Original Article

Adverse effects of antiepileptics potentially serious in individuals with severe motor and intellectual disabilities

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Abstract

Purpose: To describe the potentially serious adverse effects of antiepileptic drugs (AEDs) in individuals with severe motor and intellectual disabilities (SMID) and to improve the quality of drug treatment for these patients.

Methods: The data of 99 SMID patients with epilepsy staying at an institute for more than 1 year were retrospectively reviewed. Each patient was taking 3.4 ± 1.6 (range, 1–8) kinds of AEDs, and clinical seizures were still prevalent in 68 patients.

Results: Discontinuation or dose reduction of AEDs ameliorated agitation and/or sleep disturbance, somnolence, vomiting, appetite loss, and stridor in the corresponding patients, and additionally resolved serious gastrointestinal or cardiorespiratory problems in three patients whose clinical courses were detailed. Patient 1 manifested aerophagia-related chronic distension of the abdomen causing mechanical ileus, requiring repeated intestinal resection. The abdominal distension improved significantly after discontinuation of acetazolamide. Patient 2 experienced progressive motor deterioration during young adulthood, with simultaneous sudden elevation in blood phenytoin level. Although motor disability persisted, resolution of hypoventilation was noted after cessation of phenytoin. Patients 3 had long-term use of carbamazepine and exhibited episodic bradycardia (heart rate as low as 25 bpm) that resolved after drug discontinuation.

Conclusions: Patients with SMID sometimes fail to effectively verbalize subjective adverse effects of medications to healthcare providers. The chronic adverse effects of AEDs, including those described in this study, should be broadly evaluated for better patient management.

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Introduction

The condition of “severe motor and intellectual disabilities (SMID)” has been broadly studied in Japan since the 1960s. At present, it generally refers to individuals with an intelligence quotient of lower than 35, who cannot ambulate independently [1]. SMID is not a diagnosis but a disability category. The etiologies include prenatal, perinatal, and postnatal insults to the central nervous system, such as hypoxic–ischemic events, intracranial hemorrhage, viral/bacterial infection, and hydrocephalus, similar to those of “cerebral palsy”. Therefore, SMID correlate with a subgroup of cerebral palsy patients with severe intellectual disturbance.

In Japan, the number of SMID cases was estimated to be 46,000 in 2003 [1], approximately 40% and 60% of whom were living at home or staying in an institution, respectively. The survival rate of patients aged 20 years and living in an institution has been assumed to be 79%. Epilepsy is a common complication of patients with SMID, constituting 50%–70% of patients [1]. Before adulthood, care provided by child neurologists for this population is often taken over by physicians who are unfamiliar with epilepsy treatment. Unfortunately, historical data providing information on the clinical course and antiepileptic drug (AED) regimen of these patients are often lost after repeated summarization during inter-hospital transition between the attending doctors during childhood and those in adolescence. It is difficult for the doctors who follow patients with SMID after transition to ascertain which drug is essential for epilepsy management and which could be terminated or replaced with other contemporary new

drugs. As a result, the AED regimen of individual patient is left unaltered during transition if epilepsy is controlled or is at an acceptable level for the patient’s daily life. In many individuals, epilepsy has been managed by polypharmacy with classical AEDs including phenobarbital (PB), carbamazepine (CBZ), and phenytoin (PHT). The inability to effectively verbalize subjective symptoms of adverse effects to healthcare providers may also be associated with a risk of serious problems due to adverse effects, as observed in the three patients described in detail below.

This study aimed to evaluate the serious adverse effects of AEDs in patients with SMID to determine the merit of termination trials of chronic AED therapy in this population.

Methods

Following the opening of Yokohama Medical and Welfare Centre Konan in June 2016, a total of 120 patients with SMID had been hospitalized for a long period of time, either transferred from home or other medical institutes. Their medical charts were reviewed and data on complications of epilepsy, AED regimen received, and any changes to the regimen until November 2019 were obtained. For this study, we recruited 99 subjects who had epilepsy and were treated with AEDs upon admission (male:female = 58:41; age, 6–55 years; mean $\pm$ standard deviation, 31.3 $\pm$ 11.5). One subject who discontinued medication for epilepsy without relapse in the subsequent 20 years was not included. According to the International League Against Epilepsy, epilepsy was defined as at least two unprovoked seizures occurring more than 24 h apart or one unprovoked seizure with the probability of further seizures comparable to

the general recurrence risk (at least 60%) after two unprovoked seizures occurring over the next 10 years [2]. The etiology of the 99 patients included perinatal insults in 35; epileptic encephalopathy in 14; cerebral malformation in 11; chromosomal abnormalities in 6; sequelae of acute encephalopathy in 5; postnatal hypoxic–ischemic encephalopathy in 5; sequelae of meningitis in 3; congenital malformation syndrome in 3; cerebral palsy with unknown cause in 3; herpes encephalitis in 2; head trauma in 2; intracranial hemorrhage in 2; dentatorubral–pallidoluysian atrophy in 2; and Angelman syndrome, tuberous sclerosis, Pelizaeus–Merzbacher disease, radiation leukoencephalopathy, GM1 gangliosidosis, and cerebellitis in 1 subject each. The disease duration of epilepsy ranged from 2 to 49 (28.0 ± 12.1) years. Seizure frequency was daily in 11, weekly in 16, monthly in 21, and yearly in 20. Thirty-one patients were in seizure remission, defined as a seizure-free period of longer than 2 years while taking AEDs. Each patient was taking 3.4 ± 1.6 (range, 1–8) AEDs including valproate (VPA) in 50; levetiracetam (LEV) in 34; CBZ in 31; zonisamide (ZNS) in 30; clonazepam (CZP) in 27; clobazam (CLB) in 27; PB in 26; lamotrigine (LTG) in 24; diazepam (DZP) in 24; nitrazepam (NZP) in 20; PHT in 13; topiramate (TPM) in 8; perampanel (PER) in 8; lacosamide (LCM) in 6; gabapentin (GBP) in 4; sodium bromide (NaBr) in 2; acetazolamide (AZA) in 2; and sulthiame, ethosuximide, and primidone in 1 patient each. Blood samples for measuring AED concentrations in each patient were essentially taken 2–3 h after taking the morning dose. The design of this study was approved by the institutional review board (2019-8).

Results

Complications potentially linked to adverse

effects of AEDs were identified as follows. Prior to admission, the clinical history revealed that acute pancreatitis in three patients and Fanconi syndrome/renal tubular dysfunction in three other patients were all attributed to VPA use. Other reported adverse events were eruptions in four patients (VPA in two and ZNS and LTG in one each), symptomatic urolithiasis in three (ZNS in three), supra-ventricular arrhythmia and sinus arrest necessitating pacemaker implantation in one (CBZ), lymphadenopathy in one (ESM), and oculogyric crisis in one (LTG). The AEDs responsible for these complications had been discontinued and replaced with other drugs. After admission, the adverse events identified were bradycardia with heart beat less than 50 bpm in five patients (CBZ in four and PHT in one), agitation and/or sleep disturbance in five (LEV in two and ZNS, TPM, PER in one each), somnolence in five (CZP in three, LEV in one, and VPA in one), vomiting in four (LTG in two, VPA in one, and ZNS in one), motor regression in three (PHT in three), appetite loss in two (VPA in one and ZNS in one), and stridor in two (CZP in two). Neurogenic bladder/urinary retention was reported in 13 patients, 4 of whom could be explained by their background conditions of spina bifida, total asphyxia with brainstem involvement, and neurodegenerative disorders. In the remaining nine patients, the most commonly prescribed AEDs were CBZ in eight patients, LEV in four, CZP in three, VPA in three, and PB in three.

Abdominal computed tomography (CT) conducted in 85 patients revealed asymptomatic, punctate renal calcification in 25 patients (ZNS in 11, TPM in three, and both in one). Electrocardiography (ECG) conducted

in 98 patients identified 1° atrio-ventricular block in 4 patients (CBZ in three and PHT in one). Laboratory findings were as follows: decreased platelet counts below $15 \times 10^4/\mu\text{l}$ in 16 patients (VPA in 14), hyponatremia below 135 mmol/l in five (CBZ in all five), elevation of liver enzymes in seven (VPA monotherapy in three, CBZ monotherapy in one, and polypharmacy in three), increased amylase level in eight (VPA in five), and hyperammonemia in five (VPA in all five). These were all mild, with no evident symptoms related to these aberrant data.

To obtain better epilepsy control and/or to alleviate the adverse effects, the AED regimen including initiation, termination, and increase/decrease of dosage, was modified in 52 patients after admission. Termination or dose reduction was implemented in 32 patients, comprising nine patients on CBZ, five on PB, five on PHT, five on ZNS, four on LEV, three on CZP, three on DZP, and two on AZA (four patients had dose reduction of two drugs). Termination or dose reduction of AEDs ameliorated agitation and/or sleep disturbance, somnolence, vomiting, appetite loss, and stridor in the corresponding patients, and additionally resolved serious gastrointestinal or cardiorespiratory problems in three patients. The clinical course of each patient is detailed in the following section. At regular check-ups, the three patients had blood selenium levels of 50–100 $\mu\text{g/l}$, and their serum albumin levels under stable health conditions were 3.5–4.0 g/dl in patients 1 and 2, and 2.5–3.0 g/dl in patient 3.

Case reports

Patient 1. The subject was a 21-year-old

woman who had cardiopulmonary arrest due to dehydration at the age of 6 months. She then manifested rigospastic tetraplegia and was not able to control her head, roll over, or utter meaningful words. Recurrent aspiration pneumonia occurred during school age, which disappeared after gastrostomy/fundoplication and tracheotomy with laryngopharyngeal separation at the age of 14 years. At 19 years of age, she was admitted to our institute, weighing 30 kg and was under medication of 100 mg PB (blood level, 19.7 $\mu\text{g/ml}$), 150 mg LTG (4.75 $\mu\text{g/ml}$), and 250 mg AZA (12.8 $\mu\text{g/ml}$), taken twice daily in equally divided doses. Upon admission, details of her history of epilepsy, including the age of onset and the course of illness, were not available. Within 2 years thereafter, seizures lasting up to 1 minute with ocular deviation, smacking, and subsequent generalization occurred twice. Interictal electroencephalography during wakefulness revealed the presence of paroxysmal discharges independently at the left frontocentral and right frontopolar regions. Chronic abdominal distension due to aerophagia (air swallowing) resulted in bowel gas retention, which was managed with mosapride, daikentyuto (Kampo medicine), and lactulose; daily enema, and anorectal bougie when necessary. At 20 years of age, the patient experienced an acute abdomen episode due to internal herniation of an ileocecal portion into postoperative intraperitoneal adhesions in the vicinity of the gastrostomy, necessitating resection of the ileocecal portion. Strangulation ileus re-occurred 8 months later (Fig. 1A), and further resection of the ileum was done. Upon readmission, abdominal gas retention was

Figure 1. Abdominal X-ray of patient 1. (A) The day of emergency transfer for surgical treatment for strangulation of the ileum. (B, C and D) Thirteen days, 34 days and 12 months, respectively, after surgery. Acetazolamide dosage was reduced from 250 to 125 mg on day 43, and was discontinued on day 55. Note that abdominal gas retention persists in B and C but is ameliorated in D.

still noted (Fig. 1B). She was under continuous infusion of enteral nutrition; however, abdominal distension worsened repeatedly and was accompanied by tachycardia and perspiration, suggesting recurrence of strangulation (Fig. 1C). During this period, smacking movements and aerophagia were induced by the uncomfortable stimulation and manipulation of the patient and during drowsiness. Suspecting that the adverse effects of AZA, including nausea, constipation, and irritability, might play a role in aerophagia development, the drug was discontinued. Following

AZA discontinuation, marked abdominal distension disappeared, with decreased bowel gas retention. The abdominal distention remained at an acceptable level for more than 12 months (Fig. 1D). Metabolic acidosis (pH 7.276–7.338 in blood gas analysis) that had persisted during the previous 2 years was soon normalized after AZA termination, and a pH range of 7.362–7.437 has been maintained. Although the patient's body weight had been 30 kg or less in the previous 2 years, she gained 5 kg in 1 year after AZA termination.

Figure 2. The clinical course of patient 2. The body weight of the patient at this period was 52 kg. PHT, CBZ and PB were given twice daily; ESM, VPA, CLB, ZNS, LTG and LEV were given thrice daily (all in equally divided doses); and CZP was given once daily. CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ESM, ethosuximide; LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbital; PHT, phenytoin; VPA, valproate; ZNS, zonisamide.

Patient 2. The subject was a 48-year-old man with a history of hemiconvulsion–hemiplegia–epilepsy (HHE) syndrome. Refractory epilepsy with daily to weekly tonic, myoclonic and atonic seizures had been treated with multiple AEDs (Fig. 2). Until his mid-20s, he was able to walk with a hemiparetic gait, and grab and manipulate objects with both hands. At 30 years of age, he started to lose his ability to ambulate. He was able to shuffle and crawl in his 30s, but gradually lost these abilities in his 40s. At 47 years of age, he was transferred to our institute due to motor regression, and was bedridden and could not roll over. He was able to follow

moving objects with both eyes, but prominent horizontal nystagmus was noted. He understood limited words and expressed a yes/no reply by vocalization. Spasticity was not apparent in four limbs, but ankle clonus was evident on the right side. Depressed deep tendon reflex was found in the upper and lower extremities. He was able to reach certain objects with his left hand but dysmetria was observed. Monthly seizures persisted, and he was medicated with 150 mg PHT, 400 mg VPA, 600 mg CBZ, 200 mg ZNS, 20 mg CLB, 0.5 mg CZP, and 2000 mg LEV for a body weight of 52 kg. Seizures with eye deviation and versive movements occurred only

Figure 3. Cranial computed tomography of patient 2 at the age of 48 years. (A and B) Marked cerebellar atrophy is noted. (C and D) Atrophy of the left cerebral cortex is speculated by the prominent sulcus compared with the contralateral hemisphere.

once after admission. Therefore, CBZ and ZNS were discontinued at the age of 48 years. During this period, cranial CT revealed marked cerebellar atrophy (Fig. 3). The motor conduction velocity (MCV) and amplitude of the median nerve were 35.8 m/s (normal $\pm$ standard deviation, 57.7 ± 4.9) and 4.42 mV (7.0 ± 3.0), respectively, and the sensory conduction velocity (SCV) and amplitude of the sural nerve were 42.9 m/s (46.2 ± 3.3) and 5.1 μ V (23.7 ± 3.8), respectively. Suspecting that PHT was responsible for the motor regression in this patient, information on the past AED regimen and blood PHT levels

were obtained. Increased PHT levels was reported at the ages of 26, 41, 43, and 47 years, despite unchanged or tapered PHT doses (Fig. 2). PHT administration was discontinued, resulting in alleviation of nystagmus, but no improvement in motor function or deep tendon reflex. Brief tonic seizures recurred but were controlled by PB and ZNS. The MCV and amplitude of median nerve were 46.4 m/s and 5.87 mV, respectively, and the SCV and amplitude of sural nerve were 39.0 m/s and 6.60 μ V, respectively, at 10 months after PHT termination. Interestingly, venous blood PCO₂ that ranged from 46.4 to 55.8

Figure 4. The clinical course of patient 3. The body weight of the patient in this period was 32 kg. Antiepileptic drugs were given thrice daily in equally divided doses. ARDS, acute respiratory distress syndrome; CBZ, carbamazepine; CLB, clobazam; HR, heart rate; LEV, levetiracetam; LTG, lamotrigine; VPA, valproate; ZNS, zonisamide.

mmHg (eight measurements) in the 12 months before termination was normalized to 30.6–41.6 mmHg (five measurements) in the subsequent 12 months. No respiratory illness was noted during these periods.

Patient 3. The subject was a 46-year-old woman who had infantile spasms at the age of 11 months, which developed into the Lennox–Gastaut syndrome accompanied by deterioration, resulting in a bedridden state. She was not able to utter or understand any meaningful words. Episodic bradycardia to as low as 40 bpm had been present for years, but the exact age of onset was not known. An atrio-ventricular block was detected on ECG. Blood CBZ level increased to 16.4 µg/ml when the patient had urinary tract infection with mild liver dysfunction, with the following laboratory results: aspartate aminotransferase, 62 U/l; alanine aminotransferase, 60 U/l; and albumin, 2.3 g/dl (Fig. 4). During recovery from urinary tract infection and suc-

cessive respiratory tract infection, the heart rate of the patient suddenly dropped to 25 bpm at midnight. She was then transferred to a hospital with a cardiology unit. A sinus pause of more than 10 seconds occurred twice but was then resolved with continuous infusion of L-isoprenaline and noradrenalin. The patient's parents and cardiologists decided not to implant a pacemaker but to administer cilostazol instead, which has an anti-bradyarrhythmic action [3]. The dosage of CBZ was also reduced. The frequency of brief tonic seizures increased to once per 2–3 days but improved with the addition of ZNS. CBZ was discontinued following another episode of respiratory infection and tracheostomy/laryngopharyngeal separation. Bradycardia did not recur for 10 months thereafter (Fig. 4).

Discussion

This study has considerable limitations. First, the data were collected retrospectively.

Table 1. Adverse effects of antiepileptic drugs in individuals with severe motor and intellectual disabilities.

Adverse effect	Antiepileptic drug
Aeropagia	AZA
Bradycardia/atrioventricular block	CBZ, OXC, LCM, PHT, fosphenytoin injection
Hypoventilation	PB, CZP, CLB, DZP, PHT
Pancreatitis	VPA, CBZ, GBP, LTG, TPM
Fanconi syndrome/ renal tubular dysfunction	VPA
Urinary retention	CBZ, LEV, CZP, DZP
Urolithiasis	TPM, ZNS, AZA, PHT
Hyponatremia	CBZ, OXC, VPA, GBP, LTG, LEV
Aggression/agitation	LEV, TPM, ZNS, PER, CZP, VPA, LTG
Oculogyric crisis	CBZ, LTG, OXC, GBP

This table focuses on the adverse effects potentially more common or severer in individuals with severe motor and intellectual disabilities (SMIDs) compared to those in general epilepsy population. The list of drugs is based on the results of the present study, reference [6–29], and package inserts of the pharmaceutical products. As a result, many hematological, gastrointestinal, and cutaneous problems, as well as certain nervous system disorders are not included.

AZA: acetazolamide, CBZ: carbamazepine, CLB: clobazam, CZP: clonazepam, DZP: diazepam, GBP: gabapentin, LCM: lacosamide, LEV: levetiracetam, LTG: lamotrigine, OXC: oxcarbazepine, PB: phenobarbital, PER: perampanel, PHT: phenytoin, TPM: topiramate, VPA: valproate, ZNS: zonisamide

Second, the sample size was small, and the patients were from a single institute. In addition, the patients were not followed for a long period. Moreover, the proportion of patients with epilepsy in our cohort was 82.5% (99/120), higher than that in the total population with SMID (50%–70%) [1] or cerebral palsy (33%–49%) [4]. However, our cohort may represent a subgroup of SMID with refractory epilepsy necessitating multiple AEDs for seizure control. This may be regarded as a condition with a higher tendency of occurrence of adverse effects. In terms of other aspects specific to SMID, a suboptimal nutritional status may result in lower serum albumin level, which in turn increases the free fraction of AEDs in the blood, leading to greater augmentation of toxicity than that expected from measured blood levels [5]. Hypoalbuminemia may also be linked to a high-

er risk of acute pancreatitis in SMID, which may enhance the patient's vulnerability to VPA-induced pancreatitis [6]. A higher incidence of VPA-induced Fanconi syndrome has been recognized in patients with SMID, which may be due to subclinical damage to the kidney caused by hypoxic–ischemic insults during perinatal asphyxia, a common etiology of brain lesions in these patients [7]. Baseline serum sodium levels are often subnormal in patients with SMID, which increase the risk of CBZ-induced hyponatremia [8]. Agitation and oculogyric crisis are often provoked by AEDs, with background cerebral damage and/or intellectual disabilities [9–13]. Table 1 summarizes the particularly significant adverse effects of AEDs in patients with SMID. Among others, urolithiasis is a well known complication due to TPM, ZNS, PHT and AZA [17–20]. In this study, CT im-

aging revealed asymptomatic renal calcification in 15 of 35 patients taking TPM, ZNS, PHT or AZA, and in 10 of 50 patients not taking the above AEDs. We observed that patients with SMID had a tendency to develop this CT abnormality, which is aggravated by the above-mentioned medications. Interestingly, patients with urinary retention without apparent spinal or brainstem lesions are often treated with CBZ and LEV, which may represent an under-recognized adverse effect [21, 22]. This issue would be confirmed if termination of these AEDs leads to resolution of the symptoms.

Pathological aerophagia is common in patients with intellectual disabilities and can cause ileus and even bowel perforation [30]. Recurrent strangulation of the ileum noted in patient 1 was assumed to be due to incarceration of the expanded intestine in postoperative adhesion regions that may have possibly formed cord-like structures. Upon observation, the patient likely swallowed air in circumstances when she felt discomfort, such as during physical examination or venous puncture, and abdominal fullness seemed to further exacerbate air swallowing. The presence of such vicious cycle and the risk of acute abdomen in patients with SMID, in whom abdominal distension is merely recognized as “constipation”, should be noted. Venting gas through a nasogastric tube or via a gastrostomy, use of a mouthpiece to inhibit deglutition, and benzodiazepines have been reported to be effective for the reduction of aerophagia [31–33]. However, air venting via the gastrostomy was not effective in patient 1. Alternatively, AZA discontinuation yielded acceptable relief of abdominal distension. The ad-

verse effects of AZA include lethargy, agitation, irritability, nausea, constipation, dysesthesia in the limbs, dry mouth, and altered tastes. The exact cause of enhanced aerophagia has not been identified, but AZA discontinuation may have reduced some of the adverse effects.

Motor regression during adulthood was an unexpected event in patient 2 who had HHE syndrome since infancy. Mutations in sodium channel subunits have been identified in some patients with HHE syndrome, allelic to the epileptic phenotype of severe myoclonic epilepsy in infancy (Dravet syndrome) [34]. Although not reported in HHE syndrome, dystonia–Parkinsonism and PHT-induced choreoathetosis may co-occur with Dravet syndrome [35, 36]. However, motor regression in the patient was far beyond the degree of disabilities associated with these phenomena and may correlate with chronic PHT administration, particularly when blood levels were elevated (>30 $\mu\text{g/ml}$) in his 40s. The presence of nystagmus and depressed deep tendon reflex, and probable peripheral neuropathy, supports this assumption. Considerable efforts have been made to keep the PHT dosage at maximum tolerable level for the management of refractory tonic/atonic seizures accompanied by frequent falls during adulthood. As a retrospective hypothesis, co-administration of CLB could have augmented the blood concentration and toxicity of PHT through interfering with the hepatic degradation of PHT [37]. Regarding the effect of PHT on the respiratory function, administration of this drug to rats blunted the augmentation of peripheral chemoreceptor activity and actual ventilation volume against hypoxia,

whereas it had no significant effect against hypercapnia [38]. This is contradictory to hypercapnia in patient 2, presumably representative of the PHT adverse effect, but the same article reported a decrease in baseline ventilation in room air [38]. Hypoventilation due to PHT at therapeutic doses has not been recognized to date. However, re-evaluation of this possibility is warranted, particularly in patients with SMID.

CBZ-induced cardiac rhythm and conduction abnormalities result from quinidine-like effects of the drug due to the structural similarity with tricyclic antidepressants [39]. Bradycardia, sinoatrial block, atrioventricular block, and sinus tachycardia have been predominantly reported in elderly adults [40-42]. These adverse effects could occur in cases with CBZ levels lower than the therapeutic range [39] and even years after the initiation of CBZ for epilepsy treatment [43]. The findings observed in patient 3 in her middle adulthood may imply a risk of CBZ-related cardiac disturbance in the SMID population. Additionally, selenium deficiency associated with enteral nutrition can cause cardiac conduction abnormalities [44]. The blood selenium levels of the patients presented in this study were subnormal compared with the reference values of healthy controls, although levels higher than 50 µg/l do not usually result in cardiac problems [44]. Substrates specific for metabolic or neurodegenerative disorders can accumulate in the lysosomes of cardiac cells, often predominantly in the conduction system [45, 46]. Whether these factors trigger the cardiac adverse effect of CBZ in SMID patients with these etiologies remains to be investigated.

In conclusion, patients with SMID are susceptible to certain adverse effects of AEDs due to severe intellectual disturbance, polypharmacy with high blood levels of AEDs for managing intractable epilepsy, and nutritional problems linked to hypoalbuminemia and possibly selenium deficiency. The problems identified in this study should be broadly acknowledged by doctors working on this disease category.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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