Original Clinical Article

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Evolution of Legg-Calvé-Perthes disease following proximal femoral varus osteotomy performed in the avascular necrosis stage:a prospective study

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Abstract

Purpose This prospective study was undertaken to describe patterns of fragmentation of the femoral epiphysis following a proximal femoral varus osteotomy (PFVO) done during stage I of LCPD and to assess the disease duration and outcome in each pattern.

Methods A total of 25 children treated by a PFVO in stage I of LCPD were followed until healing. The MRI Perfusion Index, radiographic changes in the femoral epiphysis, disease duration and the Sphericity Deviation Score (SDS) at healing were documented. The reproducibility of classification of the pattern of fragmentation, estimation of disease duration and SDS were assessed. The duration of the disease and SDS in the patterns of fragmentation were compared.

Results Four patterns of fragmentation were noted, namely, typical fragmentation, bypassing fragmentation, abortive fragmentation and atypical fragmentation with horizontal fissuring. The reproducibility of classifying the pattern of fragmentation was moderate (Kappa: 0.48) while the reproducibility of other continuous variables was excellent. The Perfusion Index was less than 50% in every affected hip. The duration of the disease and SDS were lowest in children in whom the stage of fragmentation was bypassed but these differences were not statistically significant.

Conclusion Following a proximal femoral osteotomy during stage I of LCPD the fragmentation stage may be bypassed partially or completely and the chances of a good outcome appear to be very good if fragmentation is bypassed.

Level of Evidence: Level II Prognostic Study

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Introduction

Legg-Calvé-Perthes disease (LCPD) has been divided into discrete stages of evolution based on radiographic appearances. They are the early and late stage of avascular necrosis (stages Ia, Ib), the early and late stage of fragmentation (stages IIa, IIb), the early and late stage of reconstitution (stages IIIa, IIIb) and the healed stage (stage IV).[1-4] This pattern of evolution is seen in most untreated children with the exception of those in whom the onset of the disease is in adolescence.[3,5] The evolution of the disease, however, may be altered by treatment. Some children who undergo femoral varus osteotomy during the avascular necrosis stage may not pass through the stage of fragmentation.[6-9] Previous retrospective studies suggest that the duration of the disease is appreciably shortened and that the final outcome, based on qualitative assessment of the shape of the femoral head, is very favourable in these children.[6-9] Though these observations need further scrutiny, little new information regarding the phenomenon of bypassing fragmentation has appeared in the recent literature.[10] A very recent study[10] addressed the frequency of this phenomenon and concluded by stating that 'a more rigorous definition of what constitutes bypass is warranted'.

This prompted us to undertake this prospective study to look more closely at the patterns of evolution of LCPD following containment surgery in stage Ia or Ib of the disease by a proximal femoral varus osteotomy.

The specific aims of the study were:

– To describe the patterns of changes in the femoral epiphysis, with specific reference to the stage of fragmentation, following a proximal femoral varus osteotomy done during the avascular necrosis stage (stage Ia or Ib) of LCPD;
– to determine whether the outcome following surgery differs with different patterns of evolution of the disease and;
– to determine if the duration of the disease is influenced by the pattern of evolution of the disease following surgery in stage Ia or Ib of LCPD.

Patients and methods

After obtaining institutional review board approval and informed consent the data pertaining to this study was collected prospectively. All the subjects included in the study were from south-west India and were all of the same ethnic background.

Other criteria for inclusion were:

– Children were operated on during stage Ia or Ib of LCPD;
– children had a perfusion MRI scan prior to surgery;
– children were followed up at three to four-monthly intervals for the first 24 months following surgery and at six-monthly intervals thereafter until the disease healed with anteroposterior and Lauenstein frog-lateral radiographs at each visit. Data of all consecutive cases treated over a period of five years who fulfilled these criteria and had reached the stage of healing formed the basis of this study.

Surgical containment was considered only for children in Waldenström stage Ia, Ib or IIa of the disease. Surgery was performed in children under the age of eight years at onset of the disease only if there was femoral head extrusion and in children over the age of eight years at onset of the disease with or without femoral head extrusion.

A gadolinium enhanced perfusion MRI scan was performed within two weeks of diagnosis as described by Du et al[11] and the extent the epiphysis that was devoid of blood supply and the extent that was perfused was estimated following the guidelines of these authors and the MRI Perfusion Index was computed. Scans were not done later in the course of the disease to minimize the risk of side effects of gadolinium.[12,13]

All the children were treated by performing a sub-trochanteric varus derotation open wedge osteotomy. A varus of 20° was ensured by using a pre-bent dynamic compression plate (DCP) plate to fix the bone fragments. Strict non-weight-bearing with axillary crutches was advised for six months post-operatively; thereafter, weight-bearing was permitted. Braces were not used. Compliance for not bearing weight on the limb could not be confirmed with absolute certainty, but wasting of the calf, wearing down of the bushes of the crutches and the ease with which the children walked with crutches in the clinic suggested that the children did comply with the instructions.

Sequential anteroposterior radiographs were monitored to document how the disease evolved following surgery. Each radiograph was carefully studied to see if the femoral epiphysis underwent fragmentation and if fragmentation occurred, the nature of the fragmentation was noted. For analysis of the data, the pattern of fragmentation in each child was assigned on the basis of agreement between the investigators; where there was no complete agreement among the investigators, the pattern that reflected the mode was assigned.

The disease was regarded as healed if no residual area of bony sclerosis was evident in the femoral epiphysis in both the anteroposterior and lateral radiographs. The interval between the first radiograph at presentation and the first radiograph that showed healing was taken as the duration of the disease. From the radiographs at healing the Sphericity Deviation Score (SDS) was computed.[14,15]

Reproducibility study

Five investigators, all of whom had more than ten years' experience of dealing with LCPD, evaluated 22 sets of radiographs from onset to healing to assign the pattern of fragmentation on two separate occasions with an interval of over two weeks between each evaluation. Two investigators estimated the duration of the disease, the Perfusion Index and the SDS on two separate occasion three weeks apart. The Kappa statistic was computed to assess reproducibility of the pattern of fragmentation and the Intra-class Correlation Coefficient (ICC) was computed to assess the reproducibility of other continuous variables.

Statistical analysis

Analysis of the data was performed with SPSS 20.0 (IBM SPSS, Chicago, Illinois, USA). Means, standard deviations and 95% confidence intervals were computed. Analysis of variance was applied to compare how the duration of the disease and the SDS differed with the patterns of fragmentation. A p-value < 0.05 was considered as being statistically significant.

Results

Demographic characteristics of the patients

A total of 25 children fulfilled the criteria for inclusion; the mean age at onset of symptoms was 7.32 years (SD 0.98) and the mean age at healing of the disease (the end point

of the study) was 10.63 years (SD 1.43). There were 22 boys and three girls and the left side was involved in 11 while the right was involved in 13. There was one child with bilateral disease but only the left hip was considered for the study since the criteria for inclusion were not fulfilled for the opposite hip. One child was operated on during stage Ia while 24 children were operated on during stage Ib.

Patterns of disease evolution

Four patterns of evolution were noted in this study each with distinctive characteristics with respect to the stage of fragmentation; they were typical fragmentation, bypassing fragmentation, abortive fragmentation and atypical fragmentation with horizontal fissuring.

Typical fragmentation

This pattern was noted in four children. Fragmentation begins with a fissure appearing in the avascular epiphysis (stage Ia) with the following characteristics.

The fissure runs from the articular surface of the epiphysis towards the growth plate either through the substance of the avascular sclerotic bone (i.e. the fissure is bounded by sclerotic bone on either side) or at the boundary between avascular and perfused bone (i.e. the fissure is bounded on one side by sclerotic and on the other side by normal bone). The fissure results in what appears to be a breach in the continuity of the articular margin of the bony epiphysis (Fig. 1).

As the disease evolves fragmentation progresses; more fissures appear in the same orientation (running from the articular surface towards the growth plate). The epiphysis appears to be broken up into three or more fragments (stage IIb) (Fig. 2). New bone begins to form from the periphery of the avascular epiphysis towards the centre in a 'centripetal' manner in stage III of the disease and progresses till healing is complete.

Bypassing fragmentation

Bypassing of the stage of fragmentation occurred in nine children (complete in 3 and partial in 6).

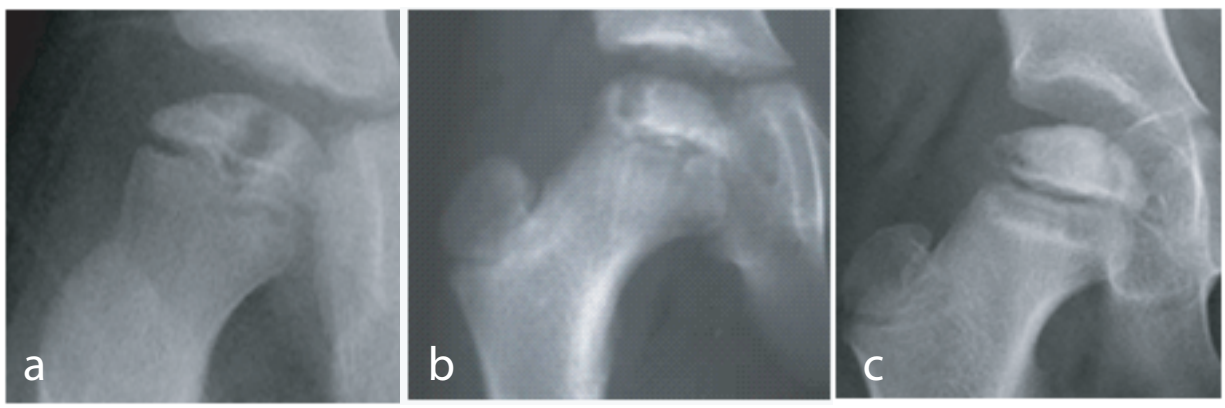

Fig. 1 Three examples of early fragmentation (stage IIa). The vertical orientation of the fissure is evident in all three hips. The position of the fissure can vary; the fissure may be in the substance of avascular bone **(a, b)** or at the boundary between avascular and perfused bone **(c)**.

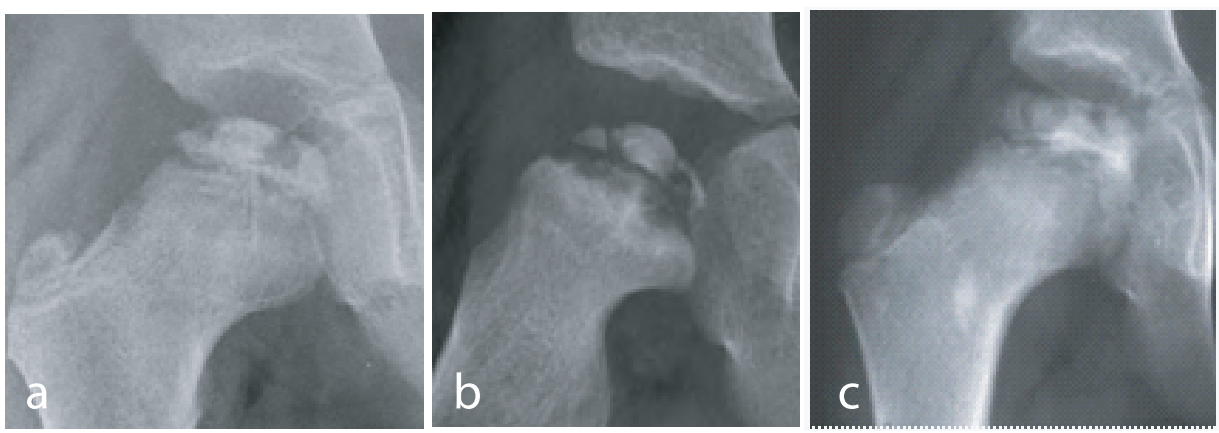

Fig. 2 Three examples of advanced fragmentation (stage IIb).

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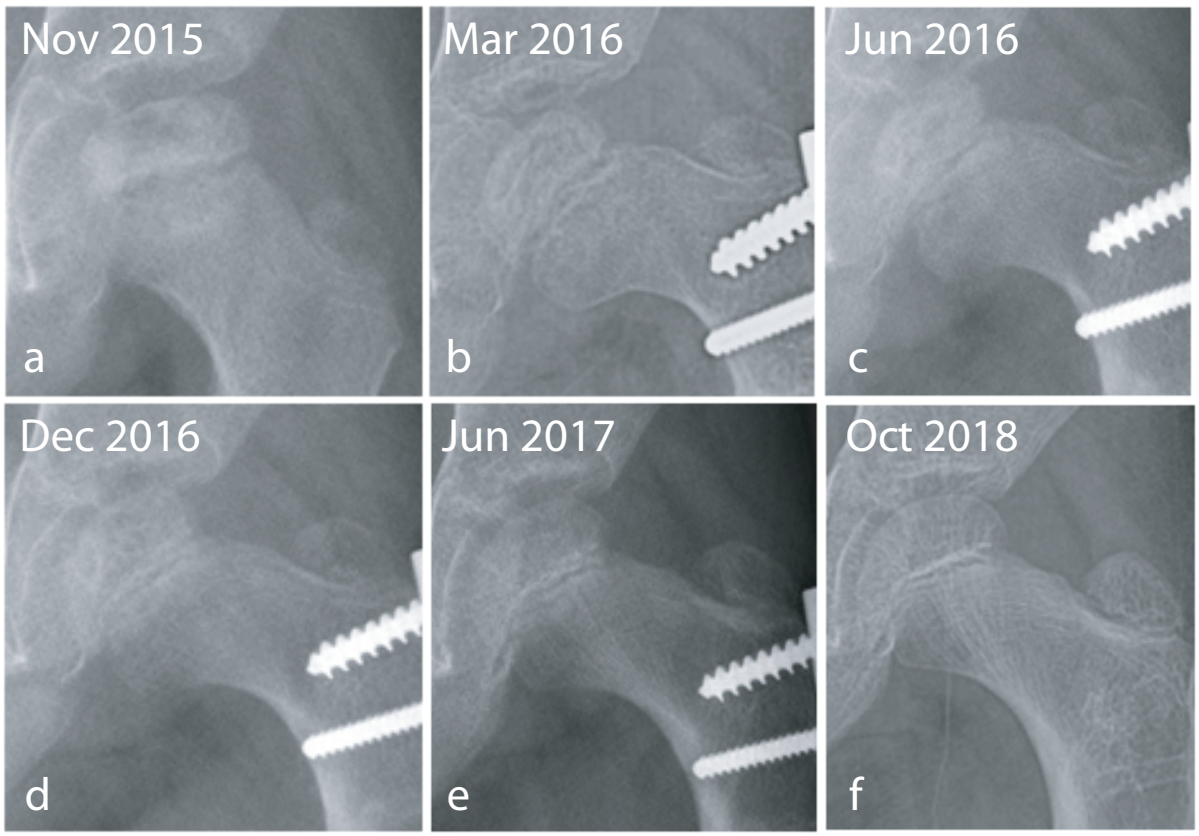

Fig. 3 Sequential radiographs of the hip of a boy with Perthes disease who underwent a proximal femoral varus derotation osteotomy within a month after presentation in stage Ib of the disease **(a)**. In none of the sequential radiographs are there fissures in the epiphysis typical of fragmentation **(b-d)**. The continuity of the articular margin of the femoral epiphysis has been maintained throughout the course of the disease. The disease healed within 17 months of surgery **(e)** and the outcome was excellent **(f)**. The stage of fragmentation has been bypassed.

Complete bypassing of fragmention

This was seen in three children. In none of the sequential radiographs are there fissures in the epiphysis. The continuity of the articular margin of the femoral epiphysis is maintained throughout the course of the disease (Fig. 3). Diffuse resorption appears to be occurring in the whole of the avascular bone with appearance of new bone simultaneously across the entire epiphysis.

Partial bypassing of stage of fragmentation - abortive fragmentation

Abortive fragmentation was seen in six children. In this pattern of evolution early fragmentation commences with one or at the most, two fissures (Fig. 4c). Within three months the fissures are poorly defined (Fig. 4d) and four months later there is no evidence of the fissures on the radiographs (Fig. 4e). Early fragmentation commences but does not progress and reconstitution rapidly supervenes (Figs 4e to 4i). Diffuse resorption and new bone formation proceed simultaneously throughout the avascular bone of the femoral epiphysis.

Atypical fragmentation with horizontal fissuring

This pattern was seen in twelve children. A horizontal fissure extending across the entire width of the epiphysis appears parallel to the growth plate roughly midway between the articular surface and the growth plate (Fig. 5c). This horizontal fissure is distinct from the subchondral fracture line that may be seen very early in the course of the disease. Resorption of the superficial avascular fragment occurs progressively (Figs 5d and 5e). Thereafter, new bone formation proceeds progressively across the entire width of the epiphysis in a 'centrifugal' direction, starting from the deep surface of the horizontal fissure (Fig. 5f) towards the articular surface till the epiphysis is completely reconstituted (Figs 5g to 5i).

Reproducibility study

The Kappa statistic for inter-observer reproducibility of classifying the pattern of fragmentation was 0.48 indicating moderate agreement.[16] There was complete concordance among the five investigators in classifying all the three instances of complete bypass of the stage of

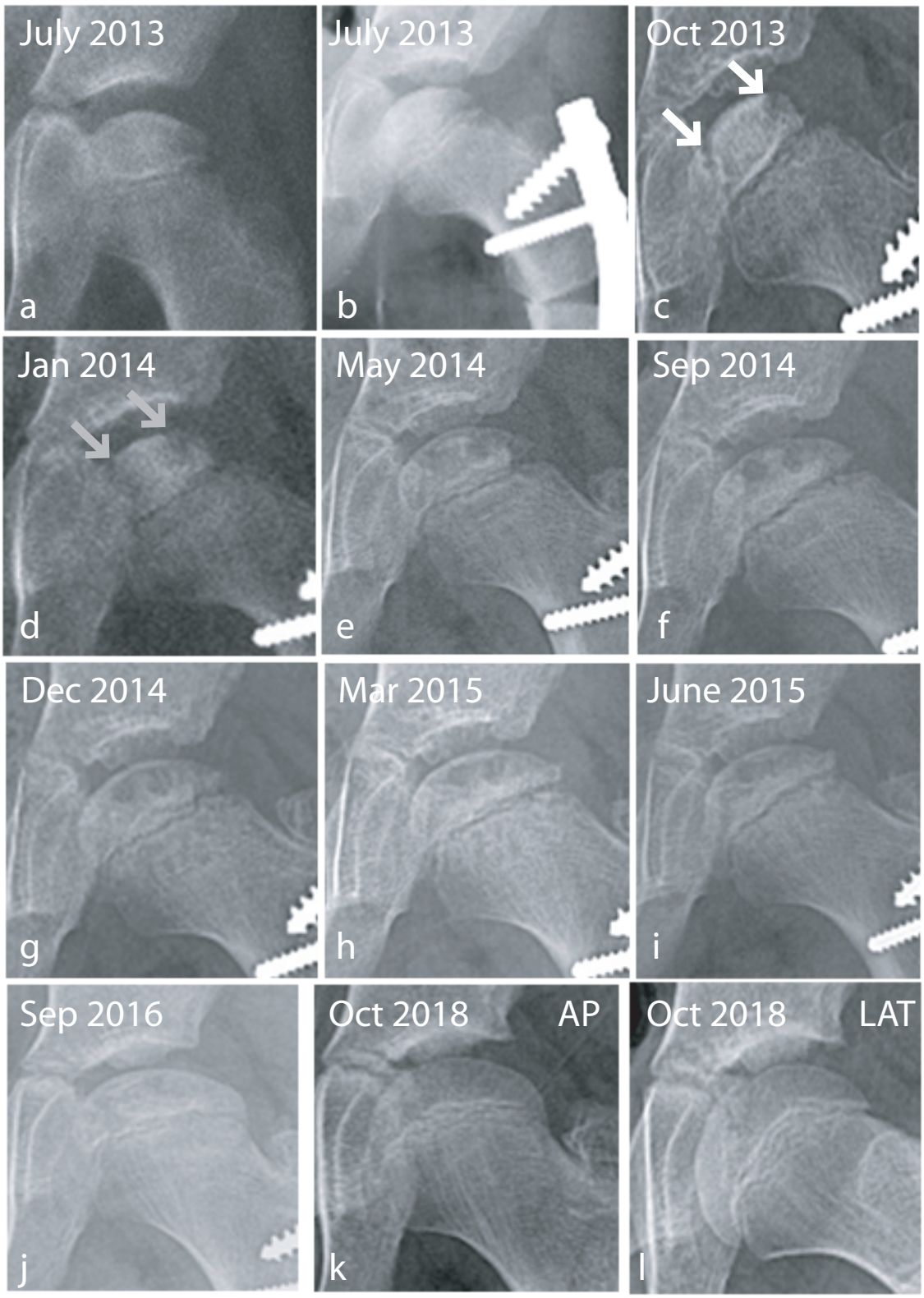

Fig. 4 Sequential radiographs of a child who underwent proximal varus femoral osteotomy in Stage Ib of the disease from presentation **(a-l)** showing the pattern of evolution of the disease. In this patient early fragmentation begins (c; white arrows). Within three months the fragmentation fissures are less clearly defined (d; grey arrows). Four months later there is no progression of fragmentation (i.e. the disease has not passed through stage IIb). The fissures of early fragmentation are also not seen. The final outcome was excellent with a spherical femoral head (**k, l**). This pattern of evolution is the abortive fragmentation pattern.

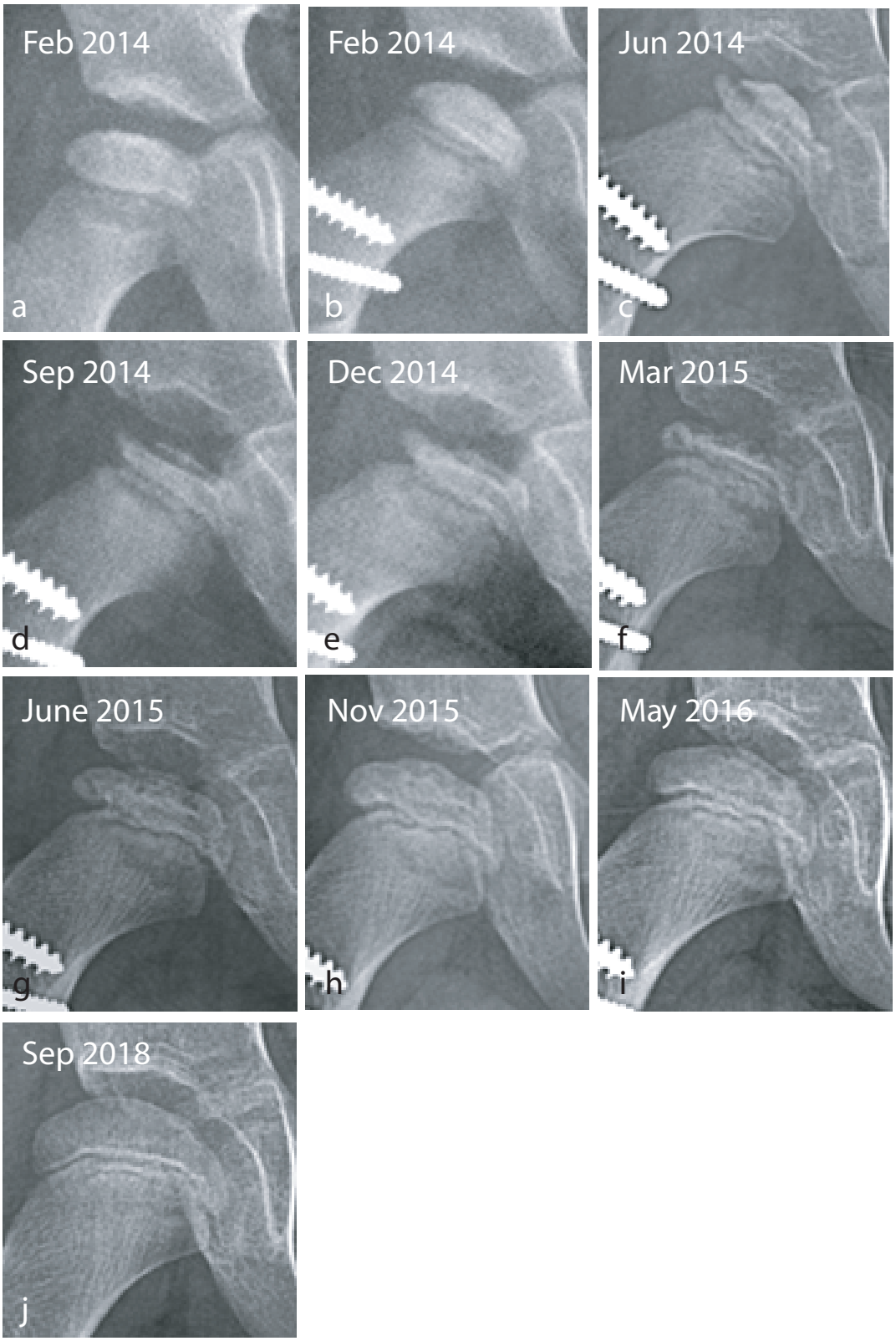

Fig. 5 Sequential radiographs of a child who underwent proximal femoral varus osteotomy in stage Ib. A horizontal fissure extending across the entire width of the epiphysis appears parallel to the growth plate **(c)**. Resorption of the superficial avascular fragment occurs progressively **(d, e)**. New bone formation then proceeds from the deep surface of the horizontal fissure towards the articular surface **(f)** until the epiphysis is completely reconstituted **(g-j)**.

Table 1 Reproducibility of measurement

Variable	Intra-class correlation coefficient	
	Inter-observer	Intra-observer
MRI Perfusion Index	0.90	0.92
Duration of disease	0.95	0.96
Sphericity Deviation Score	0.84	0.91

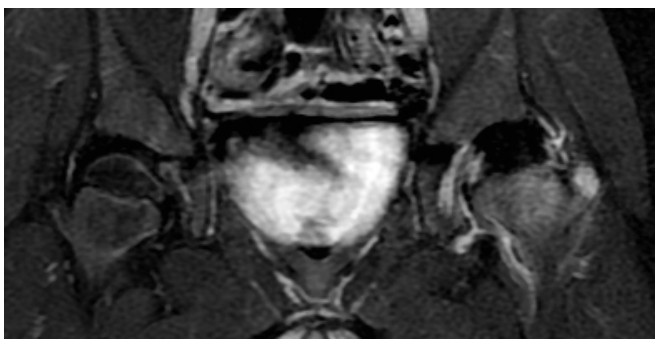

Fig. 6 Perfusion MRI scan of a child with Legg-Calvé-Perthes disease of the left hip. Close to 80% of the epiphysis is avascular.

fragmentation and in three out of the four hips that demonstrated typical fragmentation. Four out of five investigators concurred in three instances of abortive fragmentation while three out of five concurred in the other three instances. There was complete concordance in five of the twelve instances of atypical fragmentation.

The reproducibility of the different continuous variables evaluated in the study is shown in Table 1.

Extent of epiphyseal avascularity

The mean Perfusion Index was 19 (6 to 50) implying that in every child at least half the epiphysis was avascular. In the majority of instances the area of avascularity was much more than 50% (Fig. 6).

Duration of the disease

The duration of the disease (from onset to healing) noted in each pattern of evolution is shown in Table 2. The duration of the disease was lower in children in whom the stage of fragmentation was completely bypassed than in children with typical fragmentation, but the difference was not statistically significant.

Outcome of treatment

The Sphericity Deviation Scores at healing are shown in Table 3. Again, although the Sphericity Deviation Scores were lowest in children in whom the stage of fragmentation was bypassed the difference was not statistically significant.

Table 2 Duration of the disease

Pattern of evolution of the disease	Duration of the disease in months	
	Mean (SD)	95% confidence interval
Bypassed fragmentation, n = 3	24.33 (3.055)	16.74 to 31.92
Abortive fragmentation, n = 6	39.83 (9.78)	29.56 to 50.1
Atypical fragmentation with horizontal fissure, n = 12	36.6 (10.04)	29.41 to 43.79
Typical fragmentation, n = 4	44.75 (8.46)	31.29 to 58.21
Significance	NS	-

Note: NS, not significant

Table 3 Sphericity Deviation Score

Pattern of evolution of the disease	Sphericity Deviation Score	
	Mean (SD)	95% confidence interval
Bypassed fragmentation, n = 3	3.33 (4.93)	-8.92 to 15.59
Abortive fragmentation, n = 6	8.67 (10.13)	-1.97 to 19.30
Atypical fragmentation with horizontal fissure, n = 12	10.17 (12.91)	1.96 to 18.37
Typical fragmentation, n = 4	22.25 (32.08)	0 to 73.31
Significance	NS	-

Note: NS, not significant

Discussion

The study re-affirms the impression that a proximal femoral osteotomy performed during stage I of LCPD can alter the natural evolution of the disease with specific reference to the stage of fragmentation. We recognized four different patterns of evolution, namely, typical fragmentation, atypical fragmentation with horizontal fissuring, abortive fragmentation and complete bypassing of the stage of fragmentation. Among these four patterns of evolution, completely bypassing fragmentation is a pattern that was identified with perfect reproducibility. Reproducibility of classifying the other patterns of fragmentation was less optimal with complete concordance in only a few instances with each pattern. This is probably because some hips may show features of more than one pattern.

Healing of LCPD involves resorption of the necrotic avascular bone and replacement of this dead bone with healthy, vascular new bone. Irrespective of the pattern of evolution seen on sequential radiographs the catabolic process of resorption by osteoclasts and the anabolic process of new bone deposition by osteoblasts must take place for healing to occur.[17] The sequence and rate of these processes may determine the pattern of healing. When the catabolic process precedes the anabolic process by a significant time interval, the epiphysis passes through the typical stage of fragmentation which is followed by the stage of reconstitution. When the catabolic and anabolic

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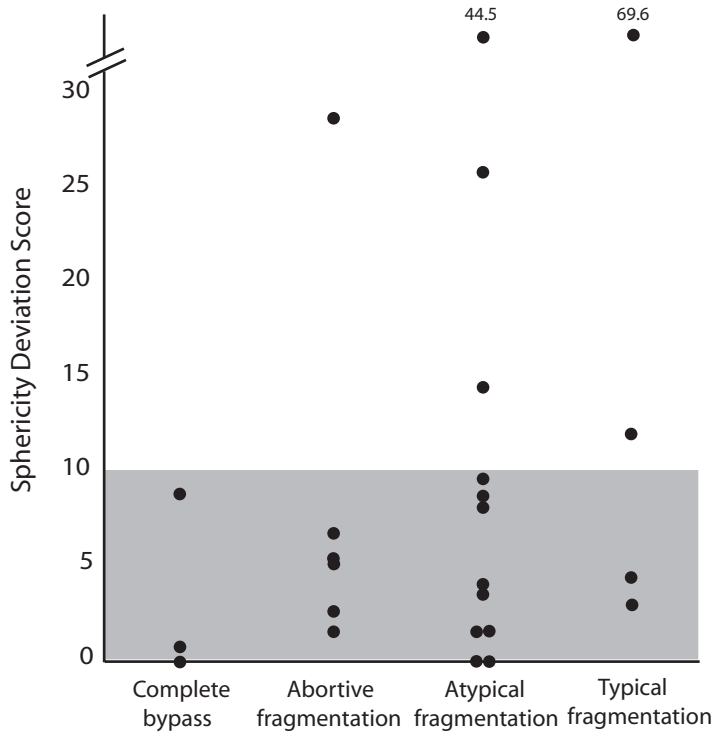

Fig. 7 Scatter diagram showing the Sphericity Deviation Scores at healing of Legg-Calvé-Perthes disease of 25 children who underwent proximal femoral varus osteotomy during stage Ia or Ib of the disease. A Sphericity Deviation Score value below 10 is regarded as a good result (shaded area).

processes run in tandem with the resorption and new bone deposition occurring almost simultaneously, typical fragmentation of the epiphysis either may not be seen at all on sequential radiographs (bypassing fragmentation) or early fragmentation may be rapidly followed by reconstitution (abortive fragmentation). However, it needs to be emphasized that although typical fragmentation of the epiphysis may not be seen, features of bone resorption may be clearly evident on the radiographs.

Another factor that may influence bypassing fragmentation is avoidance of weight-bearing in the post-operative period for six months in our patients. Experimental studies in pigs have shown that preventing the loading of the joint can prevent fragmentation and collapse of the epiphysis.[18] It is possible that the bypassing of fragmentation noted in this study may also be related to the stress protection offered by weight-relief. Further studies are needed to verify this potential association.

Based on isotope bone scans, Conway[19] identified two patterns of revascularization of the epiphysis in LCPD; an early pattern of rapid 'recanalization' which has a good prognosis and a less favourable, slow pattern of neovascularization or 'base filling'. He observed that a lateral column of recanalization develops very early in the course of the disease and if left undisturbed can lead to a good outcome. However, if fragmentation and collapse of the bony trabeculae of the lateral pillar occur the recanalized vessels can get obliterated and then revascularization of the epiphysis can only occur through the less effective base filling. Conway's hypothesis supports the clinical impression that collapse of the lateral pillar is undesirable[20] and also explains why children who bypass fragmentation have a very good prognosis.

One possible explanation for bypassing of fragmentation is that the extent of hypo-perfusion may be limited to a small area of the epiphysis in these children. However half or more of the epiphysis was devoid of blood supply in every child included in this study. A study that includes far greater numbers would be required to establish the association between the extent of hypo-perfusion and the different patterns of fragmentation.

The fact that different patterns of evolution of LCPD occur in children operated very early in the course of the disease *per se* is of little consequence unless each of these patterns has some influence on the prognosis or outcome of the disease. An SDS value of below 10 has been regarded as a good outcome.[14,15] The SDS values of the three children who completely by-passed fragmentation were all below 10 (Fig. 7) and the SDS values of five out of six children who demonstrated abortive fragmentation were also lower than 10. This seems to corroborate earlier reports based on visual qualitative estimates that the

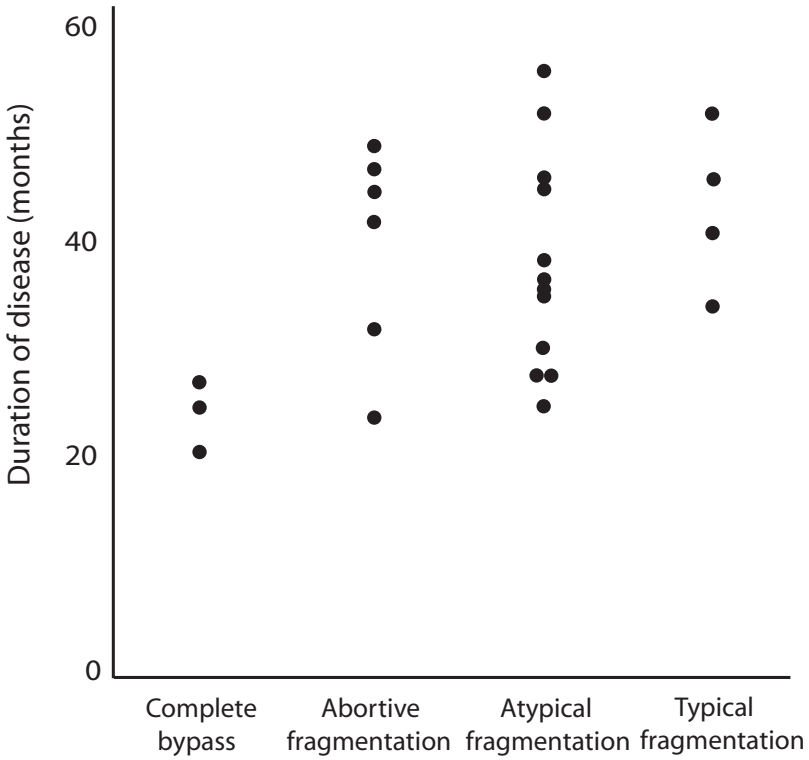

Fig. 8 Scatter diagram showing the duration of Legg-Calvé-Perthes disease in children treated by a proximal femoral osteotomy in stage Ia or Ib. The duration of the disease is around 24 months in the children who bypassed the stage of fragmentation completely.

results are good in children who bypass fragmentation.[6-9] This observation is of prognostic significance and it may be safe to inform parents of children who exhibit this phenomenon of bypassing fragmentation that the outcome is likely to be good. The outcomes of children who had atypical fragmentation with horizontal fissuring appear to be favourable in most instances though not invariably. Children who demonstrate typical fragmentation appear to have relatively poorer prognosis with higher SDS values among children operated on during stage I of LCPD, however, these differences are not statistically significant.

Though the differences in the duration of the disease in children with different patterns of fragmentation did not reach statistical significance, the duration of the disease appears to be only in the region of 24 months in the three children in whom the stage of fragmentation was completely bypassed (Fig. 8). This is to be expected since the duration of the entire stage of fragmentation is around eight months.[3]

The frequency of children who bypassed the stage of fragmentation completely or partially was almost identical to that in one previous report[9] but was greater than that observed in the more recent study which included children treated in different ways with regard to post-operative weight-bearing. It needs to be emphasized that this relatively high frequency of bypassing fragmentation was seen among children of this region who were treated by a sub-trochanteric open-wedge proximal femoral varus osteotomy followed by weight relief for a prolonged period of time. It remains uncertain whether similar changes in the evolution of the disease with this frequency would follow treatment by Salter innominate osteotomy[2] or shelf acetabuloplasty[21] or if early post-operative weight-bearing was permitted. Further studies are being planned to answer these questions.

One of the major shortcomings of this study is the small sample size, despite the fact that data collection extended over five years and it is likely that the differences in variables between the groups did not reach statistical significance on account of this. Though we could have included data of a larger number of children from the multi-centric database used in the study of Sankar et al[10] we opted not to do so. The reason for restricting the subjects to a single centre was because we felt it was important to have exactly the same treatment and the same post-operative protocol for all patients. Previous studies have attributed the phenomenon of bypassing fragmentation to treatment.[6–9] We are uncertain what aspect of treatment apart from its timing contributes to bypassing of the stage of fragmentation and by including children from one centre treated identically we could avoid confounding variables related to different treatment methods.

Finally, the need to achieve containment by stage IIa of LCPD in order to improve the chances of preserving

the sphericity of the femoral head has been emphasized in previous studies[22] and the results of this study give the impression that the chances may further improve if intervention is during stage Ia or Ib of the disease, particularly so if the stage of fragmentation is completely bypassed. However, future studies with larger numbers are needed to verify this impression.

Conclusion

The evolution of LCPD following proximal femoral osteotomy in the stage of avascular necrosis may follow one of four patterns with reference to the stage of fragmentation and the chances of a good outcome appear to be very good if the stage of fragmentation is bypassed.

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COMPLIANCE WITH ETHICAL STANDARDS

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OA LICENCE TEXT

ETHICAL STATEMENT

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Institutional review board approval was obtained and informed consent of the data pertaining to this study was collected prospectively.

ICMJE CONFLICT OF INTEREST STATEMENT

None declared.

AUTHOR CONTRIBUTIONS

All the listed authors contributed substantially to the study design, data collection, analysis and preparation of the manuscript. The final draft has been approved by all the authors.

REFERENCES

1. **Waldenstrom H.** The classic. The first stages of coxa plana by Henning Waldenström. 1938. *Clin Orthop Relat Res* 1984;191:4-7.

2. **Canale ST, D'Anca AF, Cotler JM, Snedden HE.** Innominate osteotomy in Legg-Calvé-Perthes disease. *J Bone Joint Surg[Am]* 1972;54-A:25-40.

3. **Joseph B, Varghese G, Mulpuri K, Narasimha Rao K, Nair NS.** Natural evolution of Perthes disease: a study of 610 children under 12 years of age at disease onset. *J Pediatr Orthop* 2003;23:590-600.

4. **Hyman JE, Trupia EP, Wright ML, et al.** Interobserver and intraobserver reliability of the modified Waldenström classification system for staging of Legg-Calvé-Perthes disease. *J Bone Joint Surg[Am]* 2015;97:643-650.

5. **Joseph B, Mulpuri K, Varghese G.** Perthes' disease in the adolescent. *J Bone Joint Surg[Br]* 2001;83-B:715-720.

6. **Axer A, Schiller MG, Segal D, Rzetelny V, Gershuni-Gordon DH.** Subtrochanteric osteotomy in the treatment of Legg-Calvé-Perther' syndrome (L.C.P.S.). *Acta Orthop Scand* 1973;44:31-54.

7. **Axer A, Gershuni DH, Hendel D, Mirovski Y.** Indications for femoral osteotomy in Legg-Calvé-Perthes disease. *Clin OrthopR elat Res* 1980;150:78-87.

8. **Trias A.** Femoral osteotomy in Perthes disease. *Clin Orthop Relat Res* 1978;137:195-207.

9. **Joseph B, Rao N, Mulpuri K, Varghese G, Nair S.** How does a femoral varus osteotomy alter the natural evolution of Perthes' disease? *J Pediatr Orthop B* 2005;14:10-15.

10. **Sankar WN, Lavalva SM, Mcguire MF, et al.** Does early proximal femoral varus osteotomy shorten the duration of fragmentation in Perthes Disease? Lessons from a prospective multicenter cohort. *J Pediatr Orthop* 2019 (Epub ahead of print) PMID: 31524767.

11. **Du J, Lu A, Dempsey M, Herring JA, Kim HKW.** MR perfusion index as a quantitative method of evaluating epiphyseal perfusion in Legg-Calve-Perthes disease and correlation with short-term radiographic outcome: a preliminary study. *J Pediatr Orthop* 2013;33:707-713.

12. **Holowka S, Shroff M, Chavhan GB.** Use and Safety of Gadolinium Based Contrast Agents in Pediatric MR Imaging. *Indian J Pediatr* 2019;86:961-966.

13. **Gulani V, Calamante F, Shellock FG, et al.** Gadolinium deposition in the brain: summary of evidence and recommendations. *Lancet Neurol* 2017;16:564-570.

14. **Shah H, Siddesh ND, Pai H, Tercier S, Joseph B.** Quantitative measures for evaluating the radiographic outcome of Legg-Calvé-Perthes disease. *J Bone Joint Surg[Am]* 2013;95354-361.

15. **Siddesh ND, Shah H, Tercier S, et al.** The sphericity deviation score: a quantitative radiologic outcome measure of Legg-Calvé Perthes disease applicable at the stage of healing and at skeletal maturity. *J Pediatr Orthop* 2014;34:522-528.

16. **Landis JR, Koch GG.** The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-174.

17. **Little DG, Kim HKW.** Future biologic treatments for Perthes disease. *Orthop Clin North Am* 2011;42:423-427.

18. **Kim HK, Aruwajoye O, Stetler J, Stall A.** Effects of non-weight-bearing on the immature femoral head following ischemic osteonecrosis: an experimental investigation in immature pigs. *J Bone Joint Surg[Am]* 2012;94-A:2228-2237.

19. **Conway JJ.** A scintigraphic classification of Legg-Calvé-Perthes disease. *Semin Nucl Med* 1993;23:274-295.

20. **Herring JA, Neustadt JB, Williams JJ, Early JS, Browne RH.** The lateral pillar classification of Legg-Calvé-Perthes disease. *J Pediatr Orthop* 1992;12:143-150.

21. **Carsi B, Judd J, Clarke NMP.** Shelf acetabuloplasty for containment in the early stages of Legg-Calve-Perthes disease. *J Pediatr Orthop* 2015;35:151-156.

22. **Joseph B, Nair NS, Narasimha Rao K, Mulpuri K, Varghese G.** Optimal timing for containment surgery for Perthes disease. *J Pediatr Orthop* 2003;23:601-606.