Case Report

# Apathy in a Toddler with Bronchial Hyperresponsiveness Receiving Montelukast and Inhaled Corticosteroid Resolved with Sertraline Treatment: Case Report

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A previously normally developing two and a half years old boy with bronchial hyperresponsiveness gradually developed apathy, flattened affect, and disinterest in communication. Neurological examination was unremarkable. Symptoms appeared after dosage of montelukast was increased. Concurrent administration of inhaled salmeterol and fluticasone was noted, but without any dosage change over past months. Acquired hearing problem and psychosocial adversities were ruled out. Illness course also did not correspond with anaclitic depression. Patient was diagnosed with drug-induced apathy, which is rarely reported in pediatric population. His conditions precluded drug discontinuation trial. He improved dramatically with 12.5 mg per day of sertraline. Dosage was titrated per symptoms to 25 mg per day. Symptoms remitted by six months, and sertraline was discontinued by nine months. No symptoms recurred three months later. Clinicians should be aware of apathy as a side effect of montelukast. Further study on safety, efficacy, and mechanism of action of sertraline in drug-induced apathy is needed. Literature reviews on apathy are provided.

**Keywords**: Apathy; Montelukast; Pediatric; Sertraline

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Apathy is a condition marked by reduced range of affects, emotional response to stimuli, and motivation, culminating into lack of spontaneous behaviors[1]. The condition is commonly associated with medial frontal lobe dysfunction, and is commonly seen in neurodegenerative diseases, such as frontotemporal dementia, Parkinson's disease dementia, and late stage of Alzheimer's disease[2]. Vast body of literatures on apathy are within the context of neurodegenerative diseases. Nonetheless, apathy may also be seen in psychiatric condition that involves frontal lobe, specifically schizophrenia and other schizophreniform psychoses[1]. It may also be confused with anhedonia in major depressive disorder, against which symptoms constellation must be carefully considered[3]. Apathy is also known to occur in the context of psychiatric treatment with antidepressants[4-7], the effect of which may be dose related[8]. Apathy in pediatrics, though rarer, are described in various conditions, such as pediatric brain tumor (especially posterior fossa tumor)[9,10], pediatric stroke[11], congenital cerebellar lesions[12], childhood delirium[13], AIDS[14], and drug treatment with antidepressants[15]. There is paucity of reports on course and treatment of drug-induced apathy from other drug classes, and even less so in pediatric population. The presence of montelukast-induced apathy has been suggested from data mined from patient-centered social media sites, but there is still paucity of formal case reports in toddler age group[16,17]. Data on pharmacological treatment of apathy outside those in dementia are also limited.

Data were gathered from retrospective chart review. Clinical symptoms and responses were reviewed from clinician's notes and the recorded Clinical Global Impression, severity (CGI-S) and improvement (CGI-I) scales. Consent for publication was obtained from the patient's guardian. Study protocol was approved by the Human Research Ethics Committee of Srinakharinwirot University (number: SWUEC/E-270/2563).

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## Case Report

A two and a half years old boy underwent psychiatric consultation during his hospitalization for pneumonia because the pediatrician found him to be mute.

At the time of consultation, the child was afebrile, no difficulties breathing, and not in distress. Physical examination revealed normal pulse lung examination was normal, neurological examination was unremarkable. The rest of physical examination was normal. Complete blood counts and electrolyte panels were normal. However, he displayed an unchanging flat affect. There was minimal anxiety toward unfamiliar faces, and the child rarely showed distress upon undergoing nursing procedures. However, he still sought proximity of his grandmother, who was present throughout his hospitalization, when undergoing airway suction procedure. This was a subtle sign of anxiety and developmental reliance on attachment figure. The pediatrician's attempted to introduce toys, picture books, and the ward's miniature playground, to which the child was familiar from his past hospitalizations, but could not elicit any positive reaction. Video calls to his mother, previously known to be eliciting joy, also failed to change in flattening affect.

His grandmother, the principal caregiver, recalled the child's flattening of affect to have begun sometime around one month prior to the current admission. The child, then, gradually lost interest in video calls with his mother, and in playing with his father and grandmother. There were no changes in feeding or sleeping pattern, nor were there any behavioral disturbances. The family recalled no psychosocial circumstances that would have contributed to the affect changes. The family felt concerned and tried to introduce novel toys, picture books, treats, and playmates, but to no avail. From the physician's side, his mutism was briefly noted during his previous admission two months earlier and affective change was not prominent back then, for which the hearing problem was suspected as the child was undergoing treatment with ototoxic amphotericin B. The suspicion was dropped after hearing test (auditory brainstem response) came out normal and the child spontaneously resumed talking within a few days without intervention.

Past history revealed neither language developmental delay nor social-emotional difficulties. Other domains of development were also normal. His weight and height have been around the twenty-fifth percentile. There were no tentative history or findings of abuse, neglect, or other forms of psychological trauma. The boy had been frequently ill and hospitalized every few months for pneumonia. The most recent admission was two months prior. He had been diagnosed with bronchial hyperresponsiveness since the age of nine months. He received inhaled budesonide from the age nine to twelve months, after which his physician switched to inhaled salmeterol or fluticasone due to poor symptom control. He briefly received a few doses of montelukast at the age of nine month, during which there was no observable change in affect. He started receiving continuous treatment with 4 milligrams per day of montelukast at the age of 1 year and 4 months. The dose of montelukast was increased to 5 milligrams per day due to the change in supplies of drug formulary from granules to 'half' a tablet, at the age of 2 years and 5 months, coincident with the changes in symptoms. As for upbringing, the boy was raised by his maternal grandmother, who took care of him since his first few months of life and appeared to be the attachment figure. She was warm and caring and took care of him full-time. His parents migrated to bigger cities for work and came back to visit during long holidays. There was no family history of psychiatric disorder. Summary of clinical progression is shown in Table 1.

Mental status examination revealed a regular-build toddler, sitting beside his grandmother. The patient appeared fully conscious but did not express noticeable anxiety upon psychiatrist's approach. His affect was mostly flat and apathetic. He was disinterested toward introduction of toys and picture books. Despite not showing facial expression of anxiety, the child sought the grandmother's proximity upon introduction of new materials. Throughout the examination, the child seemed intact in receptive language, and could communicate back with gestures, but did not talk at all. The boy was mute toward physicians, nurses, and his grandmother. As his disturbances in affect coincided with change in montelukast dosage, suspicion on hearing problem previously cleared, and no indication of psychosocial stressor was found, his apathy was diagnosed as drug-induced affective disturbance. Initial CGI-S was rated at 5 or markedly ill.

The author initially attempted to engage the child in unstructured drawing and play therapy. Consistent with his behaviors at home, the child was disinterested and responded with mere blank stares at toys and drawing papers. Attempts to introduce the materials via his guardian also failed. As attempts in introducing the intervention failed,

**Table 1.** Timeline of patient's history and clinical course

| Timing | Settings | Event / Symptoms |
|---|---|---|
| 1 year and 6 months prior | Hospitalization | Started on inhaled salmeterol/fluticasone (1 puff via nebulizer, once daily) |
| 1 year and 2 months prior | Hospitalization | Started on montelukast (4 milligrams per day) |
| 2 months prior | Hospitalization | Brief display of mutism; No apathy; Spontaneously resolved; Hearing problem ruled out |
| 1 month prior | Home | Increased montelukast dose to 5 milligrams per day; Onset of apathy, gradually worsened |
| First psychiatric visit | Hospitalization | Worsened apathy, mute, failed to engage in play therapy, started on 12.5 mg/day of sertraline [CGI-S 5] |
| 6 days following start of sertraline | Hospitalization | Improved range of affect [CGI-S 3, CGI-I 1] |
| 2 weeks follow-up | Routine OPD visit* | Normalized affect, play, and engagement with family members [CGI-S 1, CGI-I 2] |
| 3 months follow-up | Routine OPD visit* | No symptom [CGI-S 1, CGI-I 4] |
| 6 months follow-up | Routine OPD visit* | Relapse of apathy without identifiable trigger; Titrated sertraline to 25 mg/day, apathy disappeared [CGI-S 2, CGI-I 5] |
| 9 months follow-up | Routine OPD visit* | No symptom; Parents decided to stop sertraline [CGI-S 1, CGI-I 2] |
| 12 months follow-up | Routine OPD visit* | No symptom [CGI-S 1, CGI-I 4] |

* No structured therapy or intervention

pharmacological treatment was opted. He received 12.5 mg of sertraline at nighttime. His affect showed notable change on the sixth day of medication, when he showed positive affect toward his grandmother. He also began to talk as he previously could. Negative affect or fear and anxiety toward suction procedure were also more pronounced. The sixth day's CGI-S was rated at 3 or mildly ill, and CGI-I was rated at 1 or very much improved. He was then discharged from hospital with the same dose of sertraline. At 2-weeks follow-up, his grandmother reported him to be as joyful as he previously was. Flat affect was rare. Plays and conversations were returned to normal. He demonstrated age-appropriate speech. His affect was euthymic, of which the range was broad. Structured non-pharmacological treatment such as play or art therapy was not reinstated because the child was deemed capable of experiencing age-appropriate socio-environmental stimulations without professional intervention. On the second week's CGI-S, he was rated at 1 or not ill at all, and CGI-I was rated at 2 or much improved. The absence of symptoms remained at 3-month follow up with CGI-S at 1 and CGI-I at 4 or no change. Brief lapse of apathetic symptoms was seen at 6-month follow up without any noticeable medical or psychosocial stressor with his CGI-S at 2 or borderline ill, and CGI-I at 5 or minimally worse. Sertraline was increased to 25 milligrams per day without additional non-pharmacological treatment. His affect recovered and remained stable. At nine months, the family decided to stop taking sertraline owing to normalized affect with CGI-S at 1 and CGI-I at 2. There was no symptom recurrence at the twelfth month follow-up with CGI-S at 1 and CGI-I at 4. Throughout the course of treatment, he did not have recurrent infection or hospitalization. There was no change in steroid or montelukast dosing owing his stable pulmonary condition. No adverse effect was observed or reported during psychiatric interviews in outpatient follow-ups. The drug was administered by the patient's grandmother, who reported no missed dose. However, formal pill counts were not performed.

## Discussion

The child presented with gradually worsened apathy. Multiple etiologies of the affective disturbance were considered. Acquired hearing problem were addressed prior to the current consultation. As no new ototoxic agent were administered, a re-test was not warranted. There were no focal neurological deficits or any history indicative or seizure or other neurologic conditions. Furthermore, since neurological examination was normal, no further investigation was indicated. Although not one of the core symptoms[18,19], apathy in 'functional' depressive disorder was also considered. Depressive disorder is relatively rare in preschool children, and would usually require a strong precipitant or high genetic loading[20,21]. His airway condition and frequent hospitalizations can function as psychosocial and physiological stressors, contributing to a functional affective disturbance. His affective change began sometime after his last hospitalization when his medical symptoms were stable. This was in contrast with the description of anaclitic depression[22]. Stress from current hospitalization was therefore unlikely to be the sole precipitant. The author then looked into parenting, attachment with his guardian, and other psychosocial circumstances, but found nothing

indicating poor parenting practice, neglect, or abuse. A child being raised by grandparents while the parent migrated to work in larger cities is a commonplace in the author's rural farming community. As per the author's clinical experience, this does not directly precipitate a psychiatric disorder unless there exists a disturbance in attachment or a remarkable deviation from norm in parenting practices.

With psychological and social precipitants being unexplanatory, the author was steered into considering possible biological stressors according to bio-psycho-social framework. At the time of onset, the child has had bronchial hyperresponsiveness for 1 year and 9 months, exposed to inhaled salmeterol and fluticasone for 1 year and 6 months and to montelukast for 1 year and 2 months with a small dosage change from 4 to 5 milligrams per day for one month. From the framework, the illness can be viewed as both the sources of biological predisposing factors contributing to systemic inflammations and resultant neurological system dysfunctions, and psychosocial predisposing factors such as mental stress from being ill and hospitalized and the inadvertent lack of developmentally appropriate experiences. The prolonged exposure to the montelukast could also have been keeping scores on psychiatric brain pathology. These culminated into an episode of apathy after the change in montelukast dosage acted as the last straw or precipitating factor. While initial pharmacological treatment kept the episode in check, the brief lapse at six month connoted an ongoing pathological process of the predisposing factors described, which were only fully suppressed after dosage increase of sertraline. The remission of symptoms despite continued exposure to montelukast may yet raise questions, whether the improvement was coincidental and, if not, whether the resolved pathologies could recur, but these would require extended period of observation. Another limitation in the evidence of diagnosis of drug-induced apathy was that discontinuation and re-challenging of montelukast to prove its part was not clinically or ethically feasible at the time owing to his difficult-to-control airway symptoms and limited availability of alternatives.

Montelukast, a cysteinyl leukotriene receptor 1 (CysLT1R) antagonist, is an agent with known neuropsychiatric side effects. Case reports and pharmacovigilance databases have associated the drug with sleep disturbance, agitation, irritability, anxiety, depression, and suicidality. The reported exposure time prior to onset of neuropsychiatric symptoms varied from days to years[23-29]. Apathy, along with nightmare, were previously reported in a one year old infant with montelukast dose of 5 milligrams and multiple concomitant steroid medications in the Swedish database[23]. The remaining concurrent medications in the present case, salmeterol and fluticasone, a combination of long-acting beta agonist and corticosteroid (LABA/ICS) in inhaled form, has a rate of mood disorder adverse reaction of less than one percent, in which apathy was not specifically reported[30]. Reports of psychiatric side effects of other inhaled LABA/ICS combinations were also sparse[31], hence the unlikeliness of contribution. The remaining medication, montelukast, was therefore viewed as precipitant owing to the temporal relationship with dosage increase and the consistency with past case report of apathy, one among many of its common neuropsychiatric side effects.

The decision to deliver treatment in the present case was deliberated from meeting between his guardian, pediatrician, and psychiatrist. The disturbance in affect was deemed an obstacle to meaningful social interactions required for normal language and socio-emotional development[32]. Previous reports of apathy in toddler were pharmacovigilance in nature and precluded reports on treatment of the condition. As attempts at non-pharmacological intervention failed, off-label pharmacological treatment with sertraline was opted owing to class efficacy in ameliorating apathy in neurodegenerative diseases and functional depressive disorder. Apathy has been noted in pathologies involving medial frontal lobe, especially anterior cingulate cortex, and is commonly found in neurodegenerative diseases affecting the site[2]. It was found that frontotemporal dementia patients have deficits in serotonergic neurons and receptors[33], and that their apathy do respond to SSRIs[34]. Response to SSRIs in late stage of Alzheimer's disease, however, is still inconclusive[35,36]. The author did not find any study associating CysLT1R, montelukast's target site, and pathologies of apathy in dementia. Whether the site is related to other mechanisms causing apathy is not known. In terms of functional depressive disorder, when apathy is manifested from the start as a facet of anhedonia[37,38], it is rational to assume that the associated pathologies are shared with those described in anhedonia itself. Dysfunctions of the prefrontal cortex and related circuits with striatum, thalamus, and amygdala, in particular, and dysregulated hypothalamus-pituitary-adrenal axis have been implicated[39]. Mechanisms by which SSRIs improve the syndrome may include monoamine receptor changes[40], transcription of trophic factors

and neuronal survivability[39], modulating dysfunction of kynurenine pathway[41], and amelioration of inflammation[42-44]. In the opposite case, when apathy emerges after SSRI treatment, pathology involving frontal lobe is also suspected[5]. Again, the author did not find study implicating the role of CysLT1R in functional depressive disorder or its treatment.

Mechanisms by which montelukast induces neuropsychiatric events, apathy included, remain an active subject of research. CysLT1R, was found to be associated with depression and neuroinflammation in an animal model[45], but it has no known direct actions on monoamine neurotransmitter systems[46,47]. Knockouts of CysLT1R was found to suppress kynurenine pathway[48], overlapping with the therapeutic effect of SSRI and make the pathway unlikely the responsible pathology. CysLT1R has been associated with inflammation, and can activate microglia to release nitric oxide[49], which is a known neurotoxin associated with depression[50]. Sertraline's ability to counteract neuroinflammation[42-44] is therefore a possible mechanism in the presented case. Owing to paucity of data, well-designed studies on the efficacy of sertraline in montelukast- and other drug-induced apathy are needed before recommendations can be made. Studies determining levels of relevant biomarkers such as pro-inflammatory cytokines and cerebrospinal fluid nitric oxide metabolites, together with standardized measures on apathy, will also aid in understanding how montelukast contributes to apathy. Determining such biomarkers pre- and post-treatment with sertraline will also aid in understanding the drug's mechanism of action in reducing apathy. Lastly, as SSRI's safety data in younger children are still limited, off-label prescriptions require judicious consideration of risks and benefits, as well as careful follow-ups of efficacy and adverse events.

## Conclusion

The author described a case of apathy in a 30 month old toddler with chronic airway problem receiving montelukast and inhaled salmeterol and fluticasone. Affective disturbance from multiple etiologies was diagnosed. His airway condition precluded discontinuation of the offending drugs. Off-label pharmacological treatment with 12.5 to 25 milligrams per day of sertraline for nine months resulted in remission of apathy. Mechanisms of action are discussed.. Clinicians should be aware of apathy as a side effect of montelukast. Further research on safety, efficacy, and mechanism of action is needed.

## What is already known in this topic?

Montelukast is known to cause neuropsychiatric side effects in pediatric population.

## What this study adds

Apathy could be among the neuropsychiatric side effects of montelukast. More study is needed to determine the pathophysiology and mechanism of pharmacological treatment.

## Conflicts of interest

The author has nothing to disclose.

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