Struvite stones causing recurrent pain in a child with cerebral palsy: a lesson for a pragmatic approach to pain in children with cerebral palsy and cognitive impairment.

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Case report

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Abstract

Background

Children with severe cognitive impairments (CI) from any cause, such as cerebral palsy (CP), dysmorphic or chromosomal syndromes, traumatic brain injury, neurodegenerative disorders, and epileptic syndromes, experience pain more frequently than healthy peers. Although it is a common problem, pain is many times unrecognized because these patients are often unable to self-verbalize it or exhibit uncommon behaviors when they experience it, leading to a delay in the recognition and management of pain by the physicians. Untreated chronic or recurrent pain profoundly affects the quality of life of these children and interferes with their performance and adaptive function. Recognition, measurement, and treatment of pain in this population is challenging, and a clinical diagnosis of urinary tract infection or lithiasis may not be immediate.

Case presentation:

We report the case of an eight-year-old child with cerebral palsy who was admitted for recurrent abdominal pain lasting for one month. While blood laboratory tests were all in the normal range, the diaper examination revealed multiple stones. Urine culture tested positive for Providencia stuartii, a Gram-negative bacteria, and an antibiotic treatment with ceftibuten was started for two weeks. The patient fully recovered in three days without any recurrence.

Conclusions

urine analysis, to detect an infection, and renal and bladder US, to rule out stones, should be systematically considered in patients with cognitive impairment with unexplained pain. In a pragmatic, concise approach, the basic principles of diagnosis and treatment of pain in children with cognitive impairment are reviewed.

Background

Children with severe cognitive impairments (CI) from any cause, such as cerebral palsy (CP), dysmorphic or chromosomal syndromes, traumatic brain injury, neurodegenerative disorders, and epileptic syndromes, experience pain more frequently than healthy peers. Although it is a common problem, pain is many times unrecognized because these patients are often unable to self-report it or may exhibit uncommon behaviors when they suffer, and physicians are sometimes less prone to recognize it. Physicians should be fully aware of this issue since untreated chronic or recurrent pain profoundly affects the quality of life of these children and interferes with their performance and adaptive function. We report struvite stones as the cause of recurrent pain in a child with cerebral palsy and we discuss the approach to the possible causes of pain in these patients.
Case Report

An eight-year-old child was admitted for five-weeks of recurrent abdominal pain. The pain was reported to be present almost daily, disrupting sleep and causing episodes of agitation and restlessness, with sudden and incessant crying and increased heart rate, particularly when the child was moved from the stroller to his bed. The mother reported a partial improvement after ibuprofen administration. His previous history was remarkable for developmental delay, cerebral palsy, spastic tetraparesis, drug-refractory epilepsy treated with vigabatrin, levetiracetam, topiramate, phenobarbital, and the placement of an apercutaneous endoscopic gastrostomy six years earlier. The parents did not report any recent history of vomiting, diarrhea, constipation, or fever. A dental evaluation ruled out tooth decay, and an orthopedic evaluation excluded an osteoarticular problem. Laboratory tests were performed to investigate possible causes of pain, including white blood cell count, glucose, alanine aminotransferase, aspartate aminotransferase, creatinine, electrolytes, bilirubin, amylase and lipase, and they were all in the normal range.

Physical examination was unremarkable, but stones were noted when the diaper was removed (Fig. 1). The stones analysis showed struvite aggregates. A urine culture was performed, testing positive for Providencia stuartii, a Gram-negative bacteria. Therefore, antibiotic treatment with ceftibuten was started for two weeks, with no pain episodes after three days. A renal ultrasound did not reveal endoluminal other stones and ruled out a pelvic or ureteral dilatation. No additional episodes were noted in the following year, and follow-up ultrasound scans did not reveal vesicoureteral reflux or incomplete bladder emptying.

Discussion And Conclusion

Pain assessment in children with cognitive impairment and chronic illness such as cerebral palsy or syndromic diseases is challenging, and a clinical diagnosis of urinary tract infection or lithiasis can be difficult. Remarkably, these patients are prone to be affected by urinary stones, due to several predisposing factors such as hypercalciuria, bone demineralization, dehydration and topiramate treatment for concomitant epilepsy. Struvite stones are a subset of kidney stones, composed of magnesium ammonium phosphate (struvite) and calcium carbonate-apatite, which form as a result of urinary tract infections with urease-producing pathogens. It is known that this type of stone is formed quickly, within a few weeks, in the presence of urease-producing bacteria, from genera such as Proteus, Providencia, Klebsiella, Staphylococcus. When the production of ammonia increases and the urine pH is high, the solubility of phosphate decreases, and struvite stones can develop.

Prevalence of struvite stones in children has decreased over the past decades: in France, they accounted for 11% of all urinary stones in the 1980s, then reduced to 6% in the 2000s. In a retrospective analysis, Gnessin et al. showed how immobile patients with musculoskeletal anomalies were prone to form struvite stones (18.4% vs. 6.2% in the control group). This event is due to the several risk factors of UTIs in this population, such as incomplete bladder emptying, vesicoureteral reflux, catheterization, neurogenic bladder.
Clinical presentation of struvite stones substantially differs from other stone types: typical renal colic is not always present, while flank or abdominal pain accounts for nearly 70%, followed by fever (26%) and gross hematuria (18%)

Diagnostic workup should include urinalysis, renal and bladder culture, and ultrasonography, which can detect a densely calcified mass, producing marked posterior acoustic shadowing; indeed, a plain radiograph can also be able to identify radiopaque images, appearing as branching calcific densities overlying the renal outline. Stone culture is recommended to identify urease-producing bacteria and direct antibiotic therapy, since bacteria identified by urine culture do not always match those cultured from the stone.

Treatment includes an initial antibiotic regimen, such as amoxicillin-clavulanate or cefixime, before an eventual removal. Timing and duration of therapy have not been definitively established: 1–2 weeks of enteral antibiotics specific for urine culture are recommended, if available, with the addition of broad-spectrum parenteral preoperative antibiotics. After treating the episode, imaging and urine cultures should be repeated within 3 months to confirm stone-free status or identify recurrence.

Pain recognition.

Since the response to pain and its expression in this population is heterogeneous, recognition may be delayed; however, the experience of pain is often persistent and frequent, sometimes even on a daily basis.

Specific pain assessment scales (r-FLACC, INRS, NCCPC-R, PPP) have been introduced based on the observation of pain behaviors, none of which are recommended on another, however all being more precise than generic pain assessment tools. The main advantage of these scales is that they include physiologic and behavioral items aiming at complete pain recognition. These scales' main disadvantage is that they require minimal specific training and are more time-consuming. The revised Face, Legs, Activity, Cry, Consolability (r-FLACC) scale (Table 1) is based on 5 items, with a score ranging from 0 to 10; it has been rated by nurses and physicians as having higher clinical utility in terms of complexity, compatibility, and relative advantage when compared to the Non-Communicating Children Pain Checklist-Postoperative Version (NCCPC-PV). The latter appears more suitable in the absence of a pre-defined pain assessment with parents, as required by the revised FLACC. Overall these scales should be used aiming at individualization of each child specific pain behaviors, such as the misleading "freezing," laughter or self-injurious behaviors, establishing a shared knowledge, and common language with parents. Broader use of these tools can help go beyond false beliefs such as the alleged indifference to the pain of some of these children or the "neuro-irritability" sometimes used to explain increased tone and movement. Remarkably, pain assessment and management in these children should never disregard a positive interaction with their parents, which remain the best proxy measure of their kids' pain. A milestone paper described how experiential learning leads mothers to "develop a sense of knowledge" of their children, managing to be competent interpreters and translators of their sons' pain and finding the best balance between pain treatment and adverse consequences of pain medications. Health professionals should support this
process so that recognition and action based on parent’s concerns will help reach the best pain-related decisions about their children. This procedure requires a specific attitude of empathy and the ability to listen. The role of parents is also crucial in distinguishing fear and anxiety from pain. In children with moderate to severe cognitive impairment, anxiety, and fear have been shown to play an essential role in procedural pain and worsen its perception and impact. Their relevance should not be underestimated and should be approached in a holistic perspective. A recent study demonstrated a significantly different cortical activation pattern during venipuncture in children with CPI compared to healthy peers, suggesting that a possible lack of frontal to limbic area connection may cause an impaired control of emotions.

Pain assessment and diagnosis.

A proposal for a possible diagnostic workup for pain in patients with cognitive impairment is shown in Fig. 2.

When trying to address the different causes from an epidemiological perspective, based on the frequency of events, various aspects should be considered.

The issue of painful contractures and dystonia should be managed, with a child neurologist and physiotherapist in order to optimize the use of splints, tutors, as well as, the need for baclofen or botulinum toxin treatment. Intractable pain due to a dislocated hip may be approached with an intra-articular steroid and a topical anesthetic injection, which may allow months of well-being.

The gastrointestinal tract is one of the most common sources of pain among these patients. Impaired gastrointestinal motility, insufficient hydration, and immobility lead to constipation in up to 75% of patients, and an adequate amount of fiber should be provided to them in a delicate balance through which high fiber formulas can slow down gastrointestinal emptying.

Gastric emptying in children with a PEG and Nissen fundoplication may be delayed causing pain and nausea. On the other hand, an accelerated gastric emptying can be facilitated by an extensively hydrolyzed formula, but can cause either a persistent unpleasant sense of gastric emptying or even a dumping syndrome with an irritable, sweaty and restless child with hypoglycemia two hours after the meal. In this perspective, a trial with a different feeding should always be thought.

GERD should be considered an unlikely cause of pain in patients already treated with adequate dosage proton-pump inhibitors, whose therapy can be continued indefinitely. If present, the PEG tube should be examined to rule out gastrostomy infections, granuloma, dislocation, occlusion, or buried bumper syndrome.

Even when no specific concerns are identified, a dental assessment should be deemed if not already performed in the past year.
Osteopenia is found in up to 95% of non-ambulating children with cognitive impairment, 20% will experience a femoral fracture during their life\(^3\), with a definite risk of recurrence. Radiography or bone scan should be performed to rule out fractures or hip dislocations when positioning, bathing, or dressing are difficult because of the pain. If osteopenia-related back pain is suspected, especially in case of pain that worsens at night or while the child is moved, an ex juvantibus trial with bisphosphonates maybe considered\(^3\). Last but not least, the urinalysis to detect an infection and renal and bladder US to rule out stones should be systematically performed\(^3\).

A consult with a child neurologist with specific experience in the field should always be considered when a clear cause is not identified, to rule out and treat possible dystonic disorders, or more rare epileptic equivalents that need a specific therapeutic approach such as tetrabenazine\(^3\).

Once ruled out the above causes, an empirical medication trial directed to neuropathic pain should be evaluated while considering further invasive diagnostic tests in children with long-standing irritability and pain behaviors.

Remarkably some syndromes, as the Noonan syndrome, are specifically associated with a higher risk of neuropathic pain\(^3\).

Given its safety and its effect on peripheral and central neuropathic pain, visceral hyperalgesia, autonomic dysfunction and spasticity in adults, gabapentin is an off-label but reasonable first-line choice\(^3\). The benefit of this therapy would indirectly confirm the neuropathic source of pain and avoid repeating testing and interventions for months in search of a cause, which often delays appropriate pain management.

Sleep quality should be addressed as this is a relevant issue in children with chronic or recurrent pain\(^3\). Remarkably, a sleep disorder can also be mistaken for chronic pain, due to the reciprocal influence of these domains\(^3\). Finally, in cases of extreme pain and dystonia that do not respond to conventional treatment, the symptomatic intranasal use of dexmedetomidine at home could be reconsidered in the setting of palliative care\(^3\).

**Declarations**

*Ethics approval and consent to participate*

Not applicable

*Consent for publication*

Obtained

*Availability of data and materials*
Not applicable

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

AT, SB, FP and AGG wrote the first draft of the manuscript. AM followed clinically the patient. EB and GC made the revision of the manuscript.

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Authors' information

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Table 1. Revised Face, Legs, Activity, Cry, Consolability (R-FLACC) scale (from Malviya et al.\textsuperscript{13}).

| Scale       | Description                                                                 | Example                                                                 |
|-------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------|
| Face        | 0 = No particular expression or smile                                       | 0 = Normal position or relaxed; usual tone and motion to limbs          |
|             | 1 = Occasional grimace/frown; withdrawn or disinterested; appears sad or worried | 1 = Uneasy, restless, tense; occasional tremors                        |
|             | 2 = Consistent grimace or frown; frequent/constant quivering chin, clenched jaw; distressed-looking face; expression of fright or panic | 2 = Kicking, or legs drawn up; marked increase in spasticity, constant tremors or jerking |
| Legs        | 0 = Normal position or relaxed; usual tone and motion to limbs               | 0 = Normal position or relaxed; usual tone and motion to limbs          |
|             | 1 = Uneasy, restless, tense; occasional tremors                             | 1 = Uneasy, restless, tense; occasional tremors                        |
|             | 2 = Kicking, or legs drawn up; marked increase in spasticity, constant tremors or jerking | 2 = Kicking, or legs drawn up; marked increase in spasticity, constant tremors or jerking |
| Activity    | 0 = Lying quietly, normal position, moves easily; regular, rhythmic respirations | 0 = Lying quietly, normal position, moves easily; regular, rhythmic respirations |
|             | 1 = Squirming, shifting back and forth, tense guarded movements; mildly agitated (e.g. head back and forth, aggression); shallow, splinting respirations, intermittent sighs | 1 = Squirming, shifting back and forth, tense guarded movements; mildly agitated (e.g. head back and forth, aggression); shallow, splinting respirations, intermittent sighs |
|             | 2 = Arched, rigid or jerking; severe agitation; head banging; shivering (not rigors); breath holding, gasping or sharp intake of breaths, severe splinting | 2 = Arched, rigid or jerking; severe agitation; head banging; shivering (not rigors); breath holding, gasping or sharp intake of breaths, severe splinting |
| Cry         | 0 = No cry/verbalization                                                    | 0 = No cry/verbalization                                                |
|             | 1 = Moans or whimpers; occasional complaint; occasional verbal outburst or grunt | 1 = Moans or whimpers; occasional complaint; occasional verbal outburst or grunt |
|             | 2 = Crying steadily, screams or sobs, frequent complaints; repeated outbursts, constant grunting | 2 = Crying steadily, screams or sobs, frequent complaints; repeated outbursts, constant grunting |
| Consolability | 0 = Content and relaxed                                                     | 0 = Content and relaxed                                                |
|             | 1 = Reassured by occasional touching, hugging or being talked to. Distractible | 1 = Reassured by occasional touching, hugging or being talked to. Distractible |
|             | 2 = Difficult to console or comfort; pushing away caregiver, resisting care or comfort measures | 2 = Difficult to console or comfort; pushing away caregiver, resisting care or comfort measures |

**Figures**
Figure 1

Brownish stones, suggestive for struvite aggregates
Obtain history and physical examination
(involves parents, appropriate pain assessment scales)

History and/or examination suggest etiology
(including common problems such as otitis media, menses, testicular or ovarian torsion, appendicitis)

Yes

Initiate interventions or perform confirmatory studies

No

Continued symptoms

Consider:

- **Constipation**: hydration, adequate amount of fibers, laxatives
- **GERD**: consider empirical proton-pump inhibitor
- **Gastrointestinal motility disorders/Dumping Syndrome**: rule out postprandial hypoglicemia, evaluate gastric emptying if a PEG is in site
- **Dystonia/Painful Contractures**: review splints, tutors, baclofen, botulinum toxin injections, intra-articular hip steroid injection
- **Fractures/Osteoporosis/Dislocations**: X-ray or bone scan, orthopedic evaluation
- **Caries**: dental assessment if not performed in 12 months
- **Renal stones and/or gallbladder stones**: urine analysis and culture, abdominal US
- **Headache**: evaluate blood pressure, consider ex iuvantibus NSAIDs
- **Seizures/Uncontrolled Dystonia**: pediatric neurology evaluation for possible changes in anti-epyleptic or tetrabenazine treatment

Yes

Improvement in symptoms following treatment

No

Empirical trials:

- **Empirical analgesic trial** with paracetamol or NSAIDs (guarantee adequate hydration)
- **Change of feeding** to modify gastric emptying
- **Bisphosphonates** if osteopenia suspected
- **Empirical neuropathic pain treatment with Gabapentin** if recurrent irritability with pain behaviours
- **Sleep quality**: after failure of conventional drugs (melatonine, benzodiazepines, anti-histamine) consider at home treatment with IN dexmedetomidine
Figure 2

Diagnostic workup for pain in patients with cognitive impairment

Supplementary Files

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- CAREchecklistEnglish.docx