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 anycause,such as cerebral palsy (CP), dysmorphic or chromosomalsyndromes,traumatic brain injury, neurodegenerative disorders, andepilepticsyndromes, experience pain more frequently thanhealthypeers[1]. Although it is a common problem,painis several times unrecognized because these patients areoftenunable to self-report it[2] or may exhibit uncommon behaviorswhenthey suffer, and physicians are sometimes less prone torecognizeit[3].Physicians should be fully aware ofthis issue since untreatedchronic or recurrent pain profoundlyaffects the quality of life ofthese children and interferes withtheir performance and adaptivefunction[4]. We report struvite stones asthecause of recurrent pain in a child with cerebral palsy andwediscuss the approach to the possible causes of pain inthesepatients.

Case Report

An eight-year-old child was admitted for five-weeks ofrecurrentabdominal pain. The pain was reported to be present almostdaily,disrupting sleep and causing episodes of agitationandrestlessness, with sudden and incessant crying and increasedheartrate, particularly when the child was moved from the strollertohis bed. The mother reported a partial improvement afteribuprofenadministration. His previous history was remarkablefordevelopmental delay, cerebral palsy, spastictetraparesis,drug-refractory epilepsy treated with vigabatrin,levetiracetam,topiramate, phenobarbital, and the placement of apercutaneousendoscopic gastrostomy six years earlier. The parentsdid notreport any recent history of vomiting, diarrhea,constipation, orfever. A dental evaluation ruled out tooth decay,and an orthopedicevaluation excluded an osteoarticular problem.Laboratory testswere performed to investigate possible causes ofpain, includingwhite blood cell count, glucose, alanineaminotransferase,aspartate aminotransferase, creatinine,electrolytes, bilirubin,amylase and lipase, and they were all inthe normal range.

Physical examination was unremarkable, but stones were notedwhenthe diaper was removed (Fig. 1). The stones analysis showedstruviteaggregates. A urine culture was performed, testing positiveforProvidencia stuartii, a Gram-negative-bacteria.Therefore,antibiotic treatment with ceftibuten was started for twoweeks,with no pain episodes after three days. A renal ultrasounddid notreveal endoluminal other stones and ruled out a pelvic orureteraldilatation. No additional episodes were noted in thefollowingyear, and follow-up ultrasound scans did not revealvesicoureteralreflux or incomplete bladder emptying.

Discussion And Conclusion

Pain assessment in children with cognitive impairment andchronicillness such as cerebral palsy or syndromic diseases ischallenging,and a clinical diagnosis of urinary tract infection orlithiasis canbe difficult. Remarkably, these patients are prone tobe affected byurinary stones, due to several predisposing factorssuch ashypercalciuria, bone demineralization,dehydration[5] andtopiramate treatment forconcomitant epilepsy[6].Struvite stones are a subset ofkidney stones, composed of magnesiumammonium phosphate (struvite)and calcium carbonate-apatite, whichform as a result of urinarytract infections with urease-producingpathogens. It is known thatthis type of stone is formed quickly,within a few weeks, in thepresence of urease producingbacteria[7], from generasuch as Proteus,Providencia, Klebsiella, Staphylococcus. When theproduction ofammonia increases and the urine pH is high, thesolubility ofphosphate decreases, and struvite stones candevelop.

Prevalence of struvite stones in children has decreased overthepast decades: in France, they accounted for 11% of allurinarystones in the 1980s, then reduced to 6% inthe2000s[8]. Inaretrospective analysis, Gnessin et al.[9] showed how immobile patientswithmusculoskeletal anomalies were prone to form struvite stones(18.4%vs. 6.2% in the control group). This event is due to theseveralrisk factors of UTIs in this population, such as incompletebladderemptying, vesicoureteral reflux, catheterization,neurogenicbladder[10].

Clinical presentation of struvite stones substantiallydiffersfrom other stone types: typical renal colic is not alwayspresent,while flank or abdominal pain accounts for nearly 70%,followed byfever (26%) and gross hematuria (18%)[11].

Diagnostic workup should include urinalysis, renal andbladderculture, and ultrasonography, which can detect a denselycalcifiedmass, producing marked posterior acoustic shadowing;indeed, aplain radiograph can also be able to identify radiopaqueimages,appearing as branching calcific densities overlying therenaloutline. Stone culture is recommended to identifyurease-producingbacteria and direct antibiotic therapy, sincebacteria identifiedby urine culture do not always match thosecultured from thestone[12].

Treatment includes an initial antibiotic regimen, suchasamoxicillin-clavulanate or cefixime, before an eventualremoval.Timing and duration of therapy have not beendefinitivelyestablished: 1–2 weeks of enteral antibiotics specificfor urineculture are recommended, if available, with the additionofbroad-spectrum parenteral preoperativeantibiotics[13]. Aftertreating the episode, imagingand urine cultures should be repeatedwithin 3 months to confirmstone-free status or identifyrecurrence[11].

Pain recognition.

Since the response to pain and its expression in thispopulationis heterogeneous, recognition may be delayed; however,theexperience of pain is often persistent and frequent, sometimesevenon a daily basis[14].

Specific pain assessment scales (r-FLACC[15], INRS[16], NCCPC-R[17], PPP[18]) have been introduced based ontheobservation of pain behaviors, none of which are recommendedonanother, however all being more precise than genericpainassessment tools[19].Themain advantage of these scales is that they include physiologicandbehavioral items aiming at complete pain recognition. Thesescales'main disadvantage is that they require minimal specifictrainingand are more time-consuming. The revised Face, Legs,Activity, Cry,Consolability (r-FLACC) scale(Table 1) is based on 5items, with a score rangingfrom 0 to 10; it has been rated bynurses and physicians as havinghigher clinical utility in terms ofcomplexity, compatibility, andrelative advantage when compared tothe Non-Communicating ChildrenPain Checklist-Postoperative Version(NCCPC-PV)[20,21].The latter appears more suitable inthe absence of a pre-definedpain assessment with parents, asrequired by the revised FLACC.Overall these scales should be usedaiming at individualization ofeach child specific pain behaviors,such as the misleading"freezing," laughter or self-injuriousbehaviours, establishing ashared knowledge, and common languagewith parents. Broader use ofthese tools can help go beyond falsebeliefs such as the allegedindifference to the pain of some ofthese children or the"neuro-irritability" sometimes used to explainincreased tone andmovement. Remarkably, pain assessment andmanagement in thesechildren should never disregard a positiveinteraction with theirparents, which remain the best proxy measureof their kids'pain[22]. Amilestonepaper[23]described howexperiential learning leads mothers to "develop asense ofknowledge"of their children, managing to be competentinterpretersand translators of their sons'pain and finding the bestbalancebetween pain treatment and adverse consequences ofpainmedications. Health professionals should support this

processsothat recognition and action based on parent's concerns willhelpreach the best pain-related decisions about their children.Thisprocedure requires a specific attitude of empathy and theabilityto listen. The role of parents is also crucial indistinguishingfear and anxiety from pain. In children with moderateto severecognitive impairment, anxiety, and fear have been shown toplay anessential role in procedural pain and worsen its perceptionandimpact.. Their relevance should not be underestimated and shouldbeapproached in a holistic perspective[24]. A recent study demonstratedasignificantly different cortical activation patternduringvenipuncture in children with CPI compared to healthypeers,suggesting that a possible lack of frontal to limbicareasconnection may cause an impaired controlofemotions[25].

Pain assessment and diagnosis.

A proposal for a possible diagnostic workup for pain inpatientswith cognitive impairment is shown inFig. 2.

When trying to address the different causes fromanepidemiological perspective, based on the frequency ofevents,various aspects should be considered.

The issue of painful contractures and dystonia should bemanaged,with a child neurologist and physiotherapist in order tooptimizethe use of splints, tutors, as well as, the need forbaclofen orbotulinum toxin treatment. Intractable pain due to adislocated hipmay be approached with an intra-articular steroidand a topicalanesthetic injection, which may allow months ofwellbeing[26].

The gastrointestinal tract is one of the most common sourcesofpain among these patients. Impaired gastrointestinalmotility,insufficient hydration, and immobility lead toconstipation in upto 75% of patients, and an adequate amount offiber should beprovided to them in a delicate balance through whichhigh fiberformulas can slow down gastrointestinalemptying[27].

Gastric emptying in children with a PEG and Nissenfundoplicationmay be delayed causing pain and nausea. On the otherhand, anaccelerated gastric emptying can be facilitated by anextensivelyhydrolyzed formula, but can cause either a persistentunpleasantsense of gastric emptying or even a dumping syndromewith anirritable, sweaty and restless child with hypoglycemia twohoursafter the meal. In this perspective, a trial with adifferentfeeding should always be thought[28].

GERD should be considered an unlikely cause of pain inpatientsalready treated with adequate dosage proton-pumpinhibitors, whosetherapy can be continuedindefinitely[29]. Ifpresent, the PEG tube should beexamined to rule out gastrostomyinfections, granuloma,dislocation, occlusion, or buried bumpersyndrome.

Even when no specific concerns are identified, adentalassessment should be deemed if not already performed in thepastyear[30].

Osteopenia is found in up to 95% of non-ambulating childrenwithcognitive impairment, 20% will experience a femoral fractureduringtheir life[31],with adefinite risk of recurrence. Radiography or bone scan shouldbeperformed to rule out fractures or hip dislocationswhenpositioning, bathing, or dressing are difficult because ofthepain. If osteopenia-related back pain is suspected, especiallyincase of pain that worsens at night or while the child is moved,anex juvantibus trial with bisphosphonates maybeconsidered[32]. Lastbutnot least, the urinalysis to detect an infection and renalandbladder US to rule out stones should besystematicallyperformed[33].

A consult with a child neurologist with specific experienceinthe field should always be considered when a clear cause isnotidentified, to rule out and treat possible dystonic disorders,ormore rare epileptic equivalents that need a specifictherapeuticapproach such as tetrabenazine[34].

Once ruled out the above causes, an empirical medicationtrialdirected to neuropathic pain should be evaluated whileconsideringfurther invasive diagnostic tests in children withlong-standingirritability and pain behaviors.

Remarkably some syndromes, as the Noonan syndrome,arespecifically associated with an higher risk ofneuropathicpain[35].

Given its safety and its effect on peripheral andcentralneuropathic pain, visceral hyperalgesia, autonomicdysfunction andspasticity in adults, gabapentin is an off-label butreasonablefirst-line choice[30].The benefit of this therapy wouldindirectly confirm theneuropathic source of pain and avoidrepeating testing andinterventions for months in search of a cause,which often delaysappropriate pain management.

Sleep quality should be addressed as this is a relevant issueinchildren with chronic or recurrent pain[36]. Remarkably, a sleep disorder canalsobe mistaken for chronic pain, due to the reciprocal influenceofthese domains[37].Finally, in cases of extreme pain anddystonia that do not respondto conventional treatment, thesymptomatic intranasal use ofdexmedetomidine at home could beconsidered in the setting ofpalliative care[38– 40].

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.AMfollowed clinically the patient. EB and GC made the revision ofthemanuscript.

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Authors' information

Not applicable.

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Tables

Table 1. Revised Face, Legs, Activity, Cry, Consolability(R-FLACC) scale (from Malviya etal.[15]).

Face
0 = No particular expression orsmile
1 = Occasional grimace/frown;withdrawn or disinterested; appears sad orworried
2 = Consistent grimace or frown;frequent/constant quivering chin, clenched jaw; distressed-lookingface; expression of fright or panic
Individualizedbehaviour:_____
Legs
0 = Normal position or relaxed; usual tone andmotion to limbs
1 = Uneasy, restless, tense; occasionaltremors
2 = Kicking, or legs drawn up; marked increasein spasticity, constant tremors orjerking
Individualizedbehaviour:_____
Activity
0 = Lying quietly, normal position, moveseasily; regular, rhythmicrespirations
1 = Squirming, shifting back and forth, tense orguarded movements; mildly agitated (e.g. head back andforth, aggression); shallow, splinting respirations, intermittentsighs
2 = Arched, rigid or jerking; severe agitation;head banging; shivering (not rigors); breath holding, gaspingor sharp intake of breaths, severesplinting
Individualizedbehaviour:_____
Cry
0 = Nocry/verbalization
1 = Moans or whimpers; occasionalcomplaint; occasional verbal outburst orgrunt
2 = Crying steadily, screams or sobs, frequentcomplaints; repeated outbursts, constantgrunting
Individualizedbehaviour:_____
Consolability
0 = Content and relaxed
1 = Reassured by occasional touching, hugging orbeing talked to. Distractible
2 = Difficult to console or comfort; pushingaway caregiver, resisting care or comfortmeasures
Individualizedbehaviour:_____

Figures

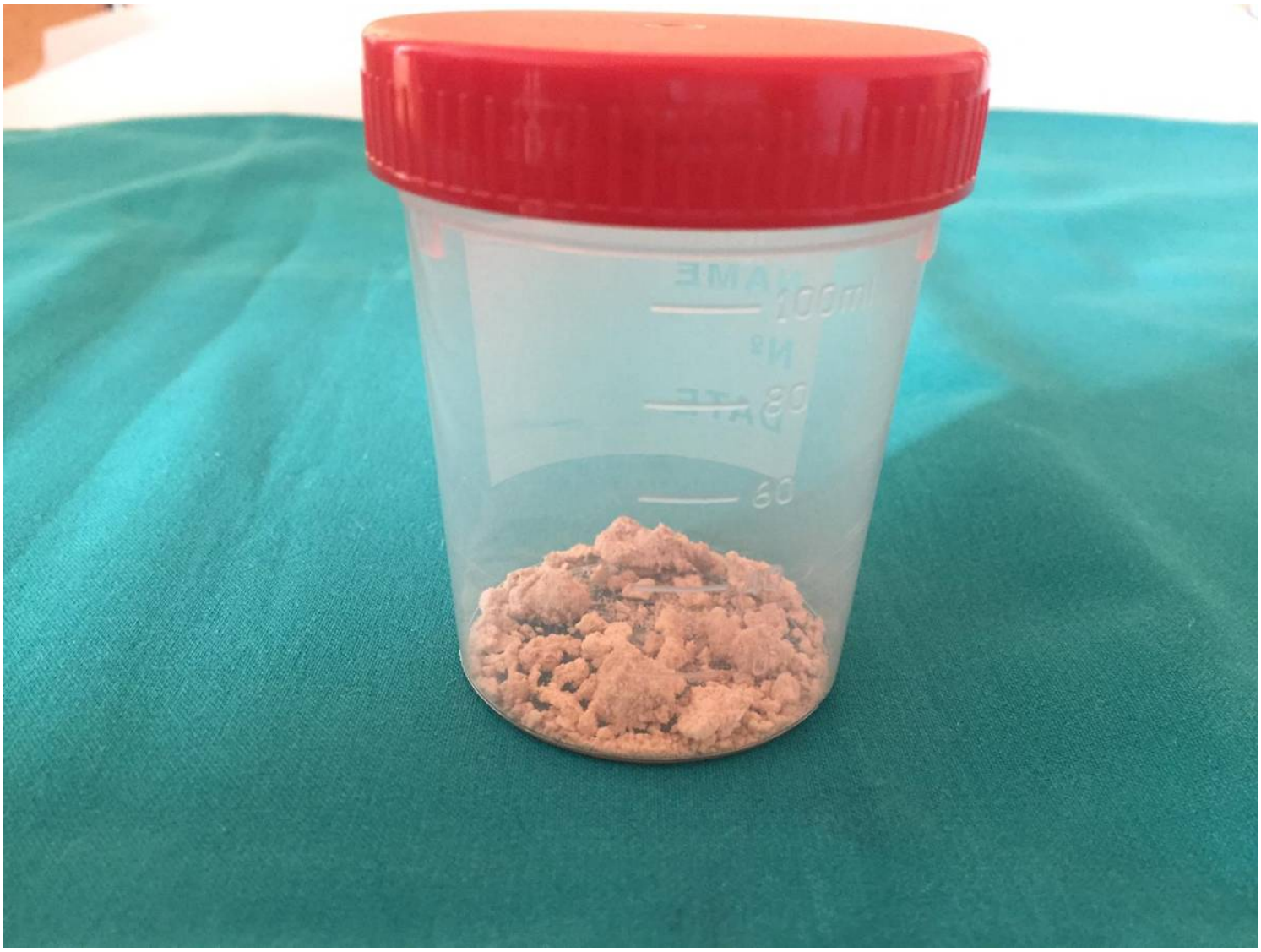
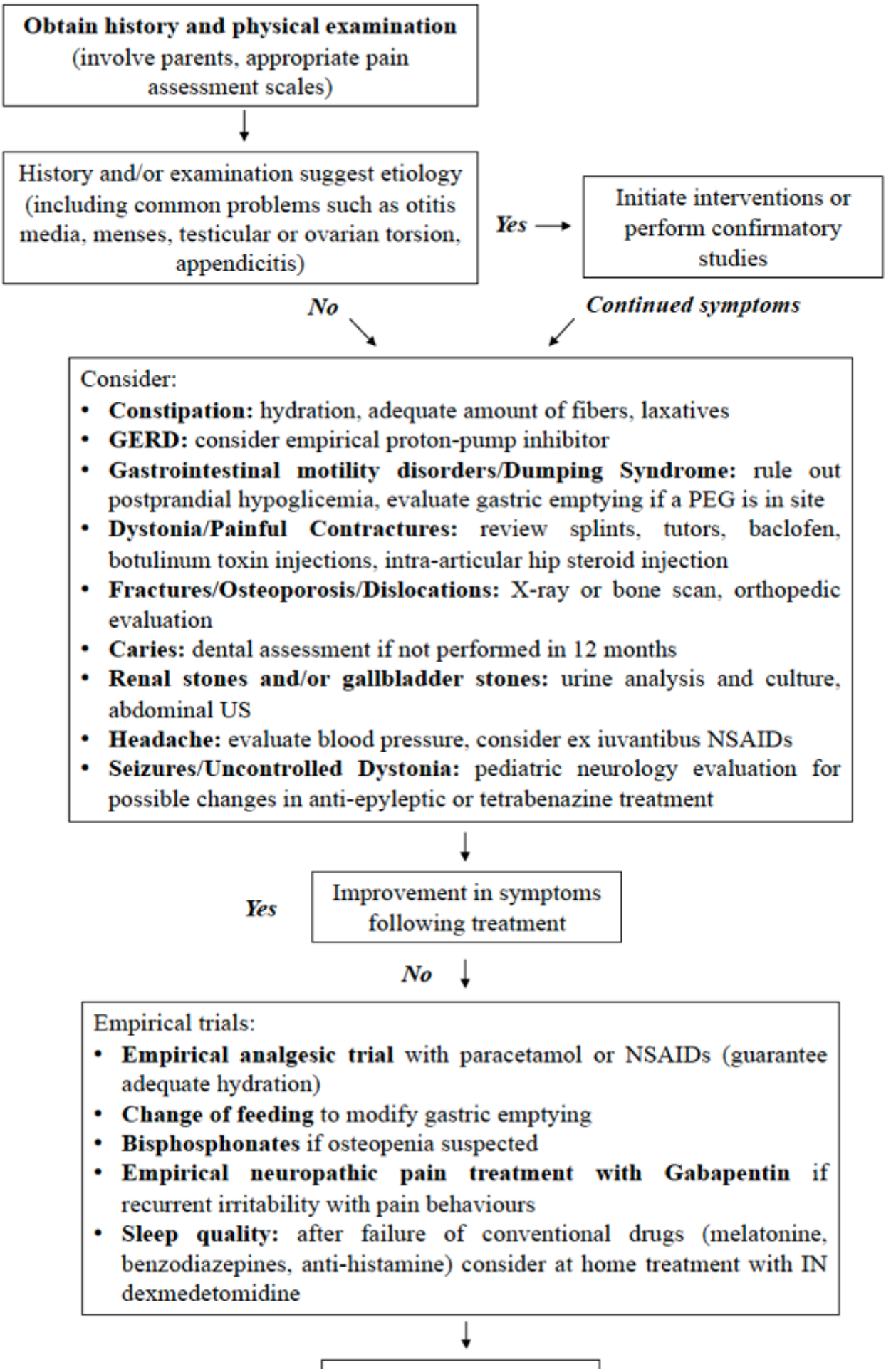


Figure 1

Brownish stones, suggestive for struvite aggregates


Obtain history and physical examination (involve 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

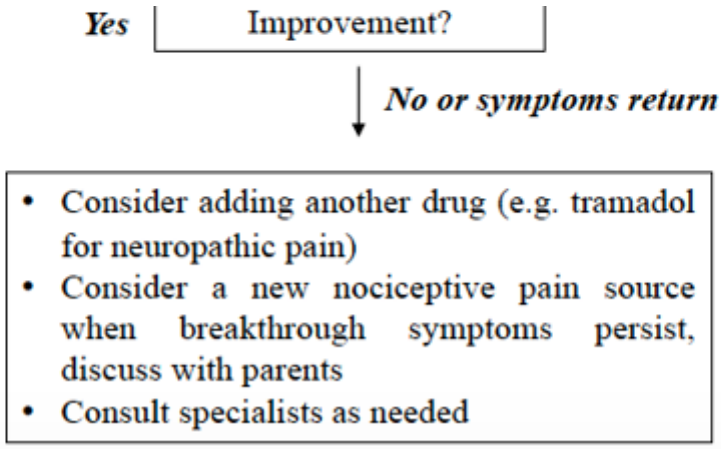


Figure 2

Diagnostic workup for pain in patients with cognitive impairment

Supplementary Files

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- CAREchecklistEnglish.docx