CASE REPORT
Congenital Sodium Diarrhea by mutation of SLC9A3 gene

14 mai 2019

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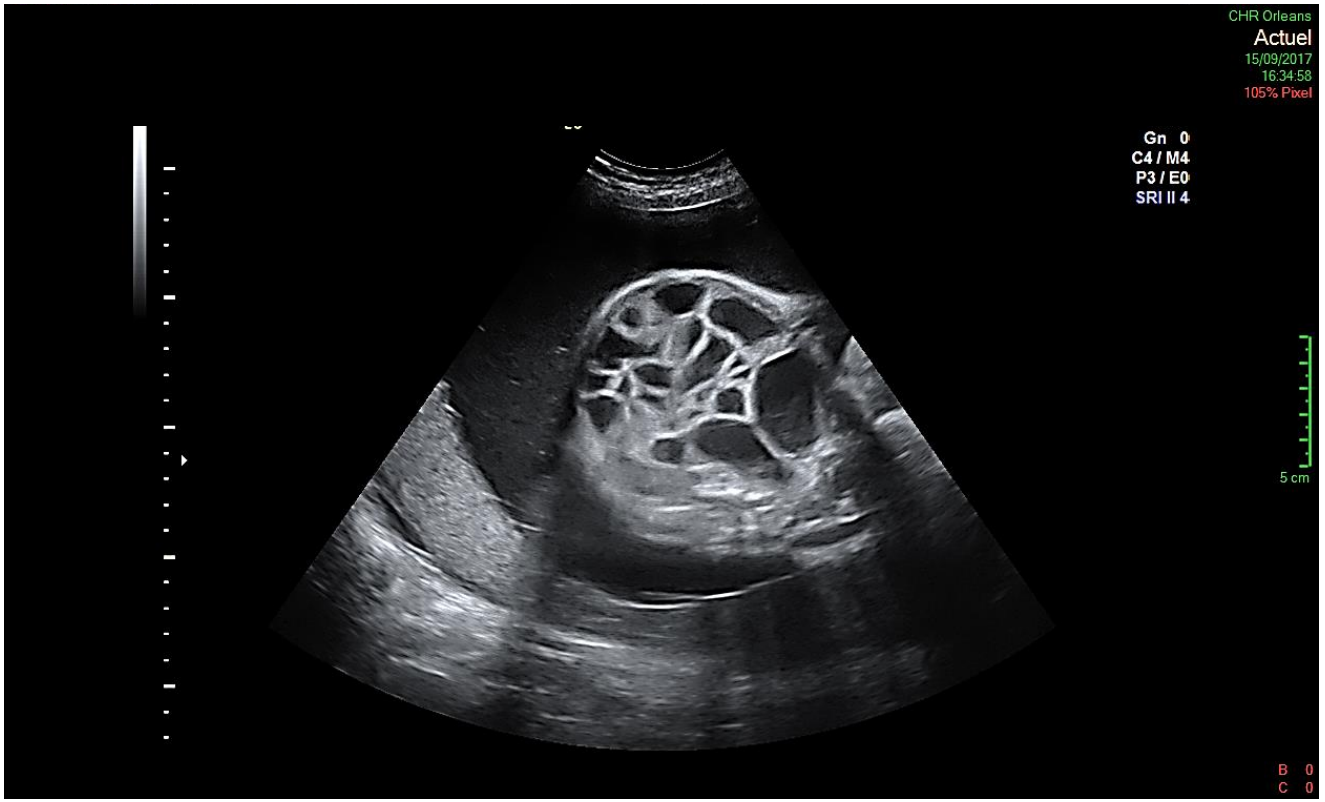
CASE REPORT

- male patient
- the first child of healthy parents.
- Parents: first degree cousins from Morocco**.**
- No family history of protracted diarrhea in infancy

CASE REPORT

Pregnancy

31 weeks' ultrasound : fetal **polyhydramnios and complete intestinal dilation**



“Honeycomb appearance” without ascites nor intraperitoneal calcifications

CASE REPORT

Pregnancy

- Karyotype on amniotic cells : no abnormality

- CFTR gene sequencing on amniotic cells: no abnormality

- Digestive enzymes in the amniotic fluid abnormally elevated:
  - *Gamma-glutamyltranspeptidase (GGTP) :2575 IU/l, >99th percentile
  - *Leucine aminopeptidase (LAP) at 339 IU/l>99th percentile
  - *Lipase at 251 IU/l>99th percentile
  - *total Alkaline phosphatases at 831 IU/l

- Normal Electrolytes in the amniotic fluid (Sodium at 135 mmol/l, chloride at 105 mmol/l)

CASE REPORT

At birth

Clinics

- 36 weeks of amenorrhea / new-born's weight 3,290 g / height 50 cm/ Apgar scores 10, 10 and 10

- Since the first day :
  - *6-8 liquid stools per day*,
  - *distended abdomen*,
  - without hemodynamic disturbances

- Exclusively breast fed during the first two weeks *without weight gain*

CASE REPORT

At birth

Explorations

- *hyponatremia at 130 mmol/l*, undetectable urinary sodium,
- normal chloride at 110 mmol/l,
- *low bicarbonates at 13 mmol/l*,
- acidotic with venous *pH between 7.25 and 7.30*.
- Fecal sodium was 99 mmol/l and stool pH was at 7**.**
- Immunoglobulins E against cow milk proteins, and microbiological stool cultures negative

Gastroduodenoscopy with duodenal and gastric biopsies at 3 weeks of life: normal

Rectal tissue: no intestinal aganglionosis.

CASE REPORT

Evolution

- No parenteral nutrition
- Electrolyte supplements (13 mmol /kg/day for sodium and bicarbonates diluted in oral rehydration solution) by nasogastric tube until the fifth month,
- and after the fifth month directly by mouth.

- From the third month on, the frequency of stools fell to 3 per day with normal consistency

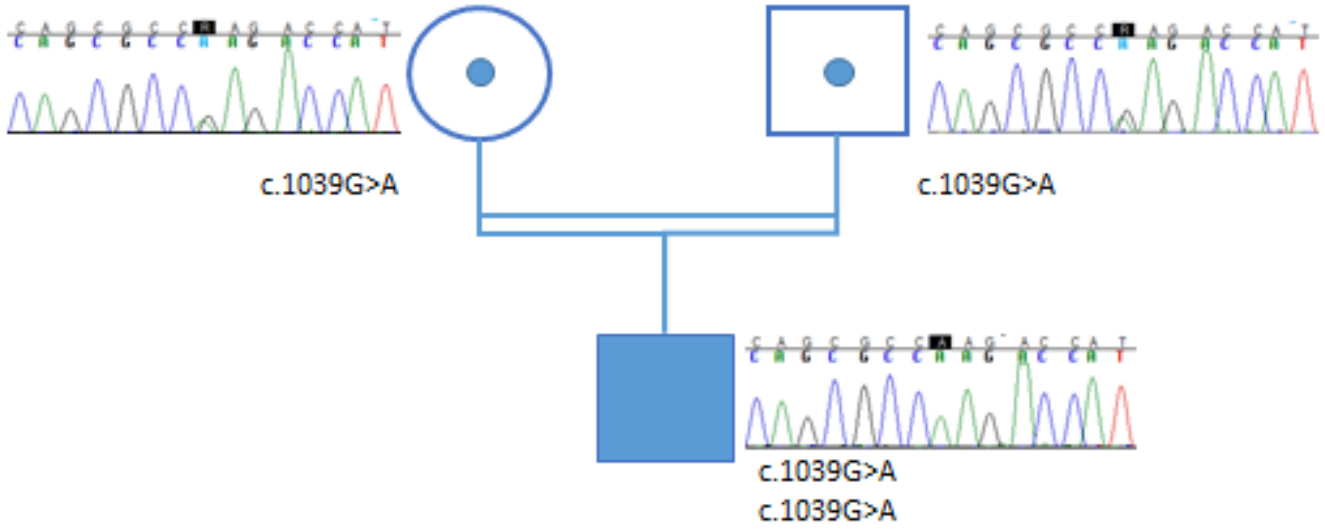
- At six months of age:
  - normal growth rate, normal neurological development, no syndromic abnormalities, and
  - bicarbonate and sodium needs fell respectively to 6 mmol /kg/day and 9 mmol /kg/day.
  - Food diversification was carried out normally

CASE REPORT

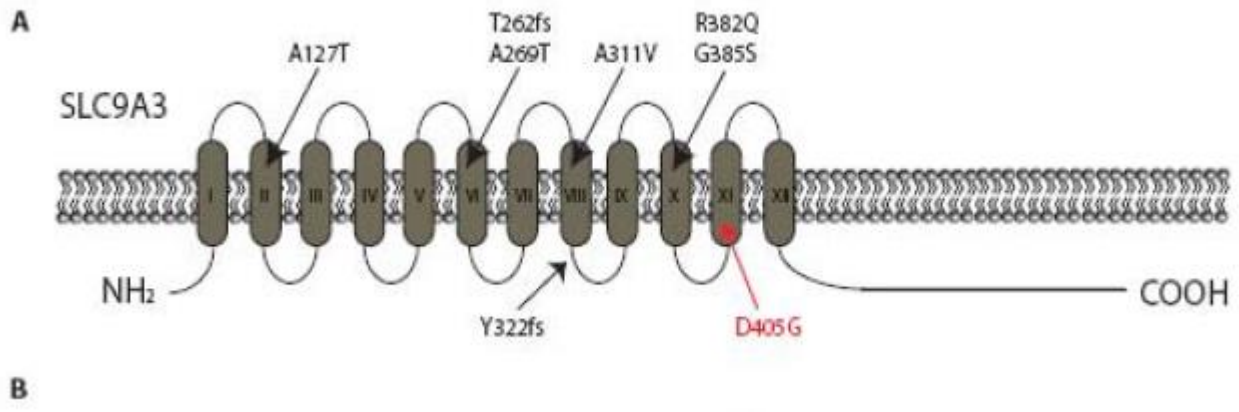
Genetic exploration

Genetic exploration looking for congenital diarrhea by *exome sequencing* and bioinformatics analysis on a list of *36 diarrhea linked disease genes*

A missense homozygous mutation in exon 6 of the SLC9A3 gene chr5



Na+/H+ antiporter 3, major intestinal brush border Na+/H+ exchanger



Gupta et al. JPGN 2019

a new case (n°11) of non-syndromic CSD linked to SLC9A3 mutation.

Differential diagnosis of Prenatal US symptoms – polyhydramnios and intestinal dilation:

- intestinal barrier (atresia, meconium peritonitis, Hirschsprung's disease)
- fetal infection
- congenital diarrhea especially congenital chloride diarrhea (CCD) due to mutation of the SLC26A3 gene

Elrefae et al. Clin Exp Gastroenterol. 2013

MRI : valuable aid in making a differential diagnosis between barrier and congenital diarrhea because the fluid-filled colon and rectum are easier to visualize

Colombani et al. Ultrasound Obstet Gynecol. 2010

The combined use of ultrasonography, MRI and enzyme analysis could increase the probability of correct antenatal diagnosis .

Garel et al.. Ultrasound Obstet Gynecol 2006

	This case	Series of Janecke and al. (2)	Gupta et al. (4)
Consanguinity	Yes	4 out of 9	Yes
Nationality/Ethnicity	French/ Morocco	Turkish (3) Canadian (2) German (2) British (1) Serbian (1) All Caucasians	South Asian
Current age (years)	1	Neonate to 37	1.3
Sex	M	4 F / 5 M	F
Gestational age (weeks)	36	34 (32 to 37)	« at term »
Birth weight (g)	3290	2553.9 (2125 to 3210)	3740
Current weight (kg/centile)	10 kg (50th)	21.7 kg (2.840 to 72) (10th to 97th)	Not reported
Height(cm/centile)	76 cm (50th)	95.7 cm (48 to 175) 34.8 th (10th to 97th)	Not reported
Polyhydramnios and dilated bowel	Yes	9 out of 9	Yes
Plasma [Na+] (132–155mmol/l)	130	137 (132 to 140)	« Normal »
Plasma pH	7.28	7.31 (7.25 to 7.37)	« Metabolic acidosis »
Plasma [HCO3–] (mmol/l)	13	19.4 (11 to 24)	Not reported
Fecal [Na+] (20–50 mmol/l)	99	109 (30 to 151)	107
Fecal pH	7	7.5 (6 to 9)	Not reported

	This case	Series of Janecke and al. (2)	Gupta et al. (4)
Fecal osmolality (320–370 mosmol/kg)	**266**	**306 (271 to 353)**	**Not reported**
Urinary [Na+] (2–28 mmol/l)	Undetectable	9 (2 to 28)	Not reported
Histology	Normal	Normal (2) Nonspecific inflammation (2) Secondary ileocolitis of CD (2) Focal lymphatic hyperplasia (1) Not done (2)	Normal
Parenteral fluids	None	7 out of 9	Yes
Current treatment	Oral	Oral (7) Oral+I.V (1) I.V. (1)	Oral
Current Na supplement (mmol/kg/d)	9	None (4) 4 (1 patient, 37 years old) 6.5 (1 patient, 6 years old) 13 (1 patient, 1 ½ years old) N.I. (2)	Not reported
Outcome	Normal, fully breast-fed, normal diversification No diarrhea since third month of life	Watery diarrhea (4) IBD (2) Growth retardation (2) Normal (1)	Infrequent diarrhea Normal growth

- some patients develop inflammatory bowel disease: two out of ten in the series of Janecke et al.

- polymorphism rs11739663 situated in or close to the location of SLC9A3 in chromosome 5 is a single nucleotide polymorphism (SNP) associated to ulcerative colitis

Jostins et al. Nature. 2012

Our patient: specificities

- less severe phenotype

- a new missense mutation, like most of the mutations previously described

- no evidence for genotype/phenotype correlation

Conclusion

- early detection during the third trimester of pregnancy

- combined use of US signs, MRI and amniotic fluid digestive enzymes

- main differential diagnosis: barrier or CCD due to mutation of the SLC26A3 gene

- prevalence of non-syndromic CSD by SLC9A3 mutation is probably underestimated

- Studies focusing on the role of the Na+/H+ antiporter 3 in intestinal homeostasis are needed to better understand the pathophysiology of this disease

- NGS in congenital diarrheal disorders

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