Thoracolumbar Kyphosis in Siblings of Mucopolysaccharidosis: A Case Report

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Abstract

Mucopolysaccharidosis (MPS) is a group of inherited metabolic disorders caused due to abnormal storage of mucopolysaccharides in different tissues of the body. They are autosomal recessive disorders, except MPS II which has an X-linked recessive pattern. Musculoskeletal manifestations occur due to disturbance in bone remodeling and improper development of ossification centers. Thoracolumbar kyphosis is the most common spinal pathology resulting from abnormal vertebral end plate ossification and growth arrest as well as hypotonia and spinal musculature imbalance. The increased life span as a result of medical treatment and lack of osseous penetration of enzyme replacement has raised the issue of thoracolumbar dysplasia and resultant deformity. Here, we discuss a case report of progressive thoracolumbar spinal deformity in two siblings suffering from MPS who underwent spine deformity correction surgeries, and literature review for the same.

Keywords: Mucopolysaccharidosis, spine deformity, scoliosis correction

Introduction

Mucopolysaccharidosis (MPS) is a group of inherited metabolic disorders which result due to a deficiency of lysosomal enzymes that play a key role in degradation of glycosaminoglycans (GAGs). They are inherited in an autosomal recessive (AR) fashion, except MPS II which has an X-linked recessive pattern. The accumulation of GAGs leads to cellular dysfunction in various tissues of the body. Typically, the patients have a short stature, corneal clouding, hearing problems, cardiac involvement, and obstructive or restrictive pulmonary disease. Musculoskeletal involvement is common in all types of MPS. The group of musculoskeletal abnormalities that occur is termed as "Dysostosis multiplex." Thoracolumbar kyphosis and gibbus due to abnormality of vertebral end-plate development and spinal muscle imbalance is the most common early presenting feature. Other associated symptoms such as vision and hearing impairments, developmental delay, hepatosplenomegaly, and cardiac involvement may also be present. Confirmative diagnosis can be made with urinary GAGs, galactosamine-6-sulphate deficiency in leukocytes, and genetic mapping. Based on clinical and biochemical studies, MPS are classified into different types from MPS I to MPS VII. Thoracolumbar kyphosis is usually treated by initial brace management and deformity correction surgery.

Case Report

Case 1

Patient was diagnosed with thoracolumbar deformity at birth. Immediately after birth, he had been in the intensive care unit care for a week. Associated knee and foot deformities were also present. The patient had normal developmental milestones and intellect. At 16 years of age, patient presented with severe thoracolumbar kyphoscoliosis (Fig 1:c,d) with Cobb's angle on anteroposterior (AP) view of 81 degrees and in lateral view of 99.8°. On screening of the whole spine, he was found to have C1-C2 instability (Fig 1:a,b). There was no neurological involvement. Associated bilateral genu valga was also present. The patient also had bilateral hip and knee flexion deformities (Fig 2:a-c). Due to the global sagittal imbalance from progressive thoracolumbar kyphosis and bilateral hip and knee flexion contractures, the ambulation status of the patient was continuously degrading.

He underwent initially C1-C2 arthrodesis (Fig 3:a). After 6 months of first surgery, spine deformity correction surgery was undertaken. By a posterior midline incision, posterior spinal instrumentation was done, and apical osteotomy and resection was carried out, the resultant defect bridged by mesh cage

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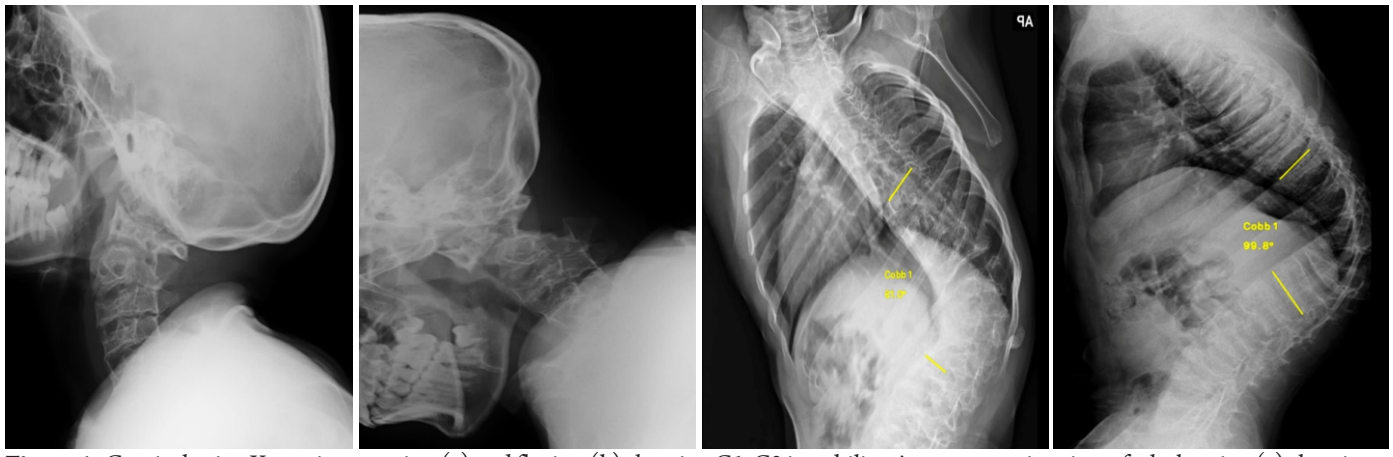

Figure 1: Cervical spine X-rays in extension (a) and flexion (b) showing C1-C2 instability. Anteroposterior view of whole spine (c) showing a scoliotic deformity of 81°. The lateral view (d) of whole spine shows a thoracolumbar gibbus, leading to a 99.8° of kyphosis. Also note, the typical platyspondyly and anterior beaking of vertebrae which are hallmarks of mucopolysaccharidosis.

Figure 2: (a-c) Pre-operative clinical photographs of the patient, demonstrating the thoracolumbar deformity (a), along with hip and knee flexion contractures (b) and associated genua valga (c).

and autologous bone graft. Posterior fusion was then done to complete circumferential arthrodesis. Post-operatively, rehabilitation was started, and patient was ambulatory, initially with walker support, then independently (Fig 4). Post-operative AP and lateral Cobb's (Fig 3:b,c) were respectively 2.3° and 34.8°. Correction of 97.2% on AP and 65.1% on lateral views was achieved with implant density of 73%.

Seven months after deformity correction surgery, reconstructive surgeries were done in bilateral knees. The patient was given calipers in the immediate post-operative period. Rigorous rehabilitation was carried out for 1.5 years, and he was able to carry out all activities of daily living, including driving vehicles. At 5-years follow-up (Fig 5:a,b), patient can walk and do all his normal activities, including driving vehicles without any support.

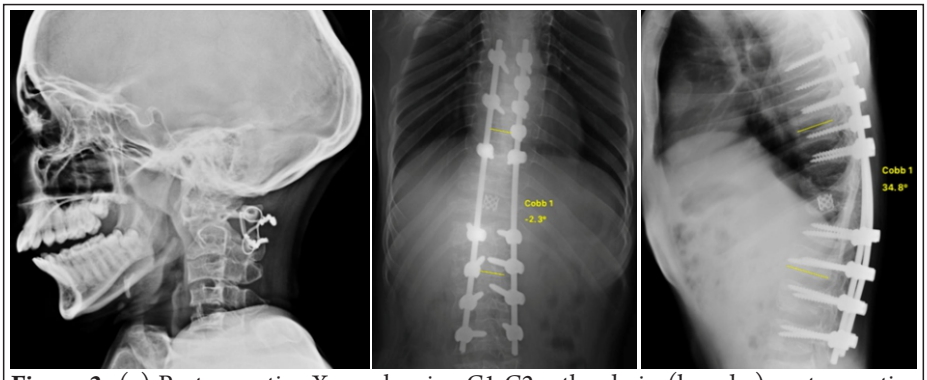

Figure 3: (a) Post-operative X-ray showing C1-C2 arthrodesis. (b and c) post-operative anteroposterior and lateral views showing correction of the thoracolumbar deformity.

Case 2

The patient was diagnosed with deformity at birth. She is the sibling of the patient described in Case 1. The perinatal and postnatal period was uneventful. All developmental milestones were normal. The patient had progressive thoracolumbar kyphosis and deformity in bilateral knees. The lateral Cobbs angle was 74°. Bilateral hips X-rays showed developmental dysplasia of bilateral femoral heads. (Fig 6, Fig 7. a & b)

She underwent bilateral knee surgery for progressive genu valgum at the age of 13 years (Fig 8). At 17 years of age, spine deformity correction surgery was undertaken (Fig 9:a,b). Through a posterior midline approach, posterior instrumentation was done along with multiple Ponte's osteotomy to obtain deformity correction. The peri-operative and post-operative periods were uneventful. Post-op Cobb's angle was 24.2°. 67.3% correction was obtained. The patient was mobilized from post-operative day 2. At 5-years of follow-up (Fig 10:a,b), the patient has no complaints and is independently mobile. She can do all activities of daily living.

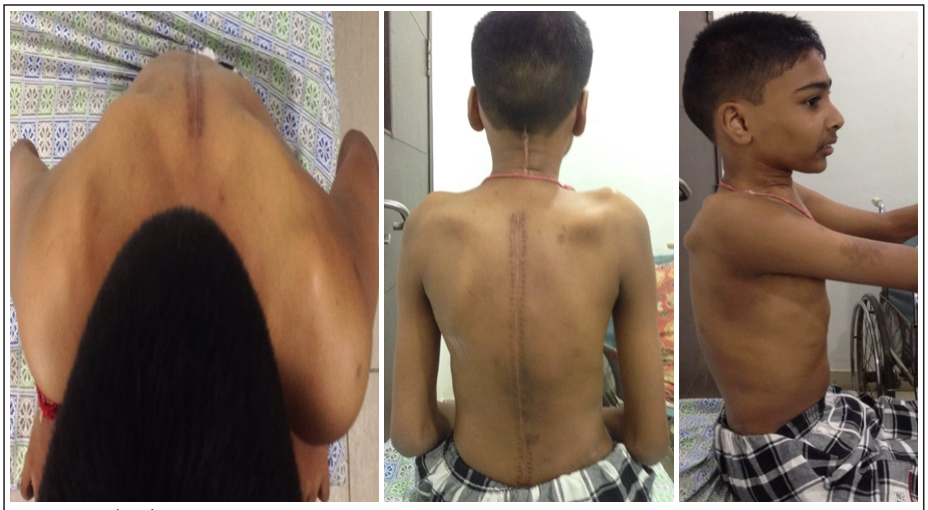

Figure 4: (a-c) Post-operative clinical photographs of the patient.

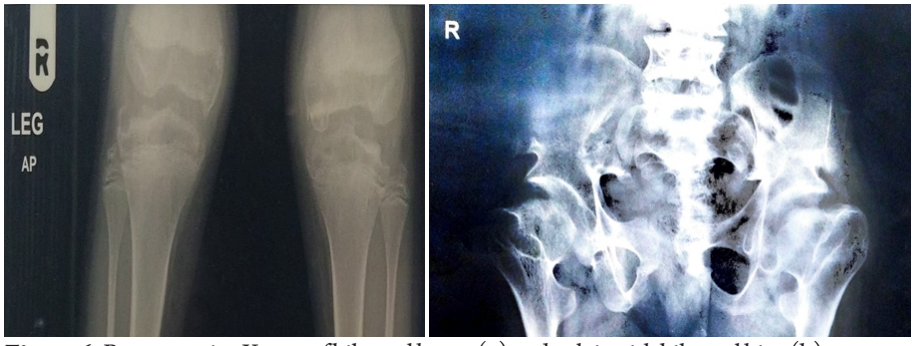

Figure 6: Pre-operative X-rays of bilateral knees (a) and pelvis with bilateral hips (b).

Discussion

MPS is a group of inherited metabolic storage disorders in which there is defective degradation of GAGs, the accumulation of which leads to cellular damage in various tissues of the body. The incidence of MPS is 1 in 100,000 live births [1]. However, the exact incidence of MPS cannot be verified due to lack of epidemiological and population-based studies [2]. One such study shows the incidence to be 1 in 22,500 persons [3]. The disorders have a chronic progressive course and varied clinical features with varying severity. Almost all patients have multisystemic involvement, abnormal facies, and musculoskeletal afflictions. There are seven major types described by the deficient enzyme- I, II, III, IV, VI, VII, IX [4]. Types V and VIII are almost always fatal in the perinatal period, hence never used. Till date, only one patient has been described to have MPS type IX [5]. MPS is an inherited disorder that follows an AR pattern, except type III which follows an X-linked recessive pattern.

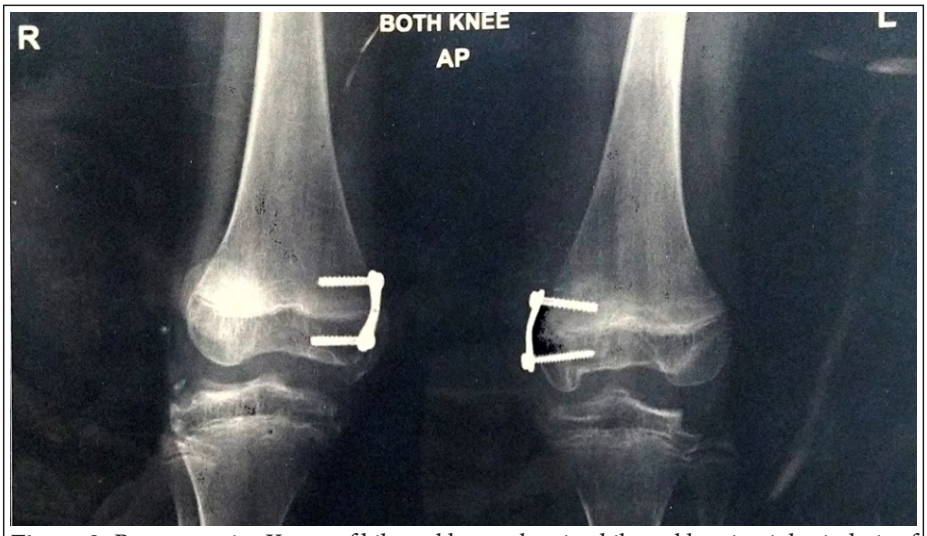

Figure 8: Post-operative X-rays of bilateral knees showing bilateral hemi-epiphysiodesis of distal femur.

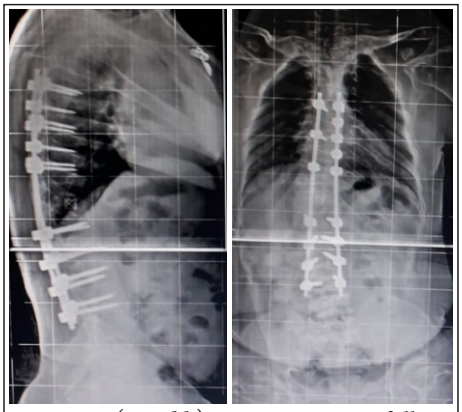

Figure 5: (a and b) X-rays at 5-years follow-up.

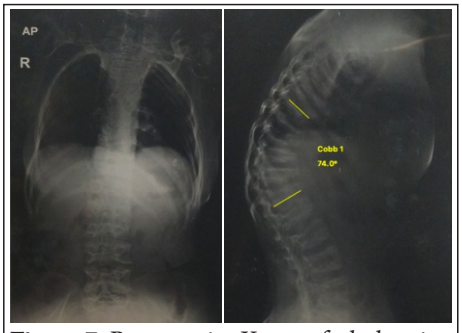

Figure 7: Preoperative X-rays of whole spine anteroposterior (a) and lateral (b) views. The X-rays also show the hallmark features of Mucopolysaccharidosis such as platyspondyly, anterior beaking of vertebral bodies, osteoporosis and thoracolumbar kyphosis.

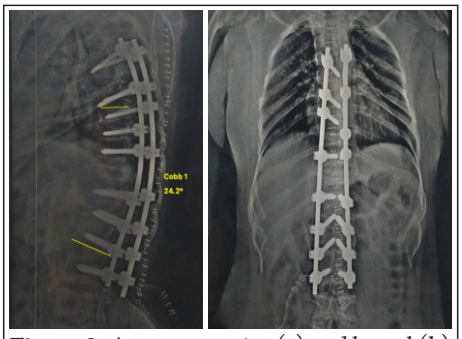

Figure 9: Anteroposterior (a) and lateral (b) views of post-operative whole spine.

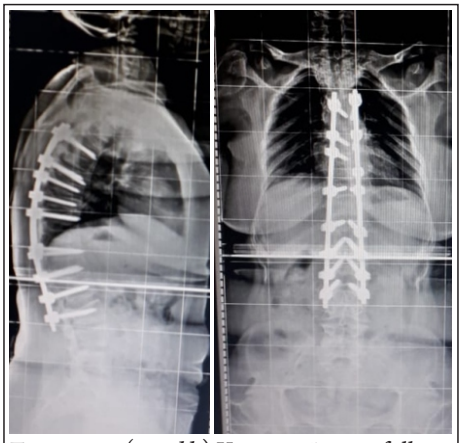

Figure 10: (a and b) X-rays at 5-years follow-up.

Hence, multiple patients in the same family can be affected by the disorder. Rekka et al. [6] reported a case series of thoracolumbar kyphosis in three siblings of the same family in which they reported oral, dental, and spine radiographic findings of MPS in the patients. Garne and Hurme [7], in their case series, described abnormalities in nine siblings diagnosed with MPS.

Coarse facial features, corneal clouding, hearing impairment, cardiac involvement, obstructive and restrictive pulmonary disease and hepatosplenomegaly, progressive neurological decline are characteristic features [8]. Musculoskeletal abnormalities such as short stature, dental problems, joint degeneration, spinal deformity, skeletal dysplasia, and limb deformity, are common in all subtypes of MPS [9, 10]. The exact pathophysiology of MPS is poorly understood. Specific enzyme deficiencies lead to accumulation of GAGs, leading to activation of main osteoclastic stimulator cathepsin K. This leads to joint and cartilage degeneration [11]. Accumulated GAGs stimulate cytokines and chemokines leading to apoptosis of chondrocytes and synovial destruction [12, 13]. Defect in chondrocytes, in turn, causes abnormalities in bone formation and ossification. The vertebral end-plate ossification is disturbed leading to progressive spinal deformity. Progressive thoracolumbar kyphosis is a hallmark of MPS [14]. Associated craniocervical stenosis may be present. Cranio-cervical stenosis occurs as a result of bony stenosis, soft tissue hypertrophy, and ligament thickening [15, 16, 17]. Odontoid hypoplasia leads to atlantoaxial instability [18, 19].

Both the patients of our case report had coarse facial features, skeletal dysplasia, dental involvement, thoracolumbar kyphosis, and normal intelligence. According to these clinical features, both the patients fit into MPS type VI.

The etiopathology of thoracolumbar kyphosis occurring commonly in MPS is not completely known but it may be related to muscle imbalance and hypotonia, and abnormal ossification and end-plate growth. This leads to "beaking" appearance of vertebrae on X-rays and anterior disc prolapse on magnetic resonance imaging (MRI). If left untreated, it is likely to progress, with accelerated worsening during the adolescent growth spurt [20]. About 80% patients with MPS have thoracolumbar kyphosis [21]. These typical radiological features can also be appreciated in the X-rays of both our patients.

Non-operative treatment of MPS includes hemopoietic stem cell transplantation and enzyme replacement therapy, which has significantly reduced morbidity and death rate in MPS [22]. Long-term clinical benefit and safety of laronidase in attenuated MPS patients has already been demonstrated [23]. Weekly infusions of idursulphate (human recombinant iduronate-2-sulphatase) with the dose of 0.5 mg/kg for 2 years showed sustained clinical improvement [24].

However, the musculoskeletal abnormalities do not respond well to enzyme replacement therapy due to incomplete penetrance of the enzyme into musculoskeletal tissues [25]. As a result, the skeletal deformities are progressive in nature and remain unsolved by enzyme replacement therapy [26].

There are no specific guidelines regarding surgical stabilization in thoracolumbar kyphosis in MPS. Bracing can neutralize weight-bearing forces, but it does not prevent the progression of spinal deformity [27]. Sagittal imbalance occurs as a result of weak abdominal musculature, vertebral dysplasia, hip and knee flexion contractures, and anterior shifting of the trunk. To restore this, compensatory mechanisms take over leading to thoracic lordosis and pelvic retroversion [28].

The natural progression of thoracolumbar deformity in MPS is highly variable. Evidence regarding the same is lacking. The spine deformity tends to follow a variable course in each type, but patients with Hurler's syndrome (MPS I) tend to have early, progressive, and more severe forms of thoracolumbar kyphosis. Furthermore, no relation has yet been established between phenotypic severity of the thoracolumbar deformity, enzyme levels, engraftment, and genotype [14, 20, 29].

The surgical options include anterior instrumented fusion, posterior instrumented fusion, and combined anterior-posterior fusion. Anterior instrumented fusion was first reported in a series of seven children with MPS, where good correction was obtained without complications. An extensile thoracolumbar approach is taken, which may be extended to retroperitoneal approach in the abdomen. The discs are excised until posterior longitudinal ligament is reached, thereby allowing adequate anterior decompression. Vascularized rib graft is used for fusion and maximum fusion area subjected to compressive forces leads to excellent union [30]. The theoretical disadvantages of anterior only procedures include add-on phenomenon and kyphosis at adjacent levels.

Posterior-only technique is the other option for the treatment of these

deformities. Normally, kyphosis is corrected by posterior instrumentation. But in MPS, there is bone dysplasia and growth arrest of the anterior column as well as associated anterior translation of the spine. As a result, these procedures fail to correct sagittal imbalance [31]. There is also a higher risk of pseudoarthrosis, implant-failure, and consequent neurological deficits in posterior-only procedures [32]. As a result, posterior-only procedures are seldom used.

Circumferential arthrodesis involves fusion of anterior as well as posterior column of the spine, giving best results. The procedure is performed by a single-stage thoracoabdominal retroperitoneal approach and a midline posterior approach [14]. Anteriorly, apical vertebra is excised, and the defect is bridged by autologous rib grafts. Through midline posterior approach, posterior instrumentation and fusion is performed. Circumferential arthrodesis by combined anterior-posterior approaches reduces the risk of neurogenic complications [33].

Despite good correction of the thoracolumbar deformity, there are significant medical and anesthetic risks associated in patients with MPS [29]. Respiratory insufficiency and airway obstruction are very common. A study by Van der Linden et al. showed an overall complication rate of 13.5% in surgically treated MPS patients. Cervical stenosis is described in 3.4% of MPS patients. Atlanto-axial instability due to odontoid hypoplasia is reported in 20% of patients [21]. Neurological compromise can occur due to cervical stenosis and craniocervical instability, which need to be addressed first. Screening of craniovertebral junction should always be done as craniocervical instability may be asymptomatic at the first clinical presentation. C1-C2 instability in our Case 1 was diagnosed by screening of whole spine clinically and on imaging studies. Due to disastrous complications of cervical stenosis and instability, it is imperative that it is addressed first before proceeding to other procedures such as deformity correction.

Another complication is related to the poor bone quality in patients of MPS. This can lead to poor pull-out strength of screws and subsequent implant failure. Intra-operatively, the correction procedure can lead to screw loosening or pedicle fracture, leading to neurological deficit.

Life expectancy has significantly increased in MPS patients due to enzyme replacement therapy and hematopoietic stem cell transplant. Due to this, the incidence of thoracolumbar and other musculoskeletal deformities has also increased. These problems need prompt diagnosis and treatment to ensure a better quality of life in MPS patients. Lower limb surgeries for hip and knee dysplasia are performed in early life (first decade) to prevent degradation of ambulatory status. A multidisciplinary approach is a must for MPS patients who require spine deformity correction surgery. Thoracolumbar kyphosis is a hallmark of MPS and is recognized early. It is not responsive to systemic treatments and requires surgical intervention. Anesthetic management (Airway obstruction, cervical instability, and cardiorespiratory impairment) is of utmost importance for uneventful peri- and post-operative periods.

Conclusion

MPS is an uncommon disorder. It is associated with multiple skeletal manifestations with thoracolumbar kyphosis being most common. It is associated with multiple epiphyseal dysplasia producing skeletal manifestations in hips and knees. Being an AR disorder, it can be present in siblings. Progressive kyphosis along with other skeletal deformities can lead to severe disability in ambulation. Progressive thoracolumbar kyphosis can be successfully treated surgically.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the Journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Conflict of Interest: NIL; **Source of Support:** NIL

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