Interpreting Osteogenesis Imperfecta Variants of Uncertain Significance in the Context of Physical Abuse: A Case Series

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Abstract

Keywords

- ▶ variant of unknown significance
- ▶ osteogenesis imperfect
- ▶ child physical abuse

Unexplained childhood fracture(s) warrant consideration of physical abuse and osteogenesis imperfecta (OI). Genetic OI testing may identify “variants of unknown significance (VUS).” Interpretation of VUS in context of potential abuse may have protective, criminal, and medical impacts. This case series explores practices regarding clinicians’ interpretation of VUS during child abuse evaluations. Variability was noted regarding factors considered for interpreting clinical significance. Based on these cases, recommendations for careful and thorough evaluation are detailed, including proposed use of a limited follow-up skeletal survey in 3 months, as a consideration to assess healing of prior fractures and to look for any additional injuries.

Introduction

Osteogenesis imperfecta (OI) is a genetic condition most often caused by gene mutations in type I collagen production (COL1A1 and COL1A2) known to predispose affected patients to fracture.¹ While few unsuspected cases are found, genetic testing for OI and other metabolic diseases of bone are common in the workup of potential child physical abuse involving fractures to assure consideration of all possible causes.^{2–8} During the course of genetic testing, patients may have test results reported as “variants of unknown significance” (VUS) which are “sequence variants of uncertain pathogenicity in genes known to cause inherited Mendelian diseases in which molecular genetic testing has a proven clinical validity and utility.”^{9,10} VUS are identified with recognition that the clinical significance of any given sequence variant falls along a gradient, ranging from those in which the variant is pathogenic, likely pathogenic, likely benign, or benign.¹¹

Due to the range of potential clinical expression, having guidance to understand these variants may assist in further analyzing these complex situations. There have been practice guidelines published for the laboratory evaluation of OI in situations where there is clinical suspicion for the disease.^{7,12} The European Medical Genetics Quality Network’s best practice guidelines for the laboratory analysis of OI recommends that VUS be identified as unclassified until “segregation within the family has been investigated and/or functional evidence becomes available”¹¹. However, guidelines have not been established for the management of possible child physical abuse when testing for OI identifies a VUS. As a result, there exists significant variability in clinical practice and approaches to management of potential child physical abuse that are utilized when VUS are identified.¹³ Waiting for ‘functional evidence’ may be unrealistic in cases with possible child physical abuse due to safety considerations. In an effort to better understand current practices for the management and interpretation of such results,

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we present seven patients who were found to have VUS in collagen-related genes identified in the context of a child physical abuse assessment, and how the consulted child abuse pediatrician (CAP) interpreted those data.

Methods

This study was submitted to and approved for human subject research by the New York Medical College Institutional Review Board. The cases were solicited from members of the Ray E. Helfer Society through a secure listserv from March–June 2014. Members of the Helfer Society are physicians with a special interest in child abuse cases, including board certified CAPs and other physicians from several specialties. The CAPs who chose to submit cases were provided with a questionnaire with 76 variables and asked to submit deidentified information regarding the patient's presentation, laboratory and radiologic results, the providers' own interpretation and clinical decision-making, and the outcome of any child protective services investigation. The interpretation by the CAP was rated by the two lead authors as either "VUS not clinically significant" or "VUS clinically significant." We defined these ratings as: "VUS not clinically significant" if the CAP determined that it could not explain the injuries in the patient and "VUS clinically significant" if the CAP determined that it could explain the injuries. The specific VUS in the cases below are listed in ►Table 1. The survey instrument is depicted in ►Table 2.

Cases

Case 1

A 14-month-old female presented with injuries involving multiple body systems. She was found to have multiple fractures of the right arm and leg in addition to a rib fracture. Further characterization of the fracture types was not avail-

able beyond the presence of periosteal reaction. Skin findings included scalp contusions and multiple abrasions and bruises involving the nose, ear, chest, and abdomen. Head computed tomography (CT) results were reported as "bifrontal subdural hygroma." Abdominal CT identified a liver laceration, pancreatic pseudocyst, and ascites. Ophthalmology studies were normal. There was a history of an adult accidentally stepping on the baby during a domestic altercation. The parents and siblings of the child were not tested for OI, and it is unknown whether they have a clinical history of fracture. The child was removed from the parents, and did not have any subsequent fractures diagnosed on a skeletal survey completed 6 months after presentation. The VUS was interpreted by the CAP as not clinically significant given the negative 6-month follow-up survey and the presence of the abdominal and skin findings.

Case 2

A 13-month-old male patient presented with multiple skin injuries. Skeletal survey identified multiple findings perceived to be either Wormian bones in accessory sutures or a comminuted skull fracture. Head CT identified scattered brain shear injury, brain contusion, and edema, as well as extra-axial and subgaleal hemorrhage. Skin findings included multiple bruises involving the ears, face, torso, buttocks, and extremities, as well as human bite marks. Ophthalmology studies were normal. There was no history of trauma reported. The parents and siblings of the child were not tested for OI, and it is unknown whether they have a clinical history of fracture. The child was removed from the parents and did not have any subsequent fractures. The VUS was interpreted by the CAP as not clinically significant.

Case 3

A 4-month-old female patient presented due to concern for an abdominal trauma/ascites, multiple, bilateral anterior and

Table 1 Clinical interpretation of osteogenesis imperfecta variants of uncertain significance

Age (mo)	Sex	Fractures	Other findings	Genetic mutation	Interpretation
14	Female	Multiple	Skin, brain, abdominal	COL1A2,c.2720delG; Gly907Valfs*116	Not clinically significant
13	Male	Single	Skin, brain	c580C > A transversion in exon 2 of SERPINH1	Not clinically significant
4	Female	Multiple	Skin, abdominal, hematologic	COL1A1 variation p.Arg763Pro: c228G > C	Not clinically significant
4	Male	Single	None	COL1A1,c.1249 C > G, p.Pro417A1a variant	Not clinically significant
3	Female	Multiple	Eye	COL1A2, c.2957C > T CCT > CTT, p.Pro986Leu, Pro896Leu in the triple helix.	Clinically significant
8	Female	Multiple	Skin	ARG1074LEU in the conserved C-terminal region of the COL1A1 gene	Clinically significant
1	Male	Multiple	None	COL1A2 7 c.304C > T p.Pro102Ser Pro12Ser substitution	Clinically significant

Table 2 Information requested in the survey instrument used for case data collection

Age of patient (in months) at time of presentation to you:	
How long ago (in years) was this patient evaluated by you?	
Gender of patient	
What was the reason the patient presented to your service?	
Did the patient have fracture(s)?	
If yes, please list the location, the type if applicable (transverse/spiral/etc.), and whether callous was present.	
Were there findings other than fractures that you perceived to be indicative of OI?	
If yes, describe the findings? (please be as detailed as possible)	
Were there findings other than fractures that you perceived to be concerning for abuse?	
If yes, describe the findings? (please be as detailed as possible)	
What would you characterize as the indication for testing the patient for OI? (please be as detailed as possible)	
Prior to OI result returning, was there concern for abuse?	
Please explain the basis of this impression? (please be as detailed as possible)	
Please describe the patient's birth history: (if available include: gestational age, type of delivery, instrumentation, prenatal laboratories, prenatal ultrasounds, and any other relevant information)	
What was the specific mutation that the patient tested positive for? (please copy directly from results page)	
What type of testing was utilized to identify the mutation?	
What laboratory was used?	
How long did it take for the test results to come back?	
Was it your opinion that the result of this test had any clinical significance?	
Please explain your response:	
Did the result alter your initial opinion/impression?	
Please explain your response:	
Were the following tests performed for your patient? (Please include as much detail as possible about each result including radiological reports and/or laboratory values)	
Initial skeletal survey	If yes, describe results
2-week skeletal survey	If yes, describe results
DEXA scan	If yes, describe results
Vitamin D levels	If yes, describe results
Calcium	If yes, describe results
Ionized calcium	If yes, describe results
Phosphorous	If yes, describe results
Alkaline phosphatase	If yes, describe results
Parathyroid hormone	If yes, describe results
Other (please be as detailed as possible)	If yes, describe results

(Continued)

Table 2 (Continued)

Were parents or siblings tested for OI?	
If yes, please describe how they were tested and what were their results:	
Have parents or siblings with positive results had ANY prior fractures reported?	
If yes, describe the relationship to the patient and the location and type of fracture(s)?	
Have parents or siblings with negative results had ANY prior fractures reported?	
If yes, describe the relationship to the patient and the location and type of fracture(s)?	
Was a safety plan/foster care implemented in advance of testing?	
Please explain your response:	
If yes, were there fractures after a safety plan/foster care was implemented?	
To your knowledge, at the time of writing this case report, has the child been returned to the previous caregiver?	
If yes, have there been any concerns for abuse since return? (please describe specifics)	
Have there been any fractures since return?	
Was there interpreted to be appropriate bone healing on the follow up radiographs?	
Was another skeletal survey performed beyond the recommended 2-week interval, specifically several months after the initial skeletal survey, for purposes of assessing bone healing and/or to see if there were fractures while removed from parental care?	
If yes, how long after the initial skeletal survey and what did it demonstrate?	
Please summarize your clinical impression of this case and what if any impact the "unclassified variant" result had on your impression, management, and the investigation involving your case (please include as much detail as possible).	
Were any of the following factors present, either before testing or in retrospect? (please include as much detail as possible about each finding including radiological reports and/or laboratory values)	
Blue sclera	If yes, please describe
Dentinogenesis imperfecta	If yes, please describe
Hearing difficulty	If yes, please describe
Hypodense bones	If yes, please describe
Wormian bones	If yes, how many
History of "easy bruising"	If yes, please describe
Skin ecchymosis on examination	If yes, please describe
Other skin findings	If yes, please describe
Intracranial subdural effusion	If yes, please describe
Intracranial subdural hemorrhage	If yes, please describe

(Continued)

Table 2 (Continued)

Intracranial epidural hemorrhage	If yes, please describe
Intracranial subarachnoid hemorrhage	If yes, please describe
Brain parenchymal hemorrhage	If yes, please describe
Brain ischemia	If yes, please describe
Intracranial mass	If yes, please describe
Intracranial tortuous arteries	If yes, please describe
Intracranial tortuous veins	If yes, please describe
Intracranial aneurysms	If yes, please describe
Intracranial arachnoid cyst	If yes, please describe
Other intracranial findings	If yes, please describe
Retinal hemorrhages	If yes, please describe
Retinoschisis	If yes, please describe
Papilledema	If yes, please describe
Abnormal retinal vessel branching	If yes, please describe
Other retinal or eye findings	If yes, please describe
Abdominal trauma	If yes, please describe
If you have any additional information or comments, please provide it here:	

Abbreviation: OI, osteogenesis imperfecta.

posterior rib fractures, and transverse fractures of the right radius and ulna. Skin findings included multiple bruises, one involving the eyelid. Head CT and ophthalmology studies were normal. Laboratory studies were significant for moderate normochromic anemia. The biological mother tested positive for the same VUS as the child. It is unknown whether either parent had a clinical history of fracture. The child was removed from the parents and did not have any subsequent fractures. The VUS was interpreted by the CAP as not clinically significant.

Case 4

A 4-month-old male patient presented with an unexplained spiral fracture of the femur. There were no additional injuries noted on exam or imaging studies. Ophthalmology studies were normal. He was born via normal spontaneous vaginal delivery at 36 weeks of gestational age and delivery was complicated by a humeral fracture and subgaleal hemorrhage. The parents and siblings of the child were not tested and it is unknown whether they have a clinical history of fracture. The child was removed from the parents and did not have any subsequent fractures. VUS was interpreted by the CAP as not clinically significant.

Case 5

A 3-month-old female patient presented with multiple bilateral upper and lower extremity fractures (two only classified as displaced and one classified as transverse, without further detail provided). There were no additional injuries noted on exam or imaging studies. Eye exam noted blue sclera. The biological mother was found to have the same VUS as the child and reported a history of one fracture after a minor injury. The child was removed from the parents for a period of time and did not have any subsequent fractures. The VUS was interpreted by the CAP as clinically significant to explain the fractures and the child was returned to the parents thereafter by child protective services.

Case 6

An 8-month-old female patient presented with left upper and lower extremity fractures, not further characterized, as well as had forehead bruising. Head CT, skeletal, and ophthalmology studies were normal. The biological mother tested positive for the same variant yet reported no clinical history of fracture. The child was removed from the parents and did not have any subsequent fractures. The VUS was interpreted by CAP as clinically significant and returned to the parents thereafter by child protective services.

Case 7

A 1-month-old male patient presented with unexplained multiple bilateral lower extremity fractures, not further characterized. Head CT, skeletal, and ophthalmology studies were normal, and there were no signs of bruising. The biological father tested positive for the same variant, yet reported no clinical history of fracture. The child had an unexplained humeral fracture while in foster care. The VUS was determined by the CAP as clinically significant, and returned to the parents thereafter by child protective services.

Discussion

This case series demonstrates variability with regard to the factors considered by child abuse clinicians when interpreting the clinical significance of VUS in OI genes in the context of possible child physical abuse assessments. Four of the cases had injuries and/or historical features that resulted in the interpretation that the “unclassified variant” was not of clinical significance and would not have predisposed the child to have fractures. Three of the cases were interpreted as the variant being clinically significant: one due to a parent having the same variant and a history of fracture with minor trauma; one with a parent having the same variant and no history of fractures; and one with a parent having the same variant and the child sustaining an additional fracture while in substitute care. The purpose of the survey was to optimize collection of specific data points with limitation of variability in reporting style; however, there were some data points that were not provided in some submissions, and assessment of the case information was limited by use of a nonstandardized survey. It is unclear if missing data was due to absence

of that information being collected at the time of the patient's evaluation, or was not known at the time of case submission, or both. Future studies may benefit from a study protocol, such as a prospective study, that would allow for more consistent data collection to allow for statistical analysis.

When a child is found to have a VUS during an evaluation for potential child physical abuse, it is important for clinicians to keep in mind that our understanding of the significance of OI variants changes quickly and that OI can present with fractures of varying ages and stages of healing which are reportedly occult fractures without caregiver knowledge.^{5,14,15} A limited skeletal survey at least 3 months into safe placement/care may assist as follows: (1) new fractures while a child is in safe care would lend support that the variant may be clinically relevant, although children in foster care may still be abused; (2) absence of new fractures may indicate the variant to not be clinically relevant, although this may also reflect diligent delicate handling of a child in foster care known to have potentially fragile bones. Use of a limited skeletal survey in this way has not been previously discussed in the literature; however, it may be a prudent consideration in selected children with unclassified variants.¹⁶ The rationale for timing the skeletal at 3 months is based on the outer limit of hard callus appearance being 90 days, providing the largest time window to observe potential new or healing fractures while providing useful clinical information to assist in dating when the fracture occurred.¹⁷

In addition to this repeat survey, it is important to contact the testing laboratory to confirm their criteria for variant classification and whether new information has been found. In addition, it may be helpful to send samples to at least two independent laboratories which may use different tests or classifications. This was not completed in any of the cases submitted for this paper, and the study design did not allow for these authors to conduct an independent investigation. Extended follow-up and testing of the proband child and parents can be considered, and if doubt remains, reference laboratories should be contacted to discuss the possibility of performing protein studies to investigate the effect on collagen production. Regarding testing of family members, it is important for providers to keep in mind that OI has variable penetrance, even within a single family.¹⁴ Further, the number of de novo mutations for OI varies by the severity of disease (approximately 60% of mild OI diagnoses are de novo mutations and virtually 100% of progressively deforming or perinatally lethal OI diagnoses are de novo mutations).¹⁴ Thus, testing of other family members is recommended with results placed in context of the family member's clinical history.

It is also important to recognize that science progresses rapidly and the interpretation of particular variants has changed since these cases were collected.¹⁸ For example, the variant in COL1A2, c.304C > T, p.(Pro102Ser) in case 7 is now known to be present in population databases with a frequency that is higher than expected and one homozygous individual is reported in gnomAD (<http://gnomad.broadinstitute.org/variant/7-94033892-C-T>) suggesting a strong

argument for its likely benign character.¹⁹ The presence of this variant in a healthy individual is a strong argument for this variant being benign however, there should still be appropriate counseling and additional molecular testing for other recessive OI genes with extended clinical follow-up and additional clinical testing even if the abuse concern has been ruled out. In case 5, we now know there is a strong argument that the variant in COL1A2, c.2957C > T, p.(Pro986Leu) is benign given that the population frequency is quite high (<http://gnomad.broadinstitute.org/variant/7-94055323-C-T>). The mother had sustained one fracture after minor trauma, but this is insufficient to state that she is affected. Good practice would be to initiate extended follow-up of the mother with dual energy X-ray absorptiometry (DEXA) measurements and X-rays to determine whether she is clinically affected or not.

In addition to osseous findings,²⁰ OI can involve other organ systems that overlap with findings of physical abuse,¹⁴ including cutaneous, mucocutaneous,^{21,22} retinal,^{23,24} and intracranial findings.²⁵⁻²⁷ There has been variability in the interpretation of these clinical presentations noted among a variety of pediatric providers with uncertainty in clinical diagnosis.²⁸ Given reports of potential nonosseous findings and additional bone findings over time, it is important to evaluate the totality of the context of a case using information gathered from a multidisciplinary team when evaluating the etiology and significance of fractures for potential physical abuse.⁸ One can neither exclude underlying bone disease merely on the basis of nonskeletal findings nor exclude abuse based solely on the presence of a VUS, even if the variant is determined to be clinically significant.

Conclusions

When a child who is being medically evaluated for possible physical abuse is found to have VUS with clinical or investigative uncertainty, it is important to consider the safety and welfare of the child and to expedite the disposition when possible since delays can have serious legal and neuropsychological consequences. We recommend the following:

1. Obtain a thorough history regarding prior child, sibling and parental fractures and inciting events for those fractures.
2. Test both parents and siblings for OI with specific attention to the child's VUS in conjunction with a pediatric geneticist and an experienced genetics laboratory, with consideration of input from the European Molecular Genetics Quality Network (EMQN) if indicated. A negative history for fractures in parents does not exclude clinical significance for the VUS and positive history of fracture in parents does not exclude child abuse. Testing family members can be done by full sequencing or just looking for the presence of the VUS in the family member, usually done in the original testing laboratory.
3. Contact the laboratory to confirm their methodology and interpretation and whether newer, additional studies are available.

4. Consider additional molecular genetic testing, protein studies, and skin biopsy subsequent to initial blood genetic testing for OI to assess functional collagen synthesis.
5. Consider additional testing at an independent laboratory to confirm the variant status and interpretation.
6. Educate and collaborate with investigators about OI testing and VUS.
7. Refer the parents for counseling about the potential significance of the VUS and the value of extended follow-up and testing such as DEXA measurements and X-rays.
8. Follow patients of all ages and consider repeat limited skeletal surveys in 3 months to assess healing of prior fractures and to look for any additional injuries that may not have previously come to clinical attention.
9. Explore mitigating options for assessing child safety, such as mental health assessments, family monitoring, and kinship care during a period of uncertainty.

Conflict of Interest

None declared.

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