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Capturing side-effect of medication to identify persons at risk of delirium

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Abstract

Delirium, an acute confusional state characterized by decline in attention and cognition, is a common, life-threatening, but potentially preventable clinical syndrome among older persons. Deficits in cholinergic function have been postulated to cause delirium and cognitive decline. In particular, an imbalance between levels of acetylcholine and monoamine (such as dopamine) may cause delirium. We describe two cases of delirium in hospitalized older patients, supporting the “cholinergic deficiency hypothesis”. In the first patient, hypo-reactive delirium developed a few hours after a dose of the long-acting opiate tramadol (a drug with anticholinergic effect) as analgesic for pain related to advanced peripheral artery disease. In the second patient, with vascular parkinsonism plus pre-frontal cortex vascular lesions, hyper-reactive delirium developed a few hours after a prescribed administration of L-dopa. These symptoms disappeared completely on the following day. These two “natural” experiments support the hypothesis that both hypo-reactive and hyper-active delirium may be caused by a reduction in cholinergic signaling.

Keywords

Cause and prevention; cholinergic deficiency; delirium

INTRODUCTION

Delirium, an acute confusional state with decline in attention and cognition, is a common, life-threatening, but potentially preventable clinical syndrome among persons who are 65 years of age or older (1). The development of delirium often initiates a cascade of events culminating in loss of independence, increased risks of morbidity and mortality, and increased healthcare costs. Delirium in hospitalized older patients has assumed particular importance because older patients account for half of all hospital days (1). The “cholinergic

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Conflict of interest

The authors do not have any conflict of interest in the publication of this case report, all contributed to the description and the writing of the manuscript, and approve it in its present form.

deficiency hypothesis” has been proposed as a common cause of delirium and cognitive decline (2, 3). In patients with Alzheimer’s disease (AD), a cholinergic deficit is associated with cognitive impairment, and perhaps also with the development of psychotic symptoms (4). Metabolic and perfusion imaging studies suggest that the presence of psychotic symptoms correlates with metabolic and perfusion abnormalities in the frontal cortex, where the cholinergic deficit is more marked (5). A neuro-transmitter imbalance, particularly excess of dopamine and/or cholinergic suppression, is believed to be related to many symptoms, including hallucinations, delusions and agitation (2).

We describe two cases of delirium in two hospitalized older patients in whom the cholinergic deficiency hypothesis may lie at the core of the pathophysiological mechanism leading to delirium. We suggest that the response to the anticholinergic side-effect of many drugs may identify individuals at risk of hypo-reactive delirium and dopaminergic agonists may identify individuals at risk of hyper-reactive delirium. The prescription of many medications may identify patients without delirium who are at risk of it if they are exposed to medications producing anticholinergic side-effects.

CASE REPORT

Case 1

An 82-year-old woman with moderate pain due to advanced peripheral artery disease, complicated by gangrene of the right foot, and a ten-year history of essential hypertension, was admitted to the Geriatric Unit of the University Hospital of Parma. The patient was taking three anti-hypertensive drugs (ace-inhibitors, Beta-blockers and diuretics). Physical examination revealed a bilateral plantar (Babinski) reflex, snout and grasp reflex. A brain CT scan revealed hypointense white matter changes, with bilateral ischemic lesions of the pre-frontal cortex. Because of acute pain, an analgesic was administered at five o’clock p.m., 150 mg of the long-acting opiate Tramadol. A few hours later, an hypo-reactive delirium was observed. Medication was promptly interrupted. The patient remained polite when approached, but was sleepy and did not want to eat or drink. The symptom of delirium disappeared completely on the following day.

Case 2

An 80-year-old man with a history of hypertension, atrial fibrillation and benign prostate hypertrophy was admitted to the Geriatric Unit of the University Hospital of Parma. He was taking five medications, including an antidepressant (SSRI), a loop diuretic, an angiotensin-converting-enzyme inhibitor, and a beta-blocker, as well as oral anticoagulant therapy. Overall, his health condition was stable. His wife reported that he had fallen twice during the past two months, once while turning to the left and later while he was starting to walk. Physical examination was consistent with the diagnosis of extrapyramidal syndrome. In detail, rigidity was perceived at both upper extremities, with postural instability and bradikinesia. Neurological examination was positive for snout, glabellar and palmomental reflexes, suggesting frontal lobe dysfunction. A brain CT scan revealed hypointense white matter changes. Treatment with L-Dopa (125 mg just before breakfast and 125 mg at 4 p.m.) was started. Hyper-reactive delirium was observed a few hours after the administration of

the second dose. Medication was promptly interrupted. The patient became verbally aggressive and showed carphologia. The clinical syndrome could no longer be detected during the medical examination the following day.

DISCUSSION

We briefly illustrate two case reports, supporting the hypothesis that an acute confusional state with psychotic symptoms may be associated with an excess up-regulation of dopamine combined with absolute or relative reduction by the neurotransmitter acetylcholine. We observed the occurrence of transient hypo-reactive delirium after using an opiate that has an anticholinergic effect by blocking muscarinic receptors, and hyper-reactive delirium after administration of L-Dopa, which causes a positive imbalance between dopamine and acetylcholine.

Our observations reinforce the view that a “cholinergic deficiency” is one of the main causes of delirium (6). More specifically, hypo-reactive delirium may be caused by an absolute deficiency of acetylcholine, in contrast to levels of monoamine (such as dopamine, norepinephrine and serotonin) (Fig. 1, b), whereas hyper-reactive delirium may be caused by a relative deficiency of acetylcholine with respect to dopamine, with an unbalanced ratio between these two neurotransmitters and an excess of dopamine level with respect to acetylcholine (Fig. 1, a) (2). This hypothesis is consistent with the suggestion that dopaminergic, serotonergic and noradrenergic systems, together with alterations of ascending cholinergic systems from the basal forebrain and pre-frontal cortex, play a pivotal role in attention, consciousness and the onset of psychotic symptoms (Fig. 1) (5).

Recent evidence emphasizes that the development of delirium involves interaction between the cholinergic pathway and monoamines, in particular dopamine. In the second case report, L-Dopa was administered to treat vascular parkinsonism. Although vascular parkinsonism has generally been considered to respond poorly or not at all to L-Dopa treatment, we recently proposed the routine use of L-Dopa in vascular parkinsonism, in agreement with other authors who found good improvement in about 50% of cases, especially in those with macroscopic infarcts or lacunae in the basal ganglia or substantia nigra (7). Interestingly, in the cases reported here, we observed vascular parkinsonism plus primitive reflexes, such as the snout and palmomental reflexes, expressions of frontal lesion. When the “prefrontal cortex-ventral striatal systems” are damaged, an excess of dopamine may contribute to hyper-reactive delirium by directly producing a decrease in acetylcholine levels (5). Anatomically, the dopaminergic and cholinergic pathways overlap significantly in the brain, suggesting an intimate balance between these neurotransmitters. The prefrontal cortex has D2 receptor family, which inhibits acetylcholine synthesis, and dysfunctions in the D2 receptor subtypes have been associated with hallucinations and pathological behavior (5).

It is well known that drugs with anticholinergic activity are an important precipitating factors for delirium in older persons (8). Some reports indicate that medications may be the sole precipitating factor in almost 30% of cases of delirium. More than 600 drugs have some anticholinergic effects, including the following 14 drugs (amitriptyline, chlorpromazine, clotiapine, promazine, benzodiazepine, olanzapine, digoxin, furosemide, isosorbide

dinitrate, nifedipine, warfarin, theophylline, ipratropium bromide, oxybutynin) which are some of the 25 most commonly prescribed drugs for older adults (9). In our cases, we prescribed an opiate, tramadol, as analgesic. Tramadol binds to μ -opioid receptors, and this has been considered the mechanism of antinociception. Inhibition of muscarinic receptors has been identified as a further mode of action of tramadol (10), and we propose this mechanism as the cause of the observed hypo-reactive delirium. As already reported, in both cases, we observed the complete disappearance of the delirium the day after pharmacological administration.

Other monoamines, such as serotonin, may contribute both directly and indirectly toward reducing acetylcholine tone, supporting the “cholinergic deficiency hypothesis” (2). In fact, the administration of selective serotonin reuptake inhibitors, including bupropion and fluoxetine, have been associated with delirium (11), especially if administered in the evening. Lastly, an excess of norepinephrine has also been associated with hyperactive delirium, through an increase in dopamine levels (2).

In conclusion, these two “natural” experiments support the hypothesis that both hypo-reactive and hyper-active delirium may be caused by a reduction in cholinergic signaling. More importantly, drugs may identify patients without delirium who are at risk of it if they are exposed to medication with anticholinergic side-effects.

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Fig. 1.

- Prefrontal cortex - ventral striatal system. VTA: ventral tegmental area.