patients, and not always antigen tests in the CSF were performed. Only once, antibodies against SARS-CoV-2 could be detected (Noone *et al.*, 2020). By the way, this was also reported in another patient with mania, who was not included in this review for the lack of psychotic symptoms (Lu *et al.*, 2020).

This does not differ from the situation in neurology where CSF is analysed more frequently. Reviews on the neurological complications of SARS-CoV-2 infection reported proof of the virus' presence in the brain in a small minority of cases only (Fotuhi *et al.*, 2020; Mohammadi *et al.*, 2020; Najjar *et al.*, 2020; Travi *et al.*, 2021) or not at all (Espindola *et al.*, 2020; Frontera *et al.*, 2021). It remains unclear whether this is a failure of testing techniques, caused by a rapid clearance of the virus from the brain (Espindola *et al.*, 2020), or – more probable – depicts a subordinate role for the virus itself in neural damage (Fotuhi *et al.*, 2020). With

time elapsing, it is becoming more and more clear that there is no big role for direct effects of the virus in the CNS (Johansson *et al.*, 2021; Lewis *et al.*, 2021).

If not the virus itself, then inflammation could be causal: inflammation is considered as the predominant pathogenetic factor by most authors. 'Systemic inflammatory response syndrome' (SIRS) describes the excessive reaction of the immune system to the infection with release of high amounts of cytokines and chemokines (Mohammadi *et al.*, 2020), often also termed as 'cytokine storm'. Binding of SARS-CoV-2 to angiotensin-converting enzyme 2 (ACE2) receptors might contribute importantly to a pronounced inflammatory reaction (Verdecchia *et al.*, 2020). ACE2 physiologically degrades angiotensin-II to angiotensin 1–7. Beyond its effects on sodium and fluid regulation, angiotensin-II has strong proinflammatory effects by activating immune cell populations, elevating proinflammatory cytokines and generating intracellular free radicals (Benigni *et al.*, 2010). Angiotensin 1–7 opposes these effects. Virus' binding to ACE2 leads to an accumulation of angiotensin-II and therefore promotes inflammation (de Erausquin *et al.*, 2021). The result is an upregulation of the cells of the innate immune system as monocytes, mast cells, macrophages and T-lymphocytes, with release of multiple proinflammatory cytokines. IL-6 and TNF- α are considered the main drivers of inflammation systemically and in the CNS (Medina-Enriquez *et al.*, 2020; Steardo *et al.*, 2020) and their levels correlate closely with severity of somatic symptoms and clinical outcome of COVID-19 (Jardim Vaz de Mello *et al.*, 2020; Kempuraj *et al.*, 2020; Raony *et al.*, 2020). The systemic inflammation reaches the brain in various ways, for example passage through areas without BBB, active transport of cytokines through the BBB, damaging the BBB or passage of activated immune cells through the BBB. Within the brain, inflammation mediators activate astrocytes and microglia as the brain's immune system, which produce cytokines and chemokines on their part, causing neuroinflammation (Kempuraj *et al.*, 2020; Mohammadi *et al.*, 2020; Najjar *et al.*, 2020; Raony *et al.*, 2020). Hypoxia, which can be present even in mild forms of COVID-19, and stress are further drivers of neuroinflammation (Cole *et al.*, 2015; Kempuraj *et al.*, 2020; Steardo *et al.*, 2020). In brains of deceased patients after COVID-19, massive inflammatory alterations have been found, without viral presence (Yang *et al.*, 2021).

Psychosis has been linked to inflammation in various aspects (Najjar *et al.*, 2013). Activation of microglia (leading to increased levels of proinflammatory cytokines) is considered to play a central role in the genesis of acute psychosis (De Picker *et al.*, 2017; Marques *et al.*, 2019). Neuroinflammation alters neurotransmission, disrupts neuronal connections and ultimately can lead to cell death (Kempuraj *et al.*, 2020). As found in other viral infections and maybe more frequently than in other viruses (Travi *et al.*, 2021), SARS-CoV-2 can induce para- or postinfectious processes which can lead to further psychiatric and neurologic syndromes (Kępińska *et al.*, 2020; Paterson *et al.*, 2020). Based on structural similarities (Yapici-Eser *et al.*, 2021) of virus proteins with host proteins ('molecular mimicry'), cross-reactive antibodies (Fotuhi *et al.*, 2020; Kreye *et al.*, 2020) and T-cells acting against own tissues can cause neurologic (e.g. Guillain-Barre syndrome) as well as psychiatric syndromes (e.g. autoimmune psychosis) (Endres *et al.*, 2020), which can be still present long after the virus has been cleared from the body (Kreye *et al.*, 2020).

Concerning our sample of patients, we have to admit that signs of inflammation were rarely so severe that one would call it a 'cytokine storm'. In half of the cases, somatic symptoms of COVID-19

were absent or did not necessitate inpatient treatment. About a quarter displayed no signs of inflammation and CRP was not elevated in 40%. Cytokines were only rarely assessed. Yet the lack of peripheral signs of inflammation does not preclude neuroinflammation. Many patients showed a time lag between somatic symptoms and start of psychosis so that peripheral inflammation possibly had abated at the time of psychiatric admission. Though it seems plausible that the risk for brain damage increases with intensity of inflammation, it is unclear what effect SARS-CoV-2 induced low-grade systemic inflammation has on the brain.

Possible side effects of therapeutics were frequently discussed. This report focusses on CS, CQ (only one patient) and HCQ administered before occurrence of psychosis, which happened in 30 (35.7%) patients. Yet in most of these cases, the beginning of psychosis was days till weeks after the end of administration so that a causal relationship was discarded by most authors. This was assumed only on eight occasions, concerning CS (five patients), CQ, HCQ, and the combination CS + HCQ (one each). Yet only in three patients (Benjelloun *et al.*, 2020; Grover *et al.*, 2021; Jiménez-Fernández *et al.*, 2021), the psychosis occurred during the treatment with the respective drug, in the rest 1–7 days later. How much this can contribute to occurrence of psychosis remains unclear. Even with incidence rates varying wildly, the risk for psychosis through treatment with CS is well established (Dubovsky *et al.*, 2012; Ross & Cetas, 2012). 'Steroid psychosis' is a broad term comprising severe neuropsychiatric complications, including depression, mania, delirium, and psychosis, affecting about 5% (range 2–50%) of patients treated with CS. The proportion of clear-cut psychosis among these amounts to about 15% (Lewis & Smith, 1983). The risk increases clearly with dosage and is highest during the first days of treatment, though occasionally cases at cessation of treatment have been described (Dubovsky *et al.*, 2012). The intense discussion of HCQ as a cause for psychosis is contrasted by some recent papers, which prove the relative safety of HCQ. Even for CQ, which is generally more fraught with side effects due to a longer elimination half time and greater penetration through the BBB (Hamm & Rosenthal, 2020; Kamat & Kumari, 2021), an increased risk for psychosis (Papazisis *et al.*, 2021) has not always been found (Sato *et al.*, 2020), and analyses of various data bases found no increased risk for HCQ (Garcia *et al.*, 2020; Lane *et al.*, 2020; Edington *et al.*, 2021; Papazisis *et al.*, 2021). The warning regarding the risk of psychosis seems to be based on a handful of case reports which have accumulated during the long use of this drug (Emmanuel & Östlundh, 2020; Juurlink, 2020).

Looking at patients without somatic symptoms of COVID-19 shows that the correlation of intensity of somatic symptoms with presentation of psychosis is poor: three patients were diagnosed as reactive (Jaworowski *et al.*, 2020; Parra *et al.*, 2020; Mollà Roig, 2021), in two stress was present, but not considered decisive (Huarcaya-Victoria *et al.*, 2020b). On the contrary, in four patients a 'lack of preoccupation' was documented and stress as a causal factor therefore excluded (Ferrando *et al.*, 2020) (three patients), (Alvarez-Cisneros *et al.*, 2021). One patient presented with a long-lasting manic psychosis (Russo *et al.*, 2021), two with intense organic-like psychoses (in one patients with seizures) which led to a full diagnostic workup (Losee & Hanson, 2020; Elfil *et al.*, 2021). One patient's psychosis was complicated by adrenal insufficiency which afforded additional CS replacement (Spiegel *et al.*, 2021), and one patient developed a change of behaviour over 2 months, leading to a diagnosis of schizophreniform disorder (DeLisi, 2021). Thus, the lack of somatic symptoms does neither imply that

psychosis presents with dominant reactive features, nor that it was short lived or less severe.

Also, the possibility that stressors caused the psychosis was discussed often but was considered decisive only in seven of the patients with infection. This against the background that there are those many reports of obviously stress-related psychoses that evolved in times of the pandemic without any infection. Maybe the importance of stressors has been underestimated given the presence of infection. On the other hand, the description of the cases with infection defers from the patients' without infection as delusional themes concerning the pandemic were significantly less often reported in the first. This could be an argument for the far smaller importance of pandemic-induced stress in these patients but could also be due to a reporting bias in those patients whose psychosis was thought to be virus-induced from the start.

Both groups showed a very favourable course of psychosis. Psychotic symptoms developed in both groups very acutely within a few days in the vast majority of patients, in those with infection more often (88.5%) than in those without (59.6%). For both, the duration of psychosis was less than 2 weeks in more than half the patients, full remission was attained in about two-thirds of patients. In both groups, a fast response to treatment was frequently reported, in the group without infection more often (61.3%) than in the group with infection (39.3%). Karl Menninger's paper (Menninger, 1919), describing cases of dementia praecox after the influenza pandemic of 1918, is frequently cited in these days and might foster concerns that the pandemic represents the starting point for new-onset schizophrenic disorders. Menninger himself had to revoke his diagnoses some years later (Menninger, 1994). From a clinical view, we have to underline that these first-episode 'corona-psychoses' have little in common with first-episode schizophrenia psychoses. Schizophrenia patients are very much younger and have a far longer prodromal phase. To appreciate the dramatically good outcome of these patients, a comparison with first-episode patients diagnosed with schizophrenia is helpful. In schizophrenia, only half of patients achieve a 50% reduction of psychopathological scores (PANSS or BPRS) (Zhu *et al.*, 2017) and a review calculated the weighted mean of remission with 35.6% (AlAqeel & Margolese, 2012). Age of onset also separates our patients from schizophrenia patients, because schizophrenia and schizophreniform disorder usually begin with a mean age of 25–29 years (Zarate *et al.*, 2000; Boter *et al.*, 2009; Segarra *et al.*, 2012; Kahn *et al.*, 2018), while our patients were about 20 years older. Description of Schneiderian first rank symptoms was rare, and negative symptoms were absent in these patients. Therefore, only three patients were diagnosed with schizophrenia or schizophreniform disorder. Of these, in two patients symptoms probably had already started prior to the pandemic, and only one patient can be considered as a potential manifestation of schizophreniform disorder after COVID-19.

According to DSM-5, late onset, absence of personal or family history of psychotic disorders, and visual hallucinations favour a diagnosis of PDGMC versus schizophrenia. Data on outcome and prognosis of PDGMC are scarce due to the wide variety of potential medical conditions, and DSM-5 states that the prognosis depends on the nature of the underlying somatic disorder. A paper summarising outcomes of psychosis due to chronic neurological illnesses still found outcomes and course better than in schizophrenia (Feinstein & Ron, 1998). So far, we can state that the short-term outcome of psychoses concomitant with SARS-CoV-2 infection is very good but there is no information on

the further fate of these patients. No follow-ups have been published until yet.

Limitations

We have done our best to collect a comprehensive compilation of case reports until December 2021. Case reports vary greatly in their comprehensiveness concerning symptomatology and treatment. On many occasions, it was not possible to distinguish between items not present or not reported. This might lead to bias, for example concerning the frequency of COVID-related delusions in patients with infections. Smith *et al.* (2021) in their systematic review of cases with infection rated only one-third of reports with low risk of bias. Applying statistics to these data might be misleading for the lack of uniformity in reporting. Nevertheless, we took this path for the sake of clarity of presentation, but we must underline that all conclusions need to be considered with caution.

Reporting bias might be huge for many reasons. All our cases stem from hospitals or outpatient clinics, so patients not presenting there are not covered. We must assume that the psychopathology especially of very severe COVID-19 cases is less often reported when all efforts are centred to save the patient's life. On the other hand, severe cases might be reported more frequently for heightened interest. Besides, it might be that 'first' cases have been reported more often during the course of the pandemic and later ones no more for lack of novelty. Some authors mentioned that they treated far more cases but selected only some for publication, for example (Deshpande & Livingstone, 2021; Valdés-Flórida *et al.*, 2021).

Conclusion

New-onset psychosis in the context of SARS-CoV-2 infection is not rare, even if it is not possible to determine an incidence rate. As our understanding of the pathophysiology of primary psychosis as schizophrenia is quite limited, our actual diagnostic systems classify psychosis following clinical experience and distinguish psychosis according assumed causal factors. Stress induced by the pandemic seems to be of major importance in the cases of psychosis without infection. Maybe the role of stress has been underestimated in the cases of psychosis with infection. Inflammation seems to be key for cases with infection yet there is poor concordance of the severity of peripheral inflammation with the occurrence of psychosis. Yet, the more severe the somatic symptoms of COVID-19, the more features of delirium may accompany psychosis. The mechanisms how and where the brain gets affected remain to be investigated. Research shows that processes of inflammation play a role as well in psychosis (Uptegrove *et al.*, 2014; Müller, 2018; Momtazmanesh *et al.*, 2019; Misiak *et al.*, 2021) as in stress (Cole *et al.*, 2015; Kempuraj *et al.*, 2020; Steardo *et al.*, 2020). Thus, inflammation might be the unifying process linking infection, stress, and psychosis.

While we are still not able to depict a proper description of the biological mechanisms of psychosis, we are restricted to collect risk factors and it seems that SARS-CoV-2 is such a risk factor, in a biological as well in a psychological way. It would be interesting to learn about the further fates of the patients assembled in this paper but as for now no reports could be spotted. We hope that with increasing containment of the pandemic, a more systematic investigation of these cases will be possible. As proposed in the field of neurology (Podury *et al.*, 2021), it would be very helpful to create

an international reporting system for such cases with standardised assessment tools concerning psychopathology, investigations (especially inflammation parameters) and long-term follow-up.

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