CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

# Recurrent Chronic Histiocytic Intervillositis with Intrauterine Growth Restriction, Osteopenia, and Fractures

**April Crawford,[1] Lynette Moore,[1,2] Gregory Bennett,[3] Ravi Savarirayan,[4,5] Nicholas Manton,[1,2] Yee Khong,[1,2] Christopher P. Barnett,[6,2] and Eric Haan[6,2]***

[1]Department of Surgical Pathology, SA Pathology (at Women's and Children's Hospital), Adelaide, South Australia, Australia

[2]School of Medicine, University of Adelaide, Adelaide, South Australia, Australia

[3]Australian Red Cross Blood Service, National Transplant Services, Adelaide, South Australia, Australia

[4]Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, Victoria, Australia

[5]Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia

[6]Paediatric & Reproductive Genetics, South Australian Clinical Genetics Service, SA Pathology (at Women's and Children's Hospital), Adelaide, South Australia, Australia

Manuscript Received: 19 May 2016; Manuscript Accepted: 7 July 2016

Chronic histiocytic intervillositis (CHI) is characterized by the presence of histiocytes within the intervillous space of the placenta. The pathogenesis is unclear but available evidence supports an alloimmune mechanism on the basis of the presence in maternal blood of HLA antibodies directed against paternal HLA antigens. CHI has a high risk of recurrence and of abnormal perinatal outcomes. Little is known about the effects of CHI on the developing fetus, in particular on the growth and development of the skeleton. We have studied a woman whose third pregnancy was terminated after ultrasonography showed severe intrauterine growth restriction, raising the possibility of a lethal skeletal dysplasia. Postmortem radiographs showed multiple fractures and other signs of osteogenesis imperfecta (OI). However, bone histology was not typical of OI and no abnormalities were identified by sequencing OI genes. The subsequent pregnancy was also severely growth restricted and was terminated. The placenta showed chronic histiocytic intervillositis, which, on retrospective review, had also been present in her second and third pregnancies. Her fifth pregnancy was again associated with intrauterine growth restriction and CHI but resulted in a premature birth. CHI can be associated with radiographic features that mimic OI and should be considered when fetal fractures occur in the context of recurrent miscarriage, fetal death in utero, and intrauterine growth restriction. The correct diagnosis can be made by histopathology of the placenta, supported by bone histology and normal results of molecular studies for OI.



**Key words:** chronic histiocytic intervillositis (CHI); placental pathology; bone dysplasia; osteogenesis imperfecta; fetal development; intrauterine growth restriction

**How to Cite this Article:**
Crawford A, Moore L, Bennett G, Savarirayan R, Manton N, Khong Y, Barnett CP, Haan E. 2016. Recurrent chronic histiocytic intervillositis with intrauterine growth restriction, osteopenia, and fractures.
Am J Med Genet Part A 170A:2960–2964.

## INTRODUCTION

Chronic histiocytic intervillositis (CHI), also known as chronic intervillositis (CI), chronic histiocytic intervillositis (CHIV), or chronic intervillositis of unknown etiology (CIUE) is a placental disorder of intrauterine growth restriction (IUGR) and recurrent fetal loss [Boyd and Redline, 2000; Parant et al., 2009; Contro et al., 2010]. It is identified in around 9.6 per 1,000 miscarriages and 0.6 per 1,000 sec and third trimester placentas [Boyd and Redline, 2000]. CHI can occur at any gestational age [Capuani et al., 2013].

Conflict of interest: none.

*Correspondence to:
Dr. Eric Haan, Adult Genetics Unit, South Australian Clinical Genetics Service, SA Pathology (at Women's and Children's Hospital), 72 King William Road, North Adelaide, South Australia 5006, Australia.
E-mail eric.haan@sa.gov.au

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 2 August 2016
DOI 10.1002/ajmg.a.37856

The recurrence rate is high, ranging from 67% to 100% [Boyd and Redline, 2000; Parant et al., 2009]. The condition is characterized histologically by infiltration of maternal histiocytes within the intervillous space [Boyd and Redline, 2000]. CD68 immunostaining identifies the histiocytes and is valuable in establishing the diagnosis [Heller, 2012]. Prominent intervillous fibrin deposition is another finding in some cases of CHI [Boyd and Redline, 2000]. A higher intensity of fibrin deposition in CHI is associated with early spontaneous abortion and severe IUGR [Marchaudon et al., 2011]. Fibrin deposition is seen in response to damage and repair of the syncytiotrophoblast and it is postulated that fibrin deposition interferes with materno-fetal exchange of water, solutes, gases, and other molecules between the syncytiotrophoblast and the fetal capillary endothelium [Sibley et al., 1998; Marchaudon et al., 2011]. The pathogenesis of CHI is unknown; however, an alloimmune mechanism has been proposed [Boog, 2008].

There is currently no definitive test to diagnose CHI antenatally, although the possibility of using histology of a chorionic villus sample or placental biopsy, performed at the time of fetal karyotyping, has been suggested [Rota et al., 2006]. Elevated alkaline phosphatase (ALP) levels above 600 U/L have been noted in this condition; however, this is non-specific and in 40% of cases ALP levels are not elevated [Marchaudon et al., 2011].

In CHI, there is IUGR [Contro et al., 2010] and IUGR due to various causes has been associated with reduced neonatal bone mass and increased risk of osteoporosis in adulthood [Briana et al., 2008]. However, little is known about the balance between bone formation and resorption in the fetus or the effects of CHI on fetal bone development.

We have studied a woman whose pregnancies were complicated by CHI. Two of the pregnancies had ultrasound features that raised the possibility of a lethal skeletal dysplasia and were terminated. In one pregnancy radiographic features were consistent with osteogenesis imperfecta (OI) at autopsy, but bone histology was not consistent with OI and results of genetic testing for OI were normal. We know of no previous reports linking CHI with multiple bone fractures resembling OI and, as far as we are aware, bone histology has not been studied in fetuses with CHI.

## CLINICAL REPORT

A 28-year-old woman with a past obstetric history of one uneventful term pregnancy and a miscarriage at 12 weeks was seen following termination of her third pregnancy at 27 weeks gestation. First trimester screening had placed the pregnancy at increased risk of Down syndrome (beta HCG 2.13 MoM, PAPP-A 0.19 MoM, risk 1:107); amniocentesis at 17–18 weeks demonstrated a normal female karyotype. Ultrasonography at 20 weeks showed severe IUGR, with a 6-week lag in growth, marked shortness of long bones (femur length 1.6 cm, <5th centile), and anhydramnios. Umbilical artery Doppler studies showed reverse flow. Post-termination radiographs showed under-ossification of the skull, normal vertebral bodies and posterior elements, thin ribs with multiple fractures ("beaded" appearance), multiple long bone fractures, abnormal modeling of the long bones due to fractures, and severe generalized osteopenia (Fig. 1), suggesting a severe/lethal form of OI. However, histopathology of the bone fractures was not typical of OI, showing only disorderly bone spicules, fibrosis, and callus formation (Fig. 2). The placenta was small

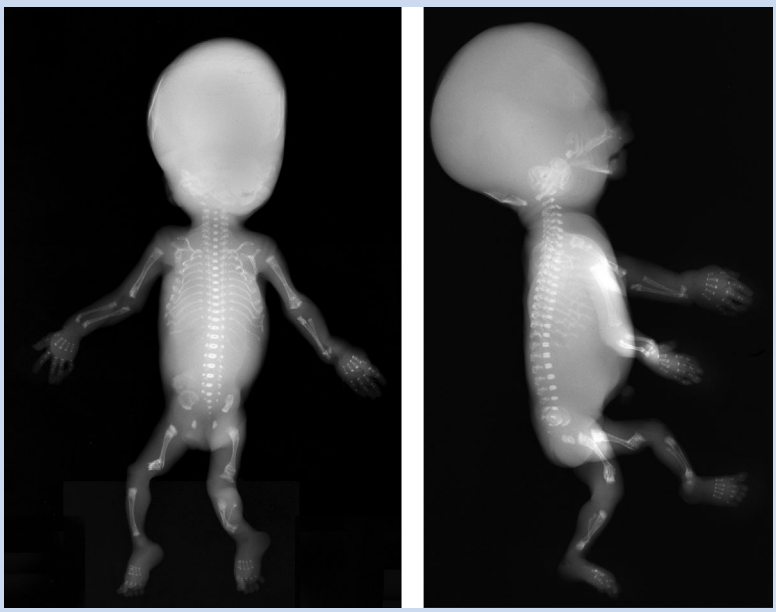

**FIG. 1. Anteroposterior and lateral views of the skeletal survey from the third pregnancy. The radiological features include multiple long bone and rib fractures, generalized osteopenia, and reduced ossification of the cranium.**

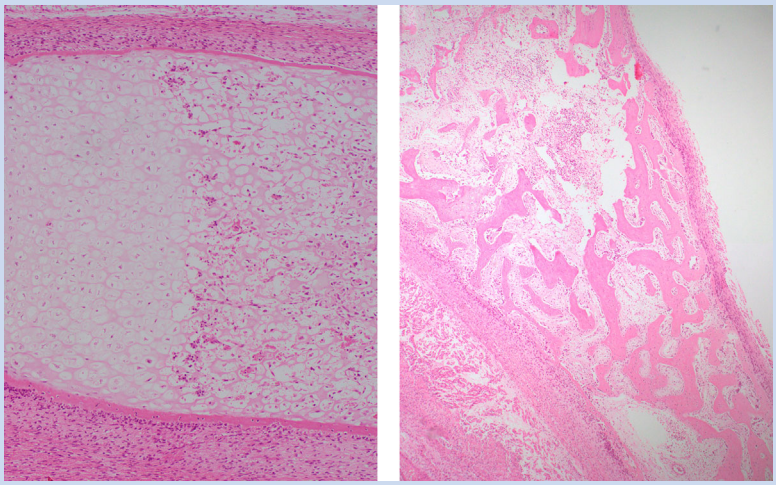

**FIG. 2. Bone histology from third pregnancy showing: normal femoral growth plate (left); and femoral shaft with fracture (upper left quadrant of image) and trabeculae not typical of osteogenesis imperfecta (right). (H&E, magnification ×4). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga].**

(92 g, <10th centile), with histopathology showing extensive subchorionic and intervillous organized hemorrhage with increased perivillous fibrin and focal intervillous thrombus with secondary infarction. Sequencing of a panel of dominant and recessive OI genes provided no support for a diagnosis of OI. Hypophosphatasia was considered but excluded on the basis of atypical radiology (e.g., the absence of metaphyseal cupping) and negative ALPL sequencing.

First trimester screening in the woman's fourth pregnancy again indicated an increased risk of Down syndrome (beta HCG 0.83 MoM, PAPP-A 0.24 MoM, risk 1:106). Fetal growth was normal at 13 weeks but IUGR was apparent at 15 weeks. At 17 weeks, there was severe shortness of the long bones, a femur length to abdominal circumference ratio (FL/AC) of 0.16, and a thoracic circumference <2.5th centile. At 21 weeks, the average ultrasound age by fetal biometry was 17 weeks; there were markedly short long bones (<5th centile) but with no evidence of long bone angulation or fractures. Frontal bossing and reduced amniotic fluid volume were also apparent. Maternal alkaline phosphatase (ALP) level was normal. It was concluded that the fetus had the same disorder as the previous fetus and the pregnancy was terminated at 21 weeks gestation. At autopsy, there was marked head-to-body discordance (brain weight normal for gestation but other internal organ weights reduced), a large head with widened fontanelles, frontal bossing, depressed nasal bridge, low-set posteriorly-angulated ears, severe micrognathia, narrow chest, reduced abdominal circumference, and prominent heels. Fetal skeletal survey showed generalized osteopenia and short long bones with metaphyseal irregularity, but no fractures or long bone angulation. Fetal karyotype was 46, XY, inv(11)(p11.2q13) pat—the inversion was considered unrelated to the fetal phenotype. Bone histology showed disorganized growth plates of rib and femur. The placenta was extremely small (trimmed weight 51 g; <10th centile) and histopathology showed diffuse CHI with increased perivillous fibrin deposition. In light of this new finding, the histopathology from the previously terminated pregnancy was reviewed and showed CHI, with previously unrecognized CD68 positive histiocytes within intervillous spaces and massive fibrin deposition (Fig. 3). Review of the histopathology from the 12-week miscarriage also showed CHI. The woman and her husband were counseled about CHI, including the high recurrence risk and likely poor outcome for a future pregnancy.

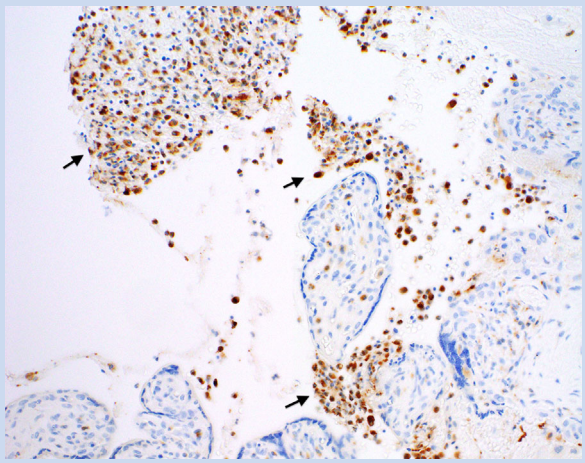

**FIG. 3. CD68 immunohistochemical stain highlighting histiocytes within the intervillous spaces in placental tissue from the third pregnancy (magnification ×20). [Color figure can be seen in the online version of this article, available at http://wileyonlinelibrary.com/journal/ajmga].**

First trimester screening in the woman's fifth pregnancy again showed a low PAPP-A (0.18 MoM) but the pregnancy was not at increased risk of Down syndrome. Amniotic fluid karyotype was 46,XX,inv(11)(p15.3q13.3) pat. Antenatal ultrasound scans showed IUGR from 15 weeks, with long bones that were short but with normal mineralization until 20 weeks at least. At 23-week gestation, HLA Classes I and II donor-specific IgG antibodies (versus spouse) [anti-DR4 mean fluorescence intensity (MFI) 19,900; Genprobe Luminex] were demonstrated. At 26 weeks, fetal biometry was consistent with that of 20 weeks; there appeared to be hypomineralization of the skull and the right femur was bowed. Maternal ALP was normal. The baby was delivered by emergency caesarean section at $32^{+5}$ weeks gestation with weight 850 g (−3.8 SD), length 32 cm (−4.8 SD), head circumference 27 cm (−1.8 SD), and Apgar scores 7 at 1 min and 10 at 5 min. Respiratory distress was treated with brief ventilation and surfactant and a patent ductus arteriosus with ibuprofen. The neonatal period was uncomplicated apart from apnea of prematurity and jaundice, and the baby was discharged home after 7 weeks. The placenta weighed 210 g (<10th centile) and histopathology showed massive perivillous fibrin deposition with mild CHI and multifocal low-grade chronic villitis. Skeletal radiographs at 6 weeks of age showed frontal bossing, poorly mineralized sutures, a number of wormian bones along the lambdoid suture (not excessive for a premature infant), and mild lateral bowing of the mid-diaphysis of both femora; bone mineralization was normal overall and there was no evidence of previous fractures.

## DISCUSSION

CHI is a rare placental condition with high risk of recurrence and poor perinatal outcome [Contro et al., 2010]. Clinical presentations may include miscarriage, severe early-onset IUGR with fetal death in utero, and preterm/term delivery associated with IUGR. The disorder has been associated with low maternal PAPP-A and increased ALP. An immune mechanism is suspected. Our patient had five pregnancies resulting in the outcomes summarized in Table I.

An ultrasound diagnosis of IUGR in the second trimester is made when the estimated fetal weight falls below the 10th centile for gestational age and is typically associated with abdominal and head circumferences also below the 10th centile [Zalel et al., 2002]. Other findings include shortened long bones (e.g., femur length <5th centile) and abnormal umbilical artery Doppler dynamics

TABLE I. Pregnancy Summaries

| Pregnancy no. | Outcome | Antenatal ultrasound | Radiographic features | Bone histology | Placental features | Other |
|---|---|---|---|---|---|---|
| 1 | Term live birth | Normal | NA | NA | NK | — |
| 2 | Miscarriage at 12 weeks | NA | NA | NA | CHI | — |
| 3 | Termination at 27 weeks | Severe IUGR at 20 weeks with anhydramnios and reverse flow on umbilical artery Doppler | Generalized osteopenia, multiple long bone fractures, rib fractures with "beaded appearance" | Bone fractures showing disordered bony spicules associated with fibrosis and callus formation not typical of OI | Extremely small (92 g, <10th centile), CHI with massive fibrin deposition | PAPP-A 0.19 MoM |
| 4 | Termination at 21 weeks | IUGR at 15 weeks; at 17 weeks, severe shortening of long bones, osteopenia, FL/AC 0.16, no long bone, angulation or fractures, reduced amniotic fluid | Generalized osteopenia, shortened long bones with metaphyseal irregularity | Disorganized growth plates of rib and femur | Extremely small (51 g, <10th centile), high grade diffuse CHI with increased perivillous fibrin deposition | PAPP-A 0.24 MoM, normal ALP |
| 5 | Emergency cesarean section with live birth at 32 weeks | IUGR from 15 weeks and short long bones; at 26 weeks, severe IUGR, hypomineralization of the skull, and bowed right femur | At 6 weeks postnatal, mild lateral bowing of the femurs bilaterally, no fractures, normal bone mineralization | NA | Extremely small (210 g <10th centile), massive perivillous fibrin deposition with mild CHI and multifocal low-grade chronic villitis | PAPP-A 0.18 MoM, normal ALP, HLA Classes I and II donor-specific IgG antibody against paternal antigens |

IUGR, intrauterine growth restriction; CHI, chronic histiocytic intervillositis; OI, osteogenesis imperfecta; PAPP-A, pregnancy-associated plasma protein A; MoM, multiples of the median; HLA, human leukocyte antigen; ALP, alkaline phosphatase, NA, not applicable; NK, not known.

[Vermeer and Bekker, 2013]. Our patient's pregnancies had IUGR associated with both severe long bone shortening and reverse flow on umbilical artery Doppler studies. In contrast, lethal OI is characterized by severe micromelic long bone shortness, fractures with demineralization, small thorax, and FL/AC ratio $<0.16$ [Parilla et al., 2003]. This patient's third and fourth pregnancies showed severe long bone shortness and generalized osteopenia, with almost no skull ossification seen in the third pregnancy. The fourth pregnancy had a FL/AC ratio of 0.16 in association with severe limb shortness and reduced thoracic circumference, consistent with recurrent lethal skeletal dysplasia.

The patient's third and fourth pregnancies showed markedly shortened long bones that raised the suspicion of a lethal skeletal dysplasia. The post mortem radiographs of the fetus from the third pregnancy showed multiple fractures and deformity of the ribs and long bones with callus formation, poor bone mineralization overall, and the absence of skull vault ossification, raising the possibility of a lethal skeletal dysplasia, most likely OI. The definitive diagnosis of CHI was made after histopathological examination of the placenta from the patient's fourth pregnancy. As far as we are aware, there are no reports of CHI presenting as severe IUGR with bony abnormalities mimicking a lethal skeletal dysplasia.

Perinatally lethal OI comprises a heterogeneous group of disorders that most often results from new dominant mutations in either the *COL1A1* or *COL1A2* genes, but can also be caused by recessive mutations in a number of other genes [Baldridge et al., 2008]. Bone histology is characterized by a normal growth plate but severe deficiency of ossification in the metaphysis, diaphysis, and cortex with the abnormal bony trabeculae composed primarily of woven bone [Gilbert-Barness, 2007]. In contrast, in IUGR, the growth plate may be irregular and show bridging and banding [Emery et al., 1967]. Histopathology of femur and rib from our patient's third pregnancy showed multiple fractures, which obscured much of the histological detail. In addition, there was a marked delay in ossification at the growth plate with irregular cartilage columns extending into the shaft of the bone but with bony trabeculae in the diaphysis away from the areas of fracture well-formed and thus not typical of OI.

As many as 33% of multiparous women have HLA antibodies in their serum [Middelburg et al., 2011]. However, in this case, the presence of multispecific HLA Classes I and II antibodies directed against the HLA type of the spouse with very high mean fluorescence intensity supports a possible immunologic mechanism as suggested by Reus et al. [2013].

## ACKNOWLEDGMENT

The authors would like to acknowledge Dr. J. Kaye, Medical Imaging, Women's and Children's Hospital, Adelaide, Australia.

## REFERENCES

Baldridge D, Schwarze U, Morello R, Lennington J, Bertin TK, Pace JM, Pepin MG, Weis M, Eyre DR, Walsh J, Lambert D, Green A, Robinson H, Michelson M, Houge G, Lindman C, Martin J, Ward J, Lemyre E, Mitchell JJ, Krakow D, Rimoin DL, Cohn DH, Byers PH, Lee B. 2008. CRTAP and LEPRE1 mutations in recessive osteogenesis imperfecta. Hum Mutat 29:1435–1442.

Boog G. 2008. Chronic villitis of unknown etiology. Eur J Obstet Gynecol Reprod Biol 136:9–15.

Boyd T, Redline R. 2000. Chronic histiocytic intervillositis: A placental lesion associated with recurrent reproductive loss. Hum Pathol 31:1389–1396.

Briana DD, Gourgiotis D, Boutsikou M, Baka S, Hassiakos D, Vraila V, Creatsas G, Malamitsi-Puchner A. 2008. Perinatal bone turnover in term pregnancies: The influence of intrauterine growth restriction. Bone 42:307–313.

Capuani C, Meggetto F, Duga I, Danjoux M, March M, Parant O, Brousset P, Aziza J. 2013. Specific infiltration pattern of FOXP3+ regulatory T cells in chronic histiocytic intervillositis of unknown etiology. Placenta 34:149–154.

Contro E, deSouza R, Bhide A. 2010. Chronic histiocytic intervillositis of the placenta: A systematic review. Placenta 31:1106–1110.

Emery JL, Kalpaktsoglou PK. 1967. The costochondral junction during later stages of intrauterine life, and abnormal growth patterns found in association with perinatal death. Arch Dis Childh 42:1–13.

Gilbert-Barness E. 2007. Osteochondrodysplasias—constitutional diseases of bone. In: Gilbert-Barness E, editor. Potter's pathology of the fetus, infant and child, 2nd edition. Philadelphia: Mosby Elsevier. pp 1836–1897.

Heller DS. 2012. CD68 immunostaining in the evaluation of chronic histiocytic intervillositis. Arch Pathol Lab Med 136:657–659.

Marchaudon V, Devisme L, Petit S, Ansart-Franquet H, Vaast P, Subtil D. 2011. Chronic histiocytic intervillositis of unknown etiology: Clinical features in a consecutive series of 69 cases. Placenta 32:140–145.

Middelburg RA, Porcelijn L, Lardy N, Briet E, Vrielink H. 2011. Prevalence of leucocyte antibodies in the Dutch donor population. Vox Sang 100:327–335.

Parant O, Capdet J, Kessler S, Aziza J, Berrebi A. 2009. Chronic intervillositis of unknown etiology (CIUE): Relation between placental lesions and perinatal outcome. Eur J Obstet Gynecol Reprod Biol 143:9–13.

Parilla BV, Leeth EA, Kambich MP, Chilis P, MacGregor SN. 2003. Antenatal detection of skeletal dysplasias. J Ultrasound Med 22: 255–258.

Reus AD, van Besouw NM, Molenaar NM, Steegers EAP, Visser W, de Kuiper RP, de Krijger RR, Roelen DL, Exalto N. 2013. An immunological basis for chronic histiocytic intervillositis in recurrent fetal loss. Am J Reprod Immunol 70:230–237.

Rota C, Carles D, Schaeffer V, Guyon F, Saura R, Horovitz J. 2006. Prognostic périnatal des grossesses compliquées d'intervillites chroniques placentaires. J Gynecol Obstet Biol Reprod 35:711–719.

Sibley CP, Birdsey TJ, Brownbill P, Clarson LH, Doughty I, Glazier JD, Greenwood SL, Hughes J, Jansson T, Mylona P, Nelson DM, Powell T. 1998. Mechanisms of maternofetal exchange across the human placenta. Biochem Soc Trans 26:86–91.

Vermeer N, Bekker MN. 2013. Association of isolated short fetal femur with intrauterine growth restriction. Prenatal Diagn 33:365–370.

Zalel Y, Lehavi O, Schiff E, Shalmon B, Cohen S, Schulman A. 2002. Shortened fetal long bones: A possible in utero manifestation of placental function. Prenat Diagn 22:553–557.