Implications
“This study is the first prospective study of high-risk youth that includes parents with both subtypes of mood disorders and controls that allowed us to prospectively identify specific forms of psychopathology that significantly predicted the onset of mood disorders,” the researchers concluded. “Our chief findings were that (a) the majority of (hypo)manic episodes are preceded by psychopathology (precursors) associated with the later onset of (hypo)manic episodes, whereas only about a third of MDD are preceded by mental disorders associated with the later onset of MDD; (b) different patterns of precursors preceded the onset of (hypo)manic episodes compared to MDD.”

The three precursors identified for BPD or MDD in high-risk youth (whose parents have mood disorders) are MDE (preceding hypomania or mania), CD, and DUD. Substance misuse was associated with hypomania only in offspring of parents with BPD.

There are different patterns of psychopathology preceding the onset of BPD and MDD, but the prediction can be complicated by the fact that a major depressive disorder can reflect either MDD or the earliest manifestations of BPD, the researchers write. “However, the psychopathology may differ between those offspring who remain unipolar over time and those who develop later (hypo)mania,” they add. “Indeed, according to additional analyses those who remained unipolar exhibited anxiety disorders preceding their first MDE more frequently than those who subsequently developed (hypo)manic episodes.” Conversely, those who subsequently developed hypomanic or manic episodes were more likely to have had subthreshold hypomania or drug use disorder which preceded their first major depressive episode.

Limitations of the study included the small number of children with hypomanic or manic episodes, the retrospective nature of 3-year evaluations, and the lack of documentation for less severe episodes of mania or depression during this interval. Finally, offspring of parents with MDD or no mood disorders still had a relatively high lifetime incidence of manic or hypomanic episodes, which the researchers said could be attributed to undiscovered BPD in their parents — however, many of these parents did have SUD.

Children of parents with BPD who have MDE, CD, or DUD should be monitored carefully to prevent conversion to BPD via interventions, the researchers conclude. They added that children with anxiety disorders should be treated to reduce their risk of developing MDD.

Also, the researchers added an important caveat — most children of parents with BPD who develop MDE, CD, or DUD will not develop BPD. This creates a challenge for early intervention, which can be harmful if not appropriate. “Accordingly, the potential benefit and harm of preventive measures should be carefully considered for each child,” the researchers concluded. “Consideration of parental history of BPD and clinical correlates including age of onset, severity, and clinical characteristics of the youth may inform treatment decision making.”

The research was funded by the Swiss National Foundation and a grant from GlaxoSmithKline Clinical Genetics.

Radaž D, Vandeule R, Ghomam M, et al. Psychopathological precursors of the onset of mood disorders in offspring of parents with and without mood disorders: Results of a 13-year prospective cohort high-risk study. J Child Psychol Psychiatry. 2020 Aug 25. doi: 10.1111/jcpp.13307. Online ahead of print.

---

What’s New in Research

Children with acute COVID-19 most likely to have CNS imaging abnormalities

By Alison Knopf

 précis

- Once thought to have only mild symptoms of COVID-19, children and adolescents can become severely ill.
- A recent study looks at CNS abnormalities in selected children throughout the world.
- Most of the children recovered, but still had the neuroimaging problems.
- The researchers recommend children be followed closely.

Central nervous system (CNS) abnormalities in children related to COVID-19 occur in acute and delayed manifestations, a recent study has found. Previously, such manifestations were described mainly in case reports. But in order to understand the full spectrum of the disease in children and adolescents, it’s important to have enough cases in aggregate to look at neuroimaging manifestations.

In background information, the researchers noted that in adults, cytokine storm and thrombogenic reactions to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection led to a high incidence of ischemic stroke and intracerebral hemorrhage; by contrast, severe CNS injury in children with COVID-19 was rarely reported.

Development of COVID-19 in children can involve an inflammatory process during the latent period of the disease. It was within this subcohort of COVID-19 cases that neurological manifestations of SARS-CoV-2 infection were first identified in children. A literature review identified an unexpectedly high incidence of neurological symptoms (34%) in children in this latent period.

Study details

For this study, researchers called internationally for pediatric cases of encephalopathy related to SARS-CoV-2 infection with abnormal neuroimaging findings. The researchers requested clinical history and associated plasma and cerebrospinal fluid data, which were reviewed by a panel
of neuroradiologists, a child neurologist, and a pediatric infectious diseases expert.

The children were categorized on the basis of their time of probable exposure to SARS-CoV-2.

Results
The researchers identified 38 children with neurological disease related to SARS-CoV-2 infection: 13 from France, eight from the UK, five from the United States, four from Brazil, four from Argentina, two from India, one from Peru, and one from Saudi Arabia.

Recurring patterns of disease were identified, with neuroimaging abnormalities ranging from mild to severe. The most common imaging patterns were:
• postinfectious immune-mediated acute disseminated encephalomyelitis-like changes of the brain (16 patients),
• myelitis (eight patients), and
• neural enhancement (13 patients).

Most children had good outcomes, but four previously healthy children died after developing atypical CNS co-infections.

The categories
• Category 1 (acute COVID-19): 12 cases in category 1, one (8%) child with necrotizing myelitis is permanently quadriplegic, all four (33%) patients with co-infections died, and seven (58%) were clinically normal at discharge.
• Category 2 (asymptomatic acute or subacute COVID-19): eight patients who did not present with clinically acute COVID-19 symptoms (based on CDC criteria) but had upper respiratory PCR tests that showed SARS-CoV-2 infection. Five (63%) children in this category were found to be serologically positive for COVID-19 exposure. One child tested negative and two were not tested for serology. Imaging abnormalities were as follows: two (25%) patients had changes in the brain and long-segment central cord myelitis; one (13%) patient had long-segment central cord myelitis and no brain imaging; one (13%) patient had changes in the brain and was diagnosed with anti-N-methyl-D-aspartate receptor (anti-NMDAR) autoimmune encephalitis; four (50%) patients had neutritis manifesting as cauda equina enhancement with variable enhancement of cranial or spinal nerves (one of whom also had myelitis and ADEM [Acute Disseminated Encephalomyelitis]-like changes); and one (13%) patient had extensive superior sagittal sinus thrombosis with parasagittal venous infarcts. The child with COVID-19 and encephalitis did poorly and remained intubated months following presentation. The other seven (88%) had good outcomes.
• Category 3 (patients with multisystem inflammatory syndrome): 11 patients. The imaging findings of these 11 patients were as follows: seven (64%) patients had splenial lesions of the corpus callosum in isolation or in combination with other brain abnormalities; seven (64%) had ADEM-like brain findings; two (18%) had cranial nerve enhancement; one (9%) had cauda equina enhancement; one (9%) had myelitis; one (9%) had multiple punctate foci of susceptibility-induced signal drop-out in the brain, consistent with microthrombi, that improved on follow-up MRI done 3 weeks after the initial study; and four (36%) had enhancing myositis of the facial or neck musculature. Follow-up was favorable in all cases, with five (45%) clinically normal and six (55%) clinically improved at discharge, most with minor residual symptoms.
• Category 4 (indeterminate cases): seven patients who had a positive SARS-CoV-2 serology test and positive neuroimaging findings. They presented at varying times during the course of the global pandemic and may or may not have had PCR testing initially (testing was not always available early on). Imaging abnormalities were as follows: four (71%) of the seven patients had neutritis; two (29%) had ADEM-like brain manifestations, of whom one also had myelitis and the other developed anti-myelin oligodendrocyte glycoprotein (MOG) antibodies; one (14%) patient had cerebellitis in addition to cranial neutritis; and one (14%) had vasculitis and a midbrain infarct unrelated to a co-infection. Outcomes at follow-up were favorable, with three (43%) children clinically normal and four (57%) having improved with residual neurological symptoms.

Implications
Early in the pandemic, there was a belief that children were unaffected, either being asymptomatic or having mild symptoms. However, more severe problems emerged, some with a Kawasaki-like syndrome labelled as MIS-C. Neurological complications in children were rarely reported, in contrast with what was being reported in adults.

“We suspect that children who were neurologically impaired through COVID-19 earlier in the pandemic might not have been identified because of an absence of available PCR testing or because the atypical or delayed symptoms shown by children were not immediately identified as COVID-19 related,” the researchers write.

That’s why they divided the cases into four categories and identified consistent neuroimaging patterns in the children. The most prevalent “resembled an immune-mediated parainfectious pattern of disease involving the brain, spine, cranial nerves, and nerve roots,” the researchers noted, noting that these were observed in 13 of 20 patients in categories 1 and 2. Throughout all four categories, this neuroimaging manifestation was found in 28 (74%) of 38 children.

“Children with COVID-19 and co-infections were the most severely ill patients in our series and all died,” the researchers conclude, noting that all co-infections occurred in the acute phase of COVID-19 and none of the children had pre-existing conditions.

Lindan CE, Mankad K, Ram D, et al. Neuroimaging manifestations in children with SARS-CoV-2 infection: A multinational, multicentre collaborative study. Lancet Child Adolescent Health. 2020 Dec 15. doi: 10.1016/S2352-4642(20)30362-X. Online ahead of print.

Report details early intervention services in every state
Adolescence is a time of heightened susceptibility to experimenting with alcohol or other drugs. Not every teen who does so will develop a substance use disorder (SUD), but this is a time period when the brain is developing and could be harmed.

continued on next page