Welcome to

The ERKNet/ESPN
Educational Webinars on Pediatric
Nephrology & Rare Kidney Diseases

WEBINAR
25/01/22

Renal tubular dysgenesis

Speaker: Laurence Heidet (Paris, France)

Moderator: Jens König (Münster, Germany)

ERKNet
The European
Rare Kidney Disease
Reference Network

european
society for
paediatric
nephrology

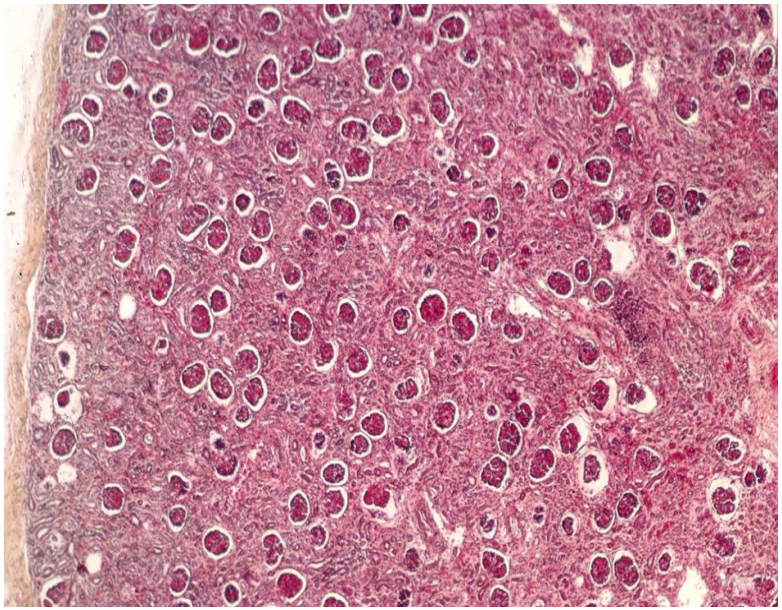
Case

- First pregnancy of a 28-year-old female affected with ADPKD and treated with sartan because of high blood pressure
- First 32 weeks of pregnancy not followed (denial of pregnancy)
- First foetal ultrasound at about 32 weeks of gestation: anhydramnios, two slightly hyperechogenic kidneys +2SD
- Spontaneous onset of labor at 32 weeks
- 1970g new born baby, hypocalvaria, respiratory distress (pulmonary hypoplasia), low blood pressure (vasopressors), no urine after 24h (empty bladder), death at H24.

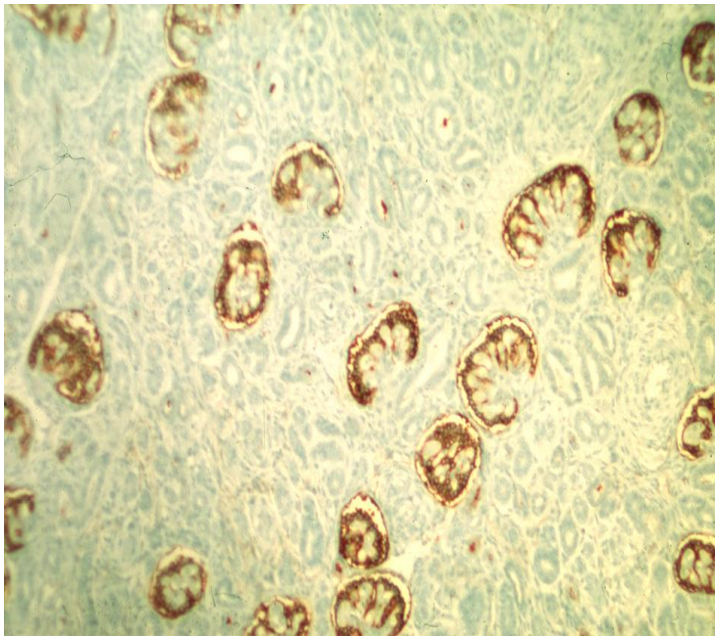
RAS blockers treatment contraindicated during 2d and 3rd trimester of pregnancy

- Several publications
  - Oligo-anhydramnios and Potter syndrome
  - Terminal renal failure with anuria
  - Low blood pressure not cured by vascular filling and refractory to catecholamine therapy
  - Hypocalvaria

Renal histology in newborns exposed to RAS blokers during foetal life : renal tubular dysgenesis

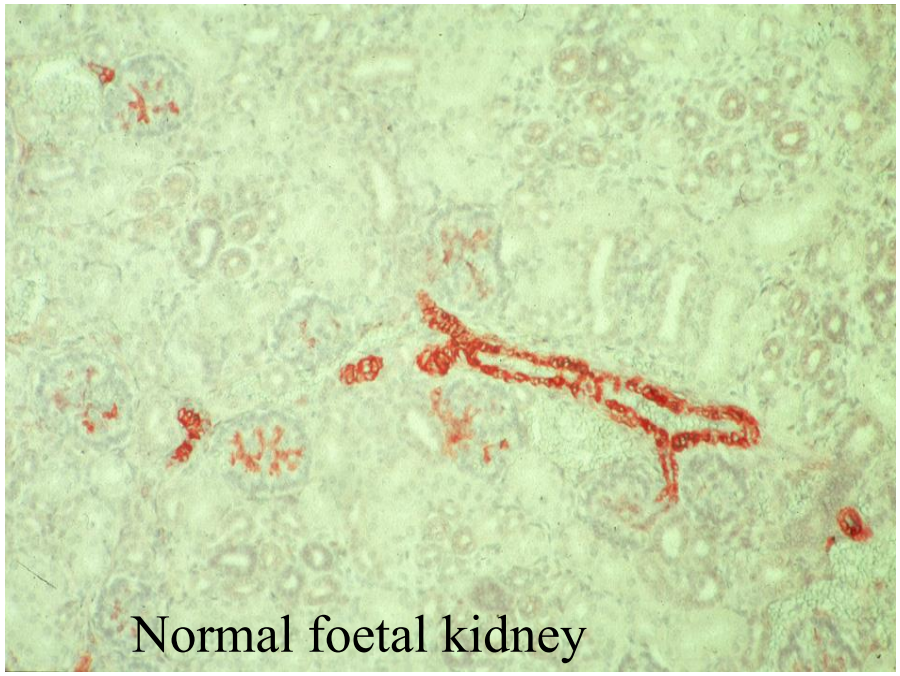


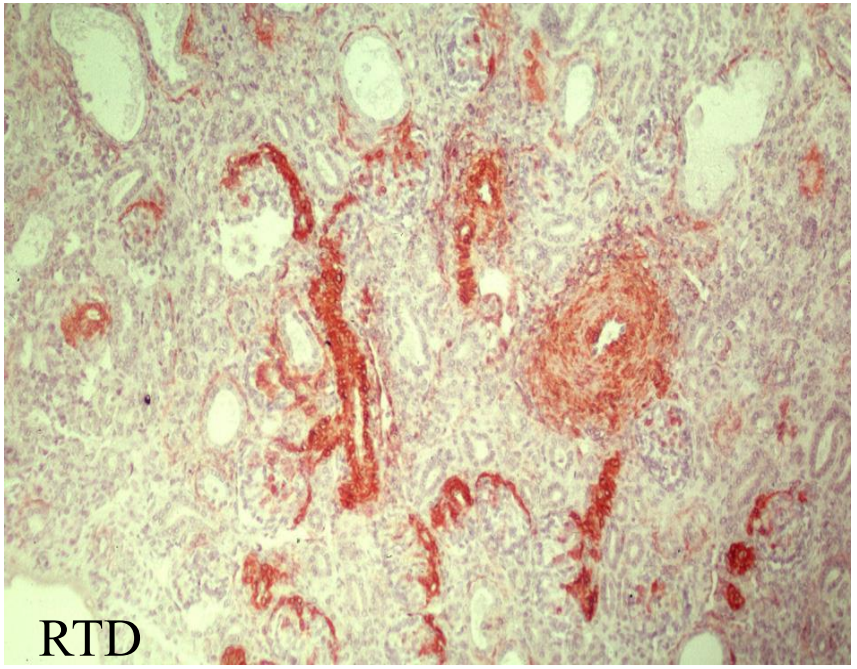
Glomeruli are closely packed together because of the absence of recognizable proximal tubule (“crowded glomeruli”)



Lack of recognized proximal tubule (anti-CD10 Ab)

Renal tubular dysgenesis : arterial abnormalities



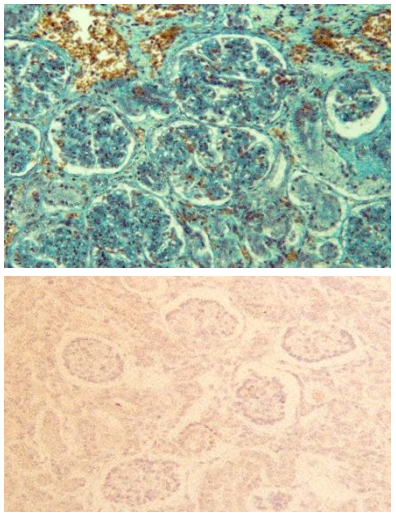


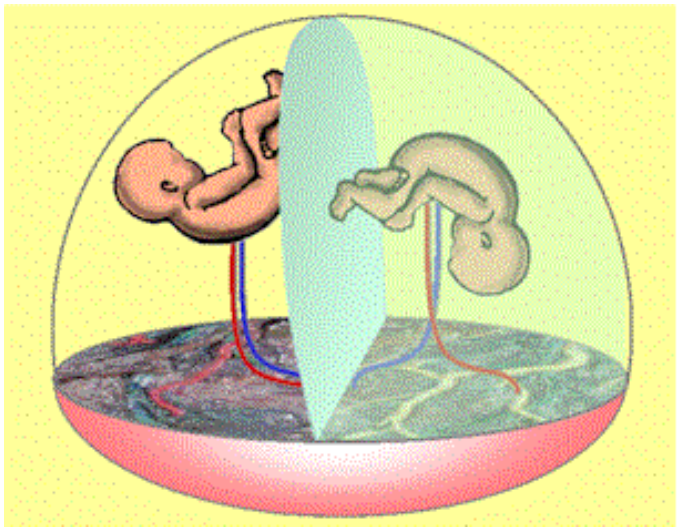
Labeling with anti-SMA antibody : arterial walls thickening +++

Other situations leading to renal tubular dysgenesis

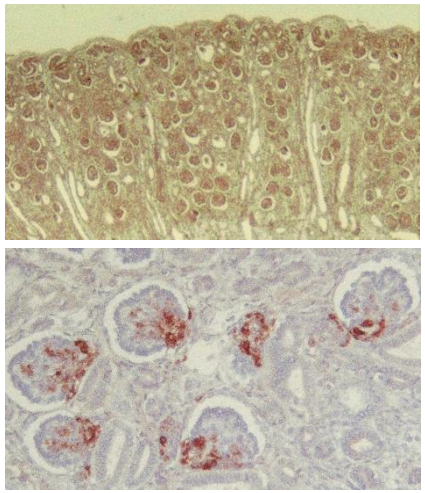
- Twin-to-twin transfusion syndrome (in donors)

recipient





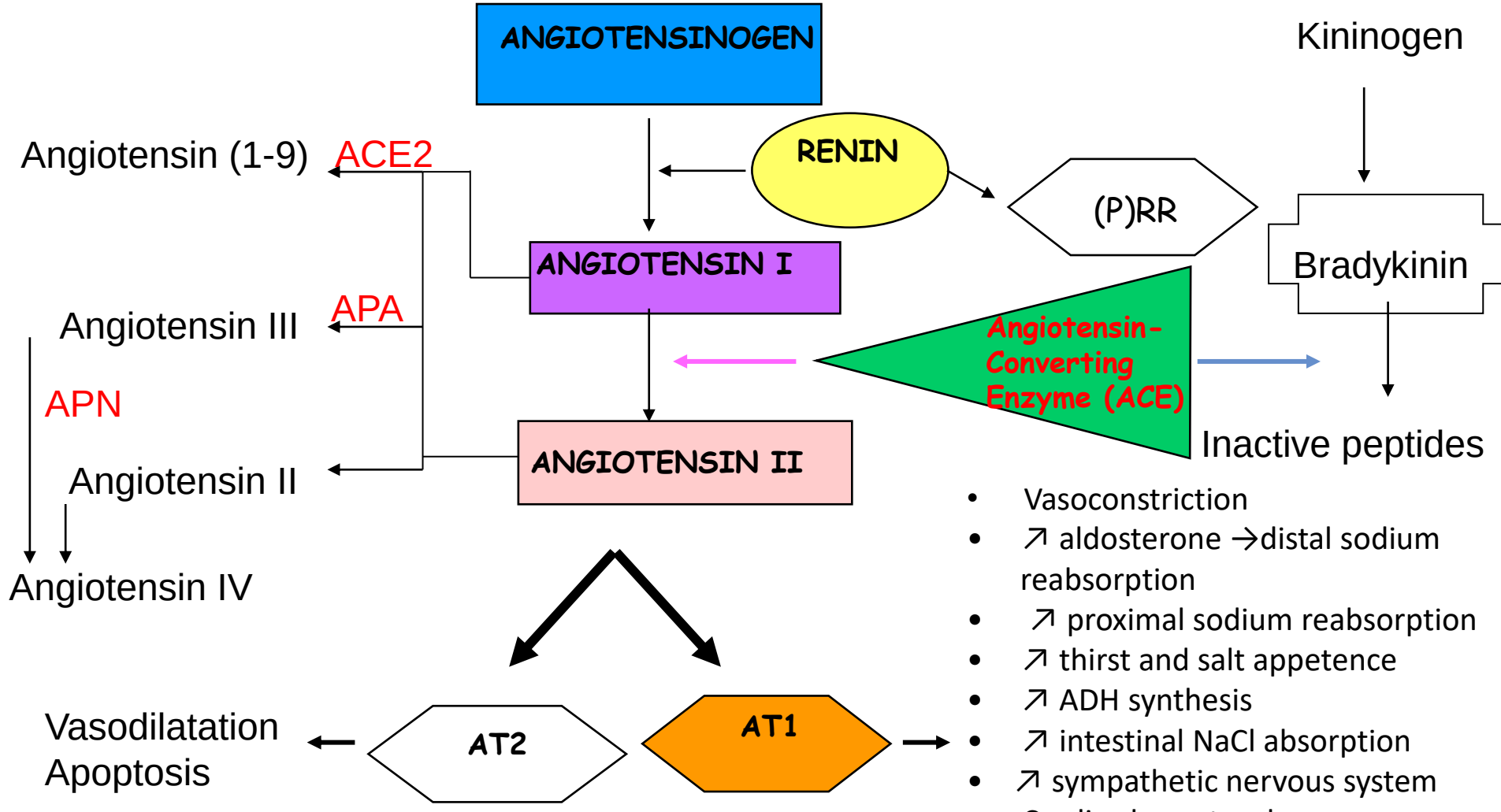
donor



- Severe renal artery stenosis
- Severe foetal cardiopathy
- Neonatal hemochromatosis

In all these situations there is a stimulation of the RAS, not a blockage

RA system



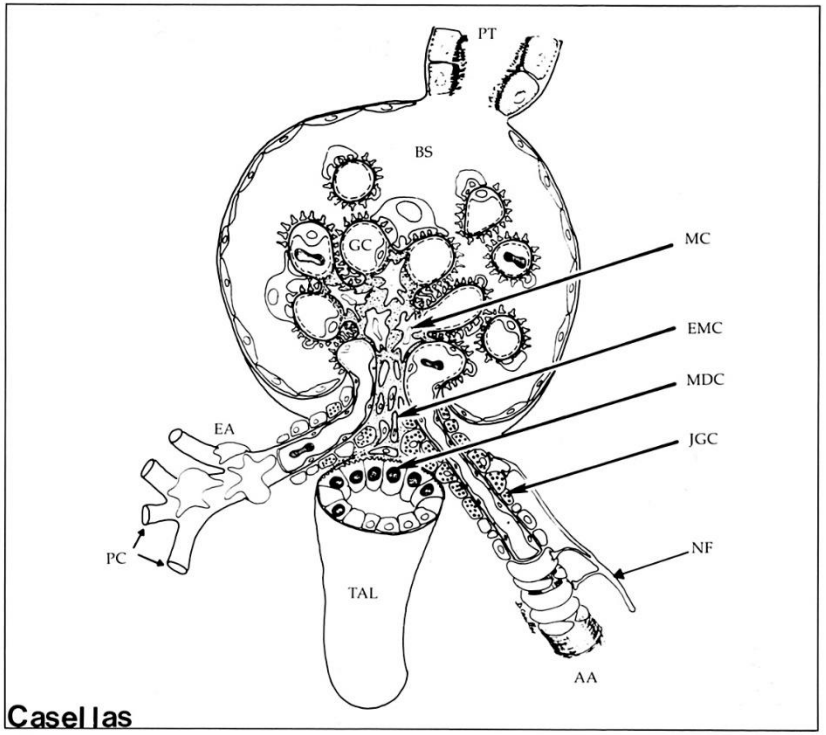
- Vasoconstriction
- ↗ aldosterone →distal sodium reabsorption
- ↗ proximal sodium reabsorption
- ↗ thirst and salt appetence
- ↗ ADH synthesis
- ↗ intestinal NaCl absorption
- ↗ sympathetic nervous system
- Cardiac hypertrophy
- Pro-inflammatory action
- Cell proliferation
- Matrix production, fibrosis

RA system

Renin, synthetized at the juxta-glomerular apparatus, is the limiting step of the cascade

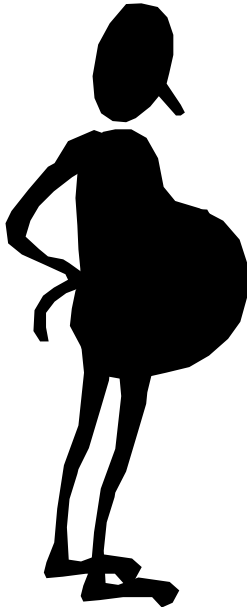
Renin secretion is regulated by:

- Baroreceptors
- Sodium concentration in the distal tubule
- Sympathetic nervous system
- Angiotensin II : inhibition of RAS leads to overexpression/overproduction of renin.



Casellas D, et al. Am J Physiol. 1994, 267:F931-6.

RA system and pregnancy



- Stimulation of the RAS in pregnant women
(increased synthesis of angiotensinogen and of inactive and active renin)

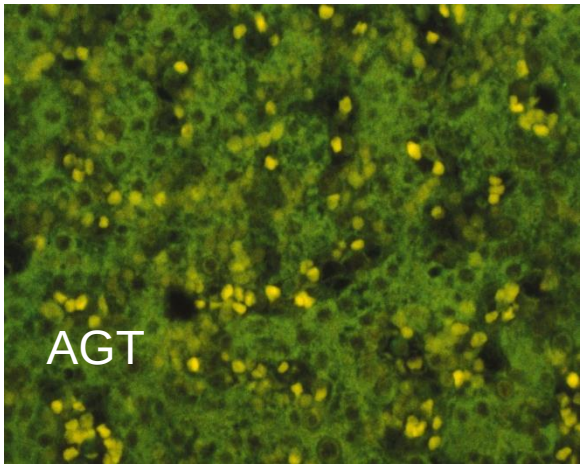
- Resistance to the effect of angiotensin II on blood pressure

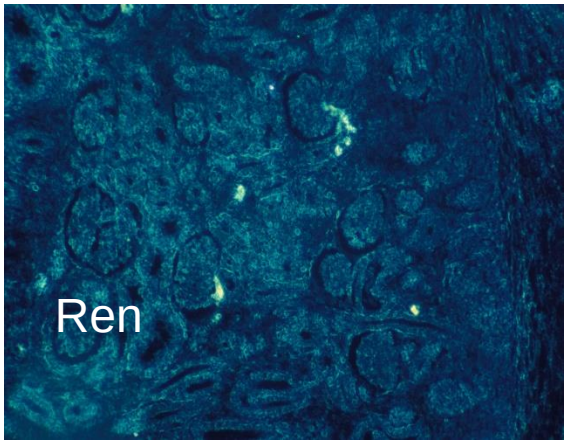
- Utero-placental RA system
  - ACE ++ vessels in placenta
  - Renin is synthetized by the chorion and secreted in the inactive pro-renin form in the amniotic fluid
  - Does the RAS have a role in the control of the placental blood flow?

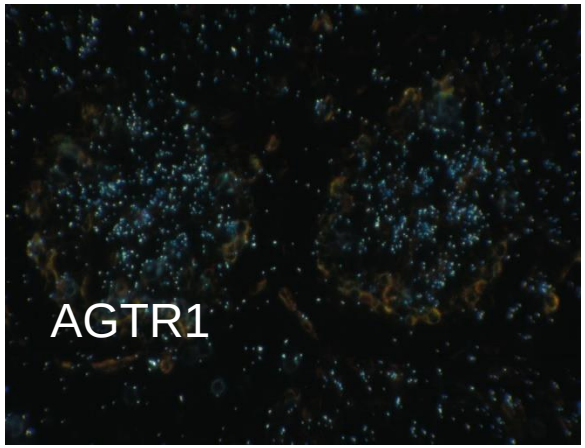
- The foetal RA system

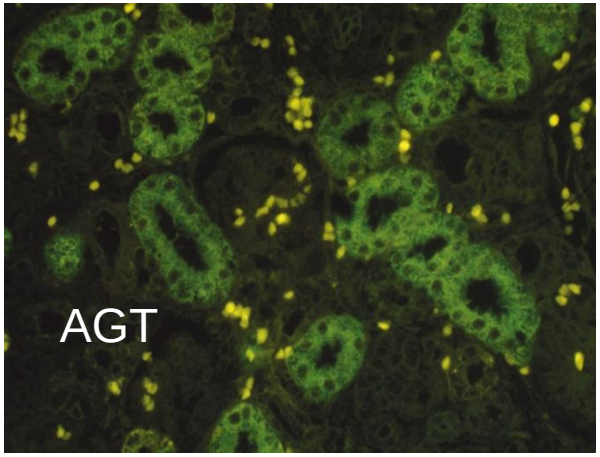
Foetal RA System

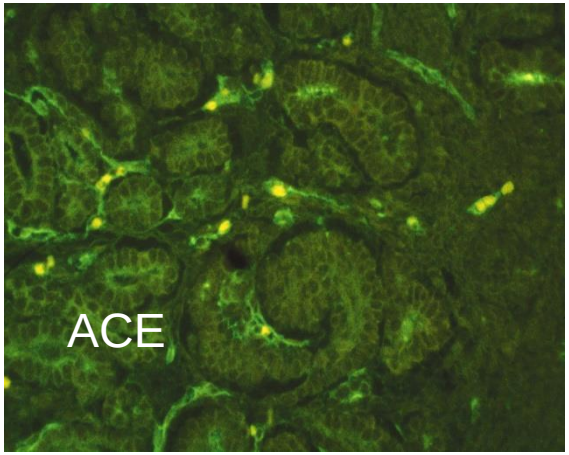
All components of the RAS are expressed early in the human foetal kidney, as soon as the 5th week of gestation (Schütz et al. 1996).

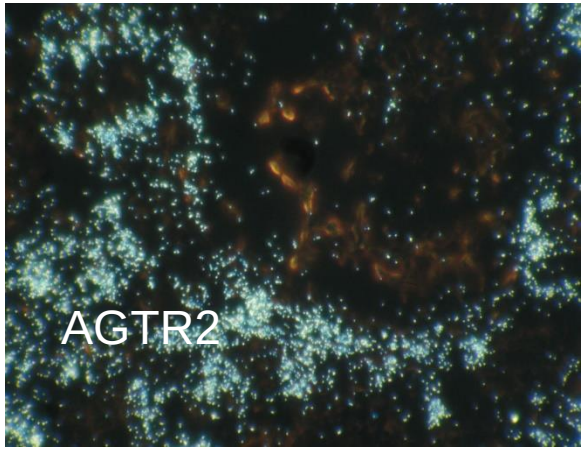












Foetal RA System

- The foetal RAS is independent of the maternal RAS
- Circulating renin concentration is higher in the foetus than in the mother and than in the new born.
- RAS is functional in the foetus (at least during the second half of gestation in the sheep). It does respond to the same stimuli as in adult RAS.
- RAS is necessary for renal development
  - Autosomal recessive renal tubular dysgenesis

Genetic cause of renal tubular dysgenesis ?

- First cases reported in 1983 (JE Allanson)
- Oligohydramnios + Potter sd at 18-20 wks of gestation (sometimes later)
- Lack or paucity of the proximal tubules, vascular lesions, lack of ossification of the skull
- But no treatment received by the mother
- No known extra-renal cause
- Foetal US : No urinary tract abnormality
  Kidneys of normal size (/sligthly increased)
  with normal or increased echogenicity
- Males and females
- Frequent parental consanguinity
- Affected siblings
- Unaffected parents

} Recessif autosomal ?

Genetic cause of renal tubular dysgenesis ? Poor prognosis

- Persistant oligohydramnios
- In utero death
- Neonatal death (respiratory failure + anuria)

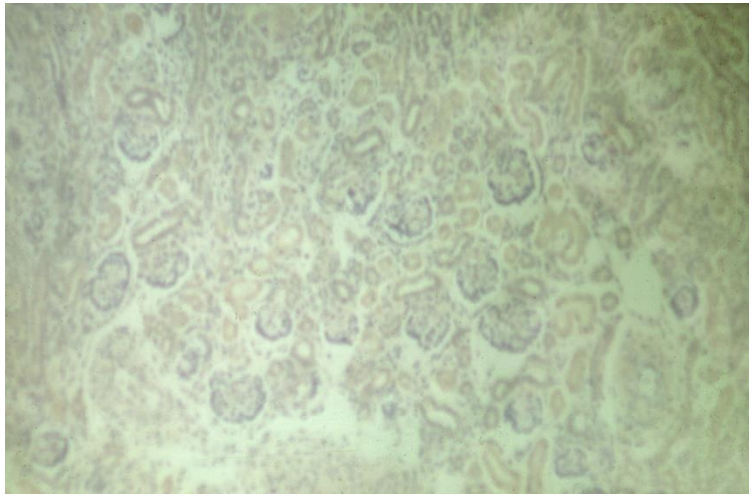
} In most cases

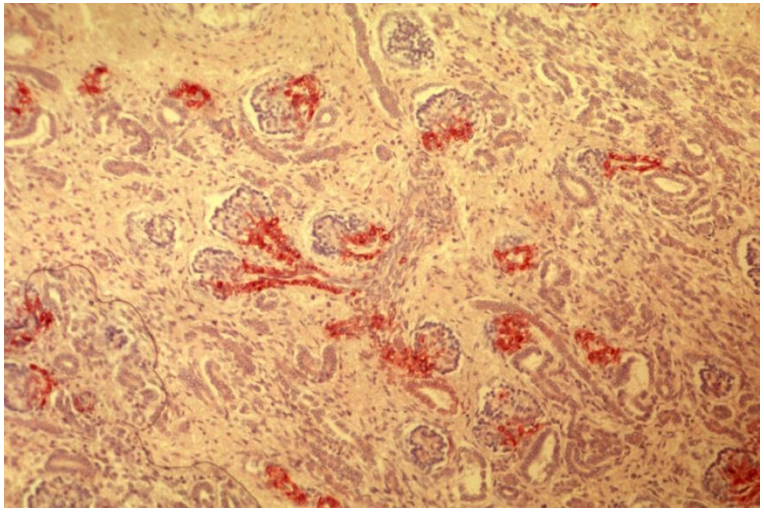
- Few cases reported to survive with dialysis +/- ventilation
- Few cases with partial recovery after a period of PD (CKD)

- When blood pressure is known : low blood pressure refractory to catecholamine therapy

- Frequent hypocalvaria

Genetic cause of renal tubular dysgenesis ?
Renal expression of RAS elements





Gribouval et al. 2005

Renin expression modifications:

Immuno-histochemistry and *in situ* hybridization :

- No expression at all in a few families

- Diffuse overexpression in most families

→ Mutations in RAS genes ?

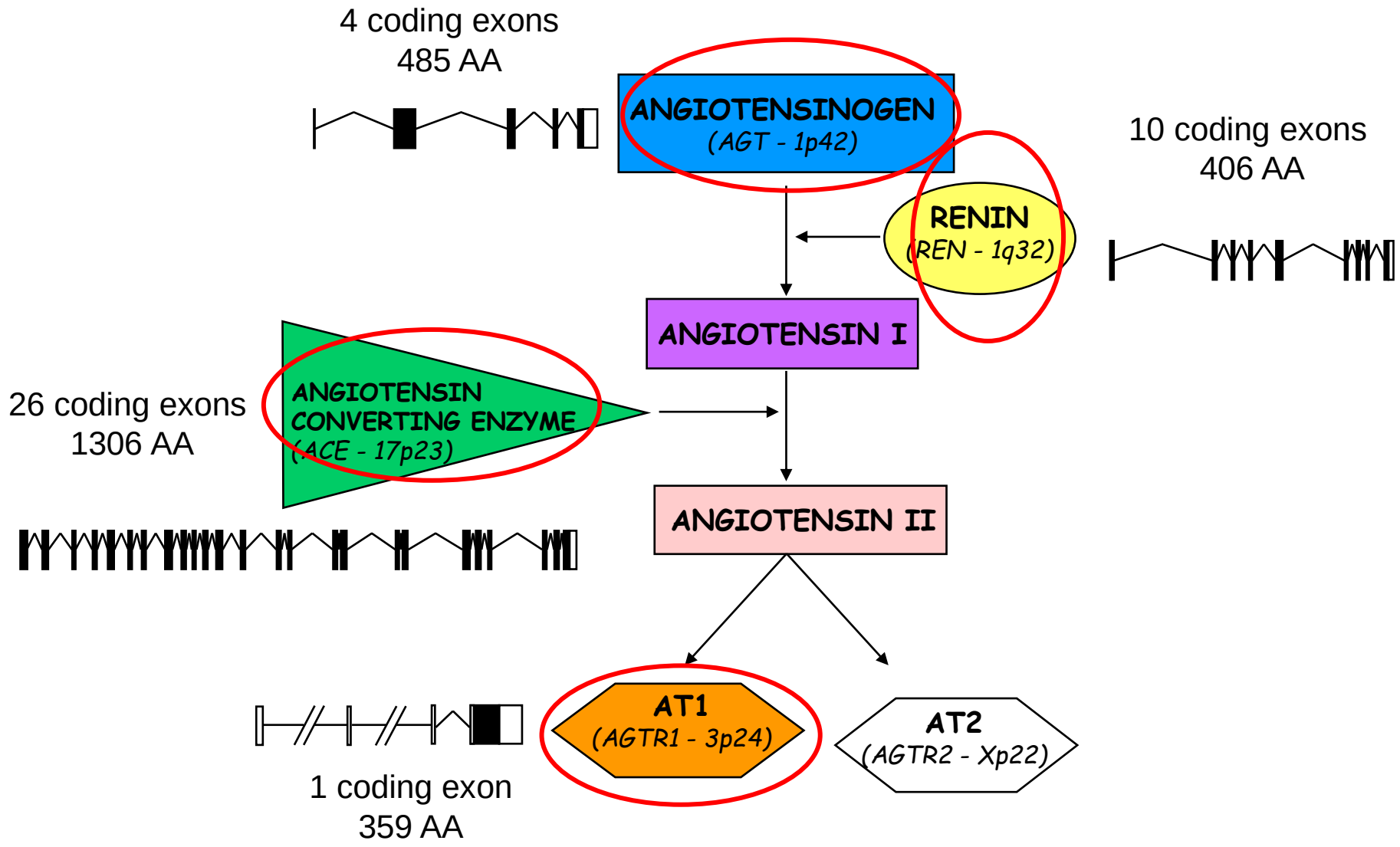
Mutations in genes in the renin-angiotensin system are associated with autosomal recessive renal tubular dysgenesis

Olivier Gribouval[1], Marie Gonzales[2], Thomas Neuhaus[3], Jacqueline Aziza[4], Eric Bieth[5], Nicole Laurent[6], Jean Marie Bouton[7], François Feuillet[8], Saloua Makni[9], Hatem Ben Amar[10], Guido Laube[3], Anne-Lise Delezoide[11], Raymonde Bouvier[12], Frédérique Dijoud[13], Elisabeth Ollagnon-Roman[14], Joelle Roume[15], Madeleine Joubert[16], Corinne Antignac[1,17] & Marie Claire Gubler[1]

Autosomal recessive renal tubular dysgenesis is a severe disorder of renal tubular development characterized by persistent fetal anuria and perinatal death, probably due to pulmonary hypoplasia from early-onset oligohydramnios (Potter phenotype). Absence or paucity of differentiated proximal tubules is the histopathological hallmark of the disease and may be associated with skull ossification defects. We studied 11 individuals with renal tubular dysgenesis, belonging to nine

tubules is due to primary defects in genes encoding factors involved in tubular growth and differentiation, but this has never been investigated. Several features of the disease point to a primary failure in renal blood supply. Loss of proximal tubule differentiation has been described in the 'endocrine kidney', produced in rats by partial occlusion of a renal artery[10]. Similar lesions have been observed beyond the site of arterial constriction in kidneys of individuals with renovascular hypertension[11,12]. Moreover, the RTD phenotype

Identification of bi-allelic pathogenic variants in genes encoding proteins of the RAS

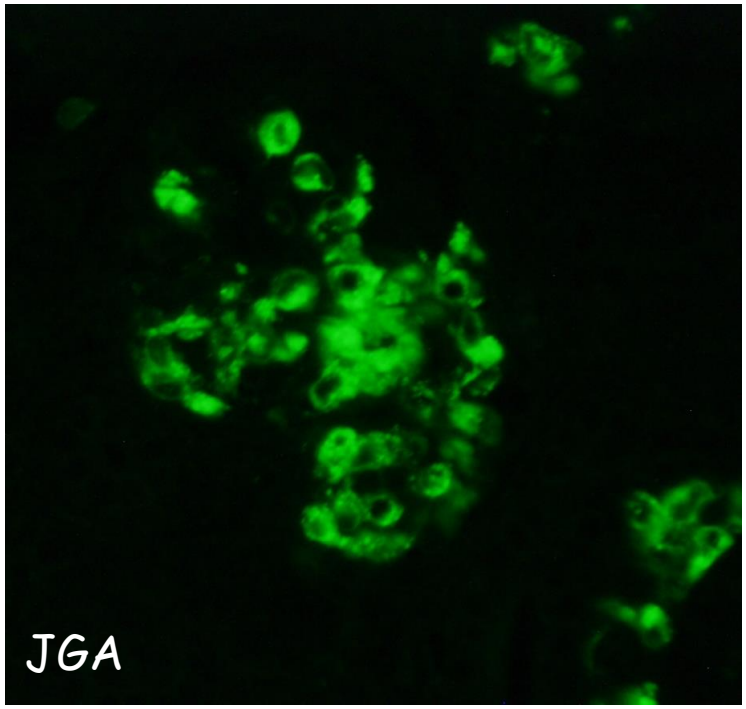


All mutations lead either to absence of angiotensin II or to ineffective angiotensin II

Autosomal recessive renal tubular dysgenesis:

pathogenic variants in *AGT*

- All types of variants
  (missense, splicing, frameshift, nonsense)
- Do not affect sequence encoding angiotensin 1, but modify the serpin domain. *In vitro* data show that this will prevent clivage by renin and production of angiotensin I
- Increased renin expression



33 aa (signal)-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-441 aa

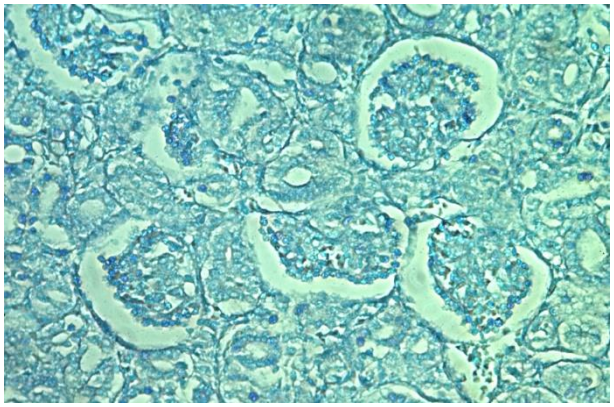
Autosomal recessive renal tubular dysgenesis :

pathogenic variants in *REN*

- Null variants

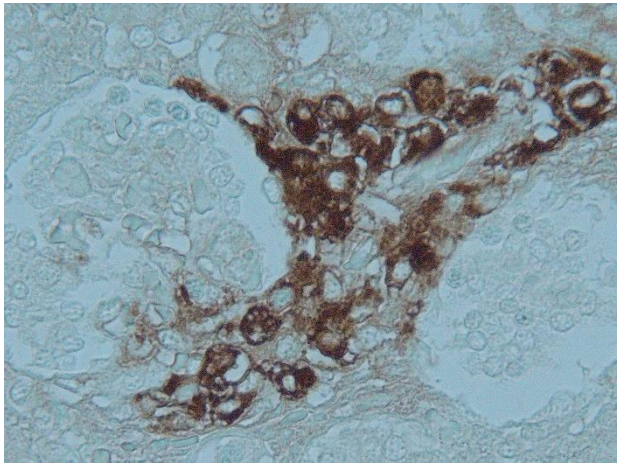
  (stop and/or frame shift/splicing)

No renin expression



- At least one missense or in frame variant

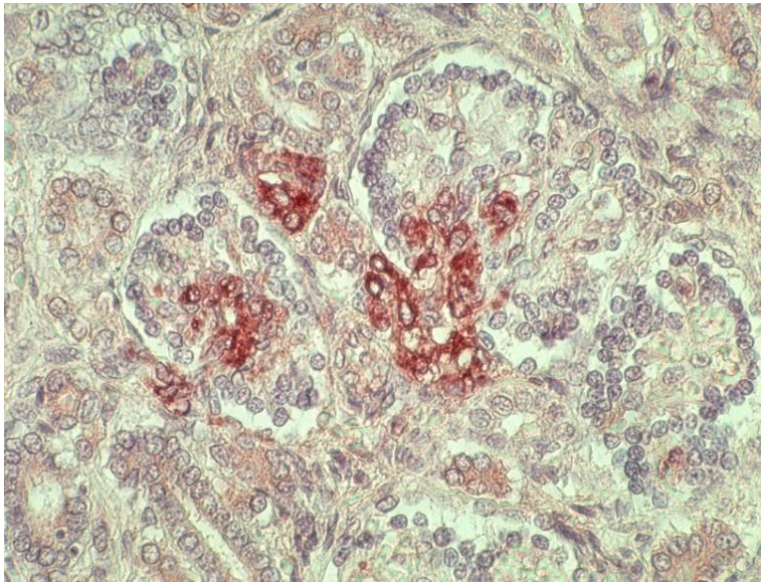
Renin expression +++



Autosomal recessive renal tubular dysgenesis :

pathogenic variants in *ACE* (most cases)

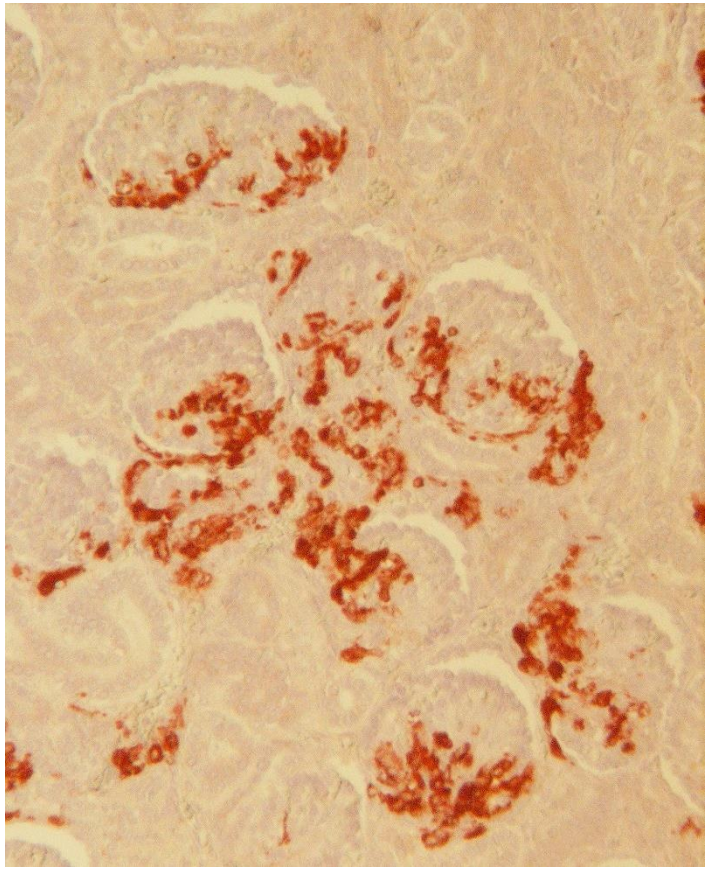
- All types : missense, splicing, frameshift mutations; mutations of signal peptide
- One recurrent mutation (c.3621delG, p.Gly1174fs) in northern Europe
- Increased renin expression



Autosomal recessive renal tubular dysgenesis :

pathogenic variants in *AGTR1*

- All types : missense, splicing, frameshift mutations
- Increased renin expression



Autosomal recessive renal tubular dysgenesis, to summarize :

- Oligohydramnios/anhydramnios
  (may be seen as early as 20 WG, but sometimes later)

- No premature rupture of membranes

- No foetal urinary tract anomaly. Normal looking foetal kidneys (sometimes enlarged/hyperechogenic)

- No RAS blockers exposure

- Pulmonary hypoplasia/respiratory distress
- Anuria and terminal renal failure
- Low blood pressure refractory to catecholamine therapy
- Hypocalvaria

Autosomal recessive renal tubular dysgenesis

Mecanisms leading to renal tubular dysgenesis?

- Lack of angiotensin II on hemodynamic (fœtal/utero-placental) ?

- Lack of angiotensin II, which is a growth factor, on tubular cells ?

  – But same tubular (and vascular) lesions in situations with hypovolemia and RAS stimulation with high angiotensin II (severe foetal cardiopathy, twin-to-twin transfusion syndrome…)

- Abnormal expression of renin ?

  – But same tubular (and vascular) lesions when
    - No renin expression (*REN*-null mutations)
    - ↗↗↗ renin expression (other mutations in RAS genes, foetal exposition to RAS blockers).

Autosomal recessive renal tubular dysgenesis

Mechanisms leading to renal tubular dysgenesis?

- Low perfusion pressure of the foetal kidneys seems to be a common mechanism in all causes of renal tubular dysgenesis:
  - Low pressure of perfusion in cases of autosomal recessive renal tubular dysgenesis and in cases of pregnant women receiving RAS blockers during 2d and 3rd trimester of pregnancy
  - Hypoperfusion of the foetal kidney in secondary renal tubular dysgenesis (renal artery stenosis, cardiopathy, twin-to-twin transfusion syndrome)

Not Always fatal

Clinical Report

A Case Surviving for Over a Year of Renal Tubular Dysgenesis With Compound Heterozygous Angiotensinogen Gene Mutations

Mitsugu Uematsu,[1]* Osamu Sakamoto,[1] Toshiyuki Nishio,[1] Toshihiro Ohura,[1] Tadashi Matsuda,[1] Tetsuji Inagaki,[4] Takaaki Abe,[3] Kunihiro Okamura,[2] Yoshiaki Kondo,[1] and Shigeru Tsuchiya[1]

[1]Department of Pediatrics, Tohoku University Graduate School of Medicine, Sendai, Japan
[2]Department of Obstetrics and Reproductive Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[3]Division of Nephrology, Endocrinology and Vascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[4]Miyagi Children's Hospital, Sendai, Japan

Received 23 January 2006; Accepted 17 July 2006

Renal tubular dysgenesis (RTD) is a developmental abnormality of the renal proximal tubules found in patients with Potter syndrome. We report a female newborn with RTD who has survived for more than 18 months. Infusions of fresh frozen plasma (FFP) in the early neonatal period were effective in raising and maintaining her blood pressure. Peritoneal dialysis was required until the appearance of spontaneous urination at 29 days after birth. Histopathological examinations of the kidney revealed dilated renal tubular lumina and foamy columnar epithelial cells in the renal tubules. Endocrinological studies showed a discrepancy between low plasma renin activity (<0.1 ng/ml/hr) and high active renin concentration (135,000 pg/ml), suggesting an aberration in the renin substrate, angiotensinogen. Direct sequencing analysis revealed two novel mutations in the coding region of the angiotensinogen gene (*AGT*): a nonsense mutation in exon 2 (c.604C > T) and a frameshift deletion at nucleotide 1290 in exon 5 (c.1290delT). The mutations were in the compound heterozygous state, because each parent had each mutation. These findings suggest that angiotensinogen deficiency is one of the causes of RTD. A treatment of the condition with FFP may help to promote long survival.

Key words: renal tubular dysgenesis; angiotensinogen; fresh frozen plasma; *AGT*

How to cite this article: Uematsu M, Sakamoto O, Nishio T, Ohura T, Matsuda T, Inagaki T, Abe T, Okamura K, Kondo Y, Tsuchiya S. 2006. A case surviving for over a year of renal tubular dysgenesis with compound heterozygous angiotensinogen gene mutations. Am J Med Genet Part A 140A:2355–2360.

Year: 2008

Inherited renal tubular dysgenesis: the first patients surviving the neonatal period

Zingg-Schenk, A; Bacchetta, J; Corvol, P; Michaud, A; Stallmach, T; Cochat, P; Gribouval, O; Gubler, M C; Neuhaus, T J

Inherited renal tubular dysgenesis: the first patients surviving the neonatal period

Pediatr Nephrol (2010) 25:2531–2534
DOI 10.1007/s00467-010-1584-0

BRIEF REPORT

Inherited renal tubular dysgenesis may not be universally fatal

Ruth Schreiber · Marie-Claire Gubler · Olivier Gribouval · Hanna Shalev · Daniel Landau

Eur J Pediatr (2009) 168:207–209
DOI 10.1007/s00431-008-0743-9

ORIGINAL PAPER

A further case of renal tubular dysgenesis surviving the neonatal period

Mitsugu Uematsu · Osamu Sakamoto · Toshihiro Ohura · Nobuhiko Shimizu · Kenichi Satomura · Shigeru Tsuchiya

Received: 21 November 2007 / Revised: 7 April 2008 / Accepted: 7 April 2008 / Published online: 14 May 2008

Abstract Renal tubular dysgenesis is a critical disorder **Introduction**

ELSEVIER MASSON

Disponible en ligne sur www.sciencedirect.com
ScienceDirect
Archives de pédiatrie 14 (2007) 1084–1087
Archives de pédiatrie
http://france.elsevier.com/direct/ARCPED/

Fait clinique

Dysgénésie tubulaire proximale et mutation du gène de la rénine

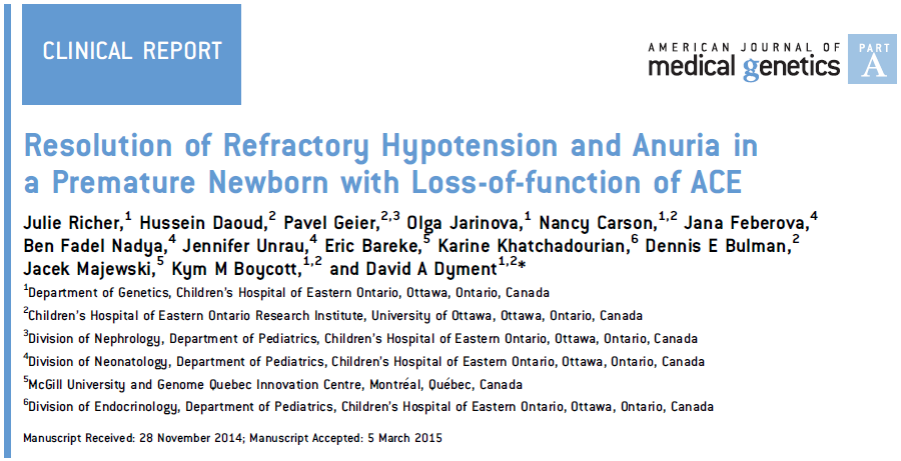
Renal tubular dysgenesis and mutation in the renin gene

J. Bacchetta[a], F. Dijoud[b], R. Bouvier[c], G. Putet[d], M.-C. Gubler[e], P. Cochat[a,*]

[a]Centre de référence des maladies rénales héréditaires, département de pédiatrie, hôpital Édouard-Herriot et université Claude-Bernard-Lyon-I, 69437 Lyon cedex 03, France
[b]Laboratoire d'anatomie pathologique, hôpital Debrousse, Lyon, France
[c]Laboratoire central d'anatomie pathologique, hôpital Édouard-Herriot, Lyon, France
[d]Service de néonatologie et réanimation néonatale, hôpital de la Croix-Rousse, Lyon, France
[e]Inserm U574, hôpital Necker-Enfants-Malades, Paris, France

Case reports of treatment with vasopressin

- Severe arterial hypotension and anuria in renal tubular dysgenesis are usually refractory to catecholamine therapy
- Reports of successful treatment with vasopressin and fludrocortisone in autosomal recessive renal tubular dysgenesis



CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Resolution of Refractory Hypotension and Anuria in a Premature Newborn with Loss-of-function of ACE

Julie Richer,[1] Hussein Daoud,[2] Pavel Geier,[2,3] Olga Jarinova,[1] Nancy Carson,[1,2] Jana Feberova,[4] Ben Fadel Nadya,[4] Jennifer Unrau,[4] Eric Bareke,[5] Karine Khatchadourian,[6] Dennis E Bulman,[2] Jacek Majewski,[5] Kym M Boycott,[1,2] and David A Dyment[1,2]*

[1]Department of Genetics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

[2]Children's Hospital of Eastern Ontario Research Institute, University of Ottawa, Ottawa, Ontario, Canada

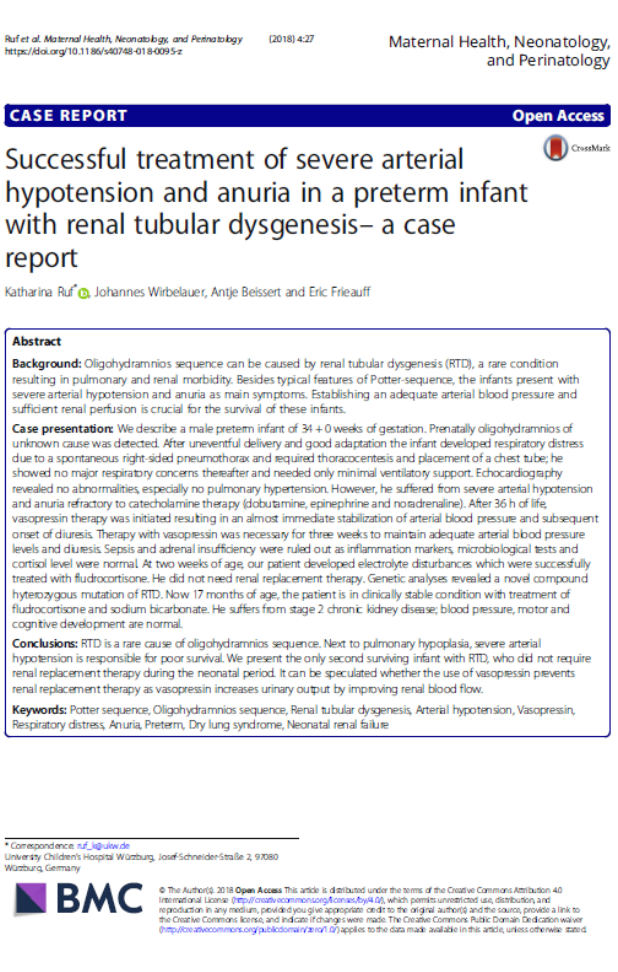
[3]Division of Nephrology, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

[4]Division of Neonatology, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

[5]McGill University and Genome Quebec Innovation Centre, Montréal, Québec, Canada

[6]Division of Endocrinology, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

Manuscript Received: 28 November 2014; Manuscript Accepted: 5 March 2015



Ruf et al. Maternal Health, Neonatology, and Perinatology (2018) 4:27
https://doi.org/10.1186/s40748-018-0095-z

Maternal Health, Neonatology, and Perinatology

CASE REPORT Open Access

Successful treatment of severe arterial hypotension and anuria in a preterm infant with renal tubular dysgenesis– a case report

Katharina Ruf*, Johannes Wirbelauer, Antje Beissert and Eric Frieauff

Abstract

Background: Oligohydramnios sequence can be caused by renal tubular dysgenesis (RTD), a rare condition resulting in pulmonary and renal morbidity. Besides typical features of Potter-sequence, the infants present with severe arterial hypotension and anuria as main symptoms. Establishing an adequate arterial blood pressure and sufficient renal perfusion is crucial for the survival of these infants.

Case presentation: We describe a male preterm infant of 34 + 0 weeks of gestation. Prenatally oligohydramnios of unknown cause was detected. After uneventful delivery and good adaptation the infant developed respiratory distress due to a spontaneous right-sided pneumothorax and required thoracocentesis and placement of a chest tube; he showed no major respiratory concerns thereafter and needed only minimal ventilatory support. Echocardiography revealed no abnormalities, especially no pulmonary hypertension. However, he suffered from severe arterial hypotension and anuria refractory to catecholamine therapy (dobutamine, epinephrine and noradrenaline). After 36 h of life, vasopressin therapy was initiated resulting in an almost immediate stabilization of arterial blood pressure and subsequent onset of diuresis. Therapy with vasopressin was necessary for three weeks to maintain adequate arterial blood pressure levels and diuresis. Sepsis and adrenal insufficiency were ruled out as inflammation markers, microbiological tests and cortisol level were normal. At two weeks of age, our patient developed electrolyte disturbances which were successfully treated with fludrocortisone. He did not need renal replacement therapy. Genetic analyses revealed a novel compound hyterozygous mutation of RTD. Now 17 months of age, the patient is in clinically stable condition with treatment of fludrocortisone and sodium bicarbonate. He suffers from stage 2 chronic kidney disease; blood pressure, motor and cognitive development are normal.

Conclusions: RTD is a rare cause of oligohydramnios sequence. Next to pulmonary hypoplasia, severe arterial hypotension is responsible for poor survival. We present the only second surviving infant with RTD, who did not require renal replacement therapy during the neonatal period. It can be speculated whether the use of vasopressin prevents renal replacement therapy as vasopressin increases urinary output by improving renal blood flow.

Keywords: Potter sequence, Oligohydramnios sequence, Renal tubular dysgenesis, Arterial hypotension, Vasopressin, Respiratory distress, Anuria, Preterm, Dry lung syndrome, Neonatal renal failure

* Correspondence: ruf_j@ukw.de
University Children's Hospital Würzburg, Josef-Schneider-Straße 2, 97080 Würzburg, Germany

Autosomal recessive renal tubular dysgenesis : broadening the spectrum of phenotypes?

Pediatric Nephrology (2020) 35:1125–1128
https://doi.org/10.1007/s00467-020-04524-4

BRIEF REPORT

Check for updates

Bi-allelic mutations in renin-angiotensin system genes, associated with renal tubular dysgenesis, can also present as a progressive chronic kidney disease

Marc Fila[1] · Vincent Morinière[2] · Philippe Eckart[3] · Joelle Terzic[4] · Marie-Claire Gubler[5] · Corinne Antignac[2,5] · Laurence Heidet[6]

Received: 15 January 2020 / Revised: 19 February 2020 / Accepted: 26 February 2020 / Published online: 20 March 2020

Biallelic *ACE* mutations in pediatric cases

- « Late » progressive chronic renal failure
- No oligo-anhydramnios
- No need RRT

- Severe non regenerative normocytic anemia (not proportional to the level of renal failure)
- Important polyuro-polydypsia

- Familial history with cases of perinatal death in siblings : modifiers?

Pediatric Nephrology (2021) 36:2731–2737
https://doi.org/10.1007/s00467-021-05018-7

ORIGINAL ARTICLE

Functional tests to guide management in an adult with loss of function of type-1 angiotensin II receptor

Daan H. H. M. Viering[1] · Anneke P. Bech[2] · Jeroen H. F. de Baaij[1] · Eric J. Steenbergen[3] · A. H. Jan Danser[4] · Jack F. M. Wetzels[5] · René J. M. Bindels[1] · Jaap Deinum[6]

Received: 18 November 2020 / Revised: 4 February 2021 / Accepted: 17 February 2021 / Published online: 25 March 2021

Abstract

Background Genetic loss of function of *AGT* (angiotensinogen), *REN* (renin), *ACE* (angiotensin-converting enzyme), or *AGTR1* (type-1 angiotensin II receptor) leads to renal tubular dysgenesis (RTD). This syndrome is almost invariably lethal. Most surviving patients reach stage 5 chronic kidney disease at a young age.

Methods Here, we report a 28-year-old male with a homozygous truncating mutation in *AGTR1* (p.Arg216*), who survived the perinatal period with a mildly impaired kidney function. In contrast to classic RTD, kidney biopsy showed proximal tubules that were mostly normal. During the subsequent three decades, we observed evidence of both tubular dysfunction (hyperkalemia

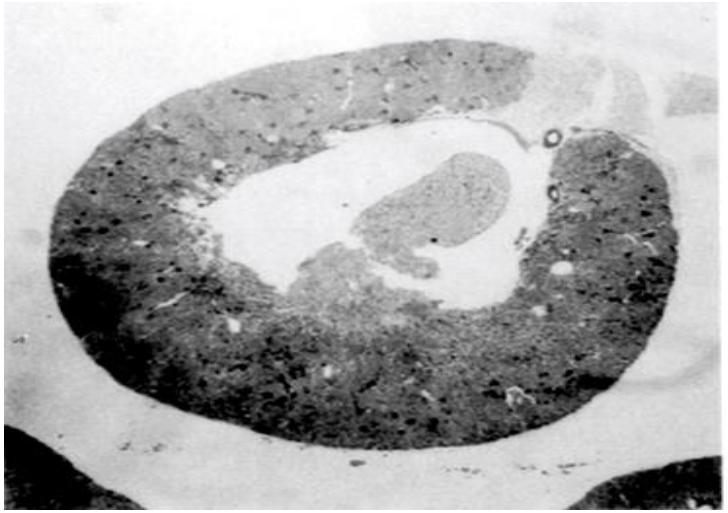
What about animal models?

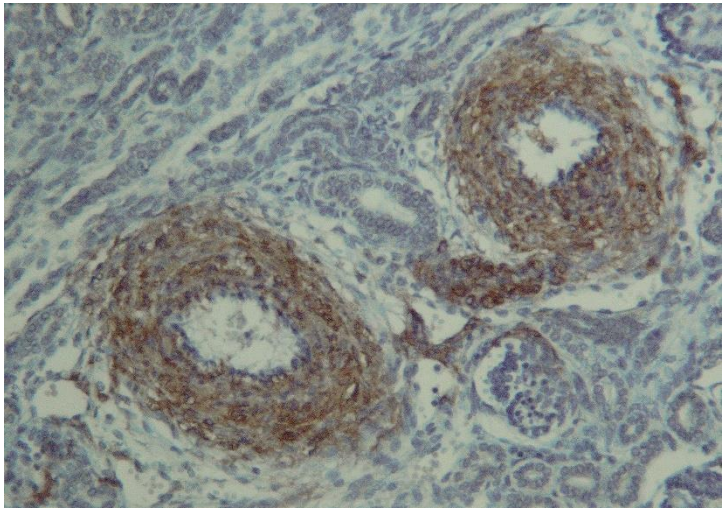
- Phenotypes observed in humans affected with autosomal recessive renal tubular dysgenesis and in mice models with inactivation of the RAS genes (or rats treated with ACE inhibitors) are different (normal survival, normal kidneys at birth, sometime delayed glomerular maturation, low blood pressure, atrophic papillae at 3 weeks of age with polyuria, lack of urinary concentration ability, thickened arteries.

- The only common features between mice and humans are low blood pressure and vascular anomalies in the kidneys

- Those differences might be due to differences in renal morphology and to differences in nephrogenesis timing

- Mechanisms responsible for vascular lesions remain to be elucidated.





Conclusions

- Renal tubular dysgenesis can be secondary to different foetal conditions or due to bi-allelic pathogenic variants in genes encoding RA system proteins.

- This autosomal recessive disease demonstrates the crucial role of the RA system during kidney development. The renal lesions may result from chronic low perfusion of the foetal kidney due to RAS inactivation.

- Clinical phenotype and histological lesions are the same when renin is absent or is overexpressed, when angiotensin II is absent or overexpressed, and whatever gene is carrying bi allelic pathogenic variants. This shows there is no redundancy between the different RAS genes, *in vivo*.

- The diagnosis of this rare disease in foetuses with anuria is important as it allows molecular screening of the RAS genes and genetic counselling in those families.

Acknowledgments

- Inserm U1163 and Imagine institute

Marie-Claire Gubler
Olivier Gribouval
Mireille Lacoste
Corinne Antignac
Vincent Morinière

ERKNet Webminars

ERKNet
The European
Rare Kidney Disease
Reference Network

Inserm
Institut national
de la santé et de la recherche médicale

Société de Néphrologie pédiatrique

ORKiD FILIÈRE ORPHAN KIDNEY DISEASES

maladies rares

THANK YOU FOR
YOUR ATTENTION !

MARHEA
Maladies Rénales Héréditaires
de l'Enfant et de l'Adulte

Necker
ENFANTS MALADES
HÔPITAL UNIVERSITAIRE

imagine
INSTITUT DES MALADIES GÉNÉTIQUES

NEXT WEBINARS

01/02/22	KDIGO Guideline on Immune GP I, Jack Wetzels (Nijmegen, Netherlands)
15/02/22	KDIGO Guideline on Immune GP II, Dario Roccatello (Torino, Italy)
22/02/22	The genetics of human renal agenesis and renal dysplasia, Adrian Woolf (Manchester, GB)

Subscribe our Newsletter
Or follow us on Twitter
@EuRefNetwork

ERKNet The European Rare Kidney Disease Reference Network

european society for paediatric nephrology

WGIKD Working Group on Inherited Kidney Disorders

IPNA