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Targeting the Causes of Intractable Chronic Constipation in Children: The Nuclear Transit Study (NTS)

Yee Ian Yik[1,5,6] et al.[*]
[1]*Department of Paediatrics, University of Melbourne,*
[5]*Murdoch Childrens Research Institute,*
[6]*Division of Paediatric Surgery, Department of General Surgery,*
Faculty of Medicine, University of Malaya
[1,5]*Australia*
[6]*Malaysia*

1. Introduction

Chronic constipation is a symptom and not a disease! It is a common and major health problem affecting both adults and children. It is a difficult health issue for the patients and their treating physicians, with major psycho-socio-economic impacts. As the underlying cause varies, there is no standard therapy for chronic constipation. Many investigations have been used in the past, both invasive and non-invasive to study colonic physiology and pathophysiology to identify the underlying cause(s) for chronic constipation, but none of these tests have been able to provide reliable information for satisfactory treatment of this complex problem.

The nuclear transit study (NTS) has begun to gain acceptance in both adults and children in recent years. At our institute (The Royal Children's Hospital, Melbourne, Victoria, Australia), nuclear transit studies were initially used to investigate total colonic transit time and to define the site where slowing occurs in children with intractable chronic constipation (Cook et al. 2005), leading to the description of slow-transit constipation (STC) in children in 1998 (Southwell et al. 2009). In addition to colonic transit, gastric emptying and small bowel transit can be characterised producing a complete picture of gastrointestinal tract dynamics.

This study reviews NTS collected over 12 years (1999-2010) at our tertiary children's hospital to identify sites of hold-up or delay in children with chronic constipation not responding to medical treatment.

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[*] David J. Cook[2], Duncan M. Veysey[2], Stephen J. Rutkowski[4], Coral F. Tudball[2], Brooke S. King[2], Timothy M. Cain[2], Bridget R. Southwell[5] and John M. Hutson[1,3,5]
[1]*Department of Paediatrics, University of Melbourne, Australia*
[2]*Department of Medical Imaging, Royal Children's Hospital, Melbourne, Australia*
[3]*Department of General Surgery, Royal Children's Hospital, Melbourne, Australia*
[4]*Australian Radiation Services Pty. Ltd., Australia*
[5]*Murdoch Childrens Research Institute, Australia*

2. Intractable chronic constipation

We defined intractable chronic constipation in children as chronic constipation with duration of symptoms > 2 years, not responding to maximal laxative therapy, behavioural therapy or a toilet training program. Most children had consulted multiple paediatricians and gastroenterologists and suffered persisting symptoms by the time they entered our program. Some of the children had been subjected to surgical interventions as a last attempt to improve their symptoms and quality of life. The majority of children with chronic constipation with a palpable faecoloma are diagnosed as having anorectal retention (AR) and are treated conservatively (laxatives, diet therapy and/or toilet training program). The most severe form of chronic constipation is slow-transit constipation (STC) and this does not respond to most therapies. We have employed a non-invasive form of therapy using transcutaneous electrical stimulation (TES), and we have successful outcomes in STC (Chase et al. 2005; Clarke et al. 2009; Clarke et al. 2009; Ismail et al. 2009). Also, we have identified a subgroup of children with rapid proximal colonic transit and AR, and found that dietary exclusion could be an important treatment strategy for this form of intractable chronic constipation (Yik et al. in press).

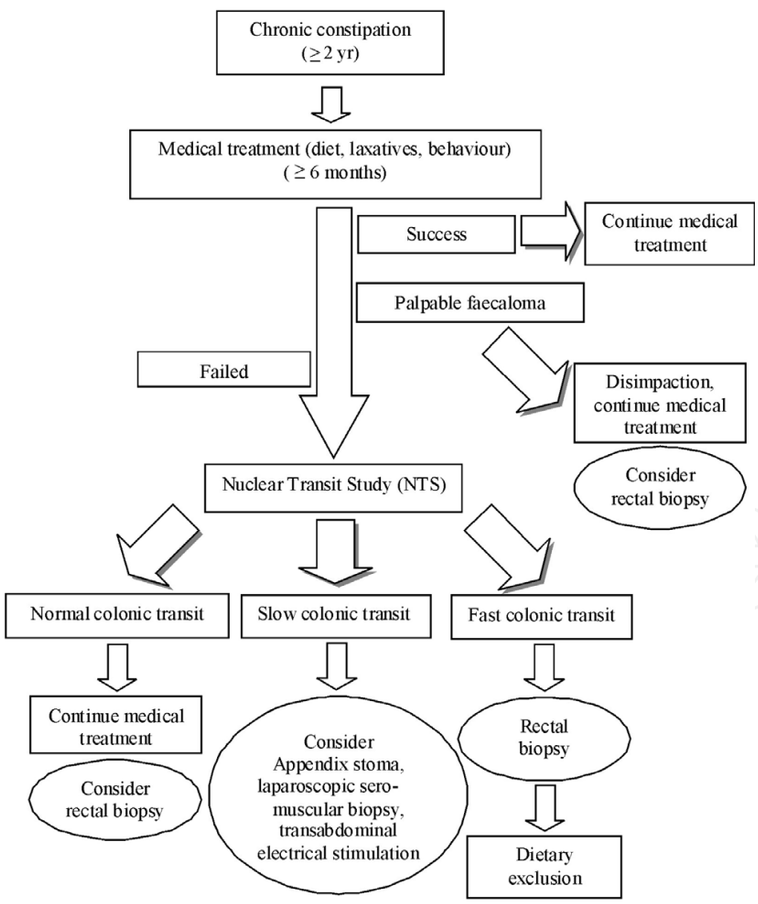

Fig. 1. Our current algorithm for the management of children with treatment-resistant constipation

The algorithm adopted in the management of children with intractable chronic constipation at our hospital is shown in Figure 1.

3. Gastrointestinal transit study

The NTS has evolved from plastic (sitz) marker studies (radio-opaque markers and X-rays), which provide a "snapshot" from which colonic transit time can be inferred. The NTS provides additional information on gastric emptying and small bowel transit, in addition to colonic transit, which permits further characterization of transit through the whole of the gastrointestinal tract. This feature, in addition to its reproducibility (Clarke et al. 2009) and the physiological characteristics of a real (labelled) meal, has led to its increasing clinical acceptance as a means for monitoring colonic dysmotility and its response to treatment. It is especially useful in monitoring the more severe form of proximal colonic dysmotility in children leading to intractable chronic constipation, i.e. slow-transit constipation (STC).

3.1 Test procedure and technique (Royal Children's Hospital, Melbourne, Victoria, Australia)

All patients are instructed to fast for a period of 4 hours prior to the study (3 hours for infants). They are to cease all medications affecting gastric motility and colonic motility (e.g. laxatives) for 5 days prior to, and for the duration of the study. After the gastric emptying phase (2 hours), patients resume their normal diet.

The test involves administration (orally, NG Tube or PEG) of a radiopharmaceutical (gallium-67 citrate) in 10-400mls labelled full cream milk (or standard formula), with the radiopharmaceutical dose calculated according to the patient's weight (dose range of 3 - 10MBq). The dose is a calculated fraction of an adult dose (10MBq), with a minimum of 3MBq (refer Table 1).

Weight (kg)	Fraction of Adult dose
10	0.30
15	0.30
20	0.50
30	0.58
40	0.70
50	0.81
60	0.89
70	0.97
80	1.00

Table 1. Example weight and dose calculation for 67-Ga Citrate for children undergoing gastrointestinal transit study (minimum dose 3 MBq)

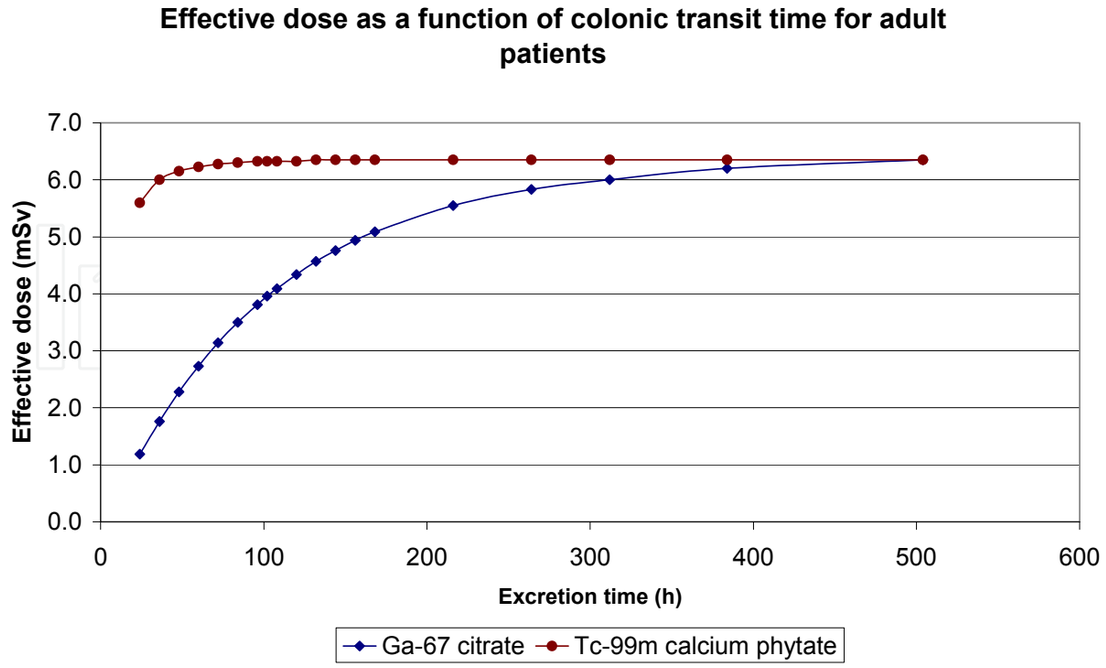

Fig. 2. Effective dose (mSv) as a function of colonic transit time (hours) for an adult-sized patient based on full excretion. The relationship between effective dose and transit is similar for children, although the magnitude differs (refer Table 2)

Gallium-67 citrate effective dose (mSv)								
Age	Weight (kg)	Administration activity (MBq)	Transit time (full excretion) (hr)					
			24	36	48	72	96	120
3	14	3	1.5	2.2	2.8	3.9	4.7	5.4
5	19	5	1.9	2.8	3.6	5.0	6.0	6.9
10	32	6	1.4	2.1	2.7	3.8	4.6	5.2
15	55	8	1.3	1.9	2.5	3.4	4.2	4.7
Adult	>71	10	1.2	1.8	2.3	3.1	3.8	4.3
Technetium-99m calcium phytate colloid effective dose (mSv)								
Age	Weight (kg)	Administration activity (MBq)	Transit time (full excretion) (hr)					
			24	36	48	72	96	120
3	14	111	10.3	11.0	11.3	11.5	11.6	11.6
5	19	111	7.9	8.4	8.6	8.8	8.9	8.9
10	32	150	6.7	7.2	7.4	7.5	7.6	7.6
15	55	211	6.1	6.5	6.7	6.8	6.9	6.9
Adult	>71	250	5.6	6.0	6.2	6.3	6.3	6.3

Table 2. Effective dose (mSv) for children undergoing NTS [effective dose is dependent on dose administered and total bowel transit time (hrs)]

Technetium-99m calcium phytate colloid was used prior to 2000 and gallium-67 citrate used post-2000 due to the preferential radiation dosimetry. The effective radiation dose to the patient has been calculated for both technetium-99m calcium phytate colloid and gallium-67 citrate as a function of patient's weight and transit time (Figure 2 and Table 2). The effective dose was calculated using MIRD methodology with standard phantom sizes (except for the 3 year-old phantom which was interpolated from the 1 and 5 year-old phantoms) with varying transit time through the gastrointestinal tract. Gallium-67 citrate delivers a lower radiation dose than technetium-99m calcium phytate, particularly for short transit times, with less than half the dose if transit takes < 100 hours (Figure 2). Due to the longer half-life of gallium-67 citrate, the effective dose continues to increase for patients with long transit times. For transit times greater than 500 hrs (approximately 21 days), the effective dose is similar for technetium-99m calcium phytate and gallium-67 citrate.

Serial static anterior and posterior images are obtained at $T_{0,}$ $T_{0+30\ mins}$, $T_{0+60mins}$, $T_{0+120\ mins}$ for the gastric emptying study, and further static images at $T_{0+6\ hours}$, $T_{0+24\ hours}$, $T_{0+30\ hours}$ and $T_{0+48hours}$ for the small bowel and colonic transit study. All images are acquired using opposed dual head detectors (anterior/posterior), with medium energy, general purpose (MEGP) collimation (using a Philips "SKYLight" or Philips "BrightView" dual-head scintillation camera). All imaging acquisition parameters, including distance of the detectors from the patient, and from each other, are recorded and are strictly maintained throughout the study. Bowel motion(s) are recorded during the period of the study to correlate with excreted activity.

Following the completion of imaging, the laxative or other regime in place prior to the investigation is reinstituted. If, following the 48 hour images, there is significant colonic retention of activity, bowel disimpaction[1] can be undertaken in the interests of radiation dose minimisation.

3.2 Gastric emptying time

Gastric half–emptying time is calculated using background and decay-corrected regions of interest (ROI) drawn around the stomach in $T_{0,}$ $T_{0+30\ mins}$, $T_{0+60mins}$, $T_{0+120\ mins}$ images. T_0 and $T_{0+120\ mins}$ are used to determine the two hour stomach retention.

3.3 Geometric centre (GC) measurement

The geometric centre (GC) at each imaging time is determined for six ROI, assigned as: 1=pre-colonic; 2=caecum/ascending colon, 3=transverse colon; 4=descending colon; 5=recto-sigmoid colon and 6=excreted.

ROI are drawn on each image as illustrated in Figure 3 (below), and counts are corrected for decay and background. Geometric mean counts are calculated from the corrected data and activity in each region is expressed as a fraction of total activity [see example below of calculation steps (Figure 4)]:

[1] Suggested protocol for bowel dismpaction at the end of NTS using Movicol® (macrogol with electrolytes): 1. 1-5 yrs: 2 sachets on day 1, then 4 sachets for 2 days, then 6 sachets for 2 days and 8 sachets daily thereafter; 2. 5-12 yrs: 4 sachets on day 1, then increase by 2 sachets daily until max of 12 sachets daily; 3. >12 yrs: 8 sachets per day for 3 days; if Movicol® is not tolerated, use Lactulose® and Senna® for disimpaction

Geometric Centre (GC) of activity = ∑ (fraction of activity x region number)
(Notghi et al. 1994)

Example for ROI are as follows:

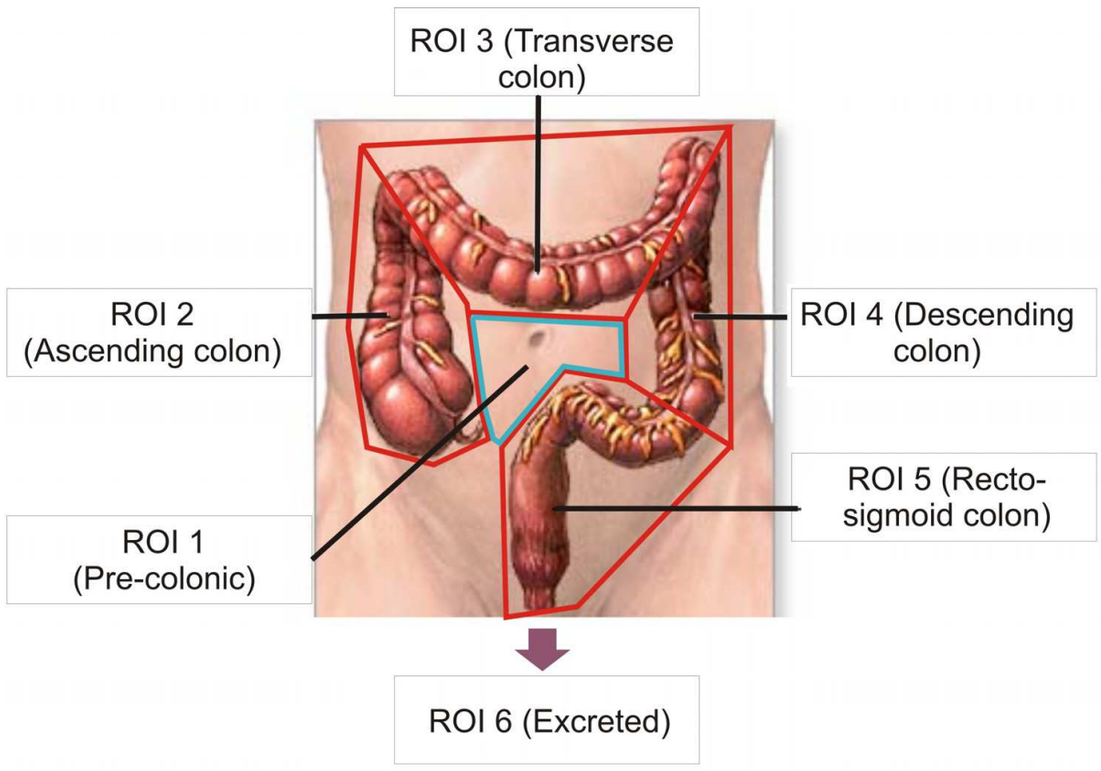

Fig. 3. Regions of interest (ROI) used for GC calculation; 1 = pre-colonic (total image activity less colonic activity after background activity correction), 2 = ascending colon, 3 = transverse colon, 4 = descending colon, 5 = recto-sigmoid colon, 6 = excreted.

A

RAW DATA

					EXPECTED COUNTS(FROM T0):			PIXELS			
ANTERIOR COUNTS					ANTERIOR		138350	128			
					POSTERIOR		75592	128			
HRS + T0	ASC CTS	PIXELS	TRANS CTS	PIXELS	DESC CTS	PIXELS	REC/SIG CTS	PIXELS	BGD CTS	PIXELS	TOTAL CTS
6.00	94457.0	665.0	0.0	0.0	0.0	0.0	0.0	0.0	54.0	25.0	131189.0
24.00	16393.0	600.0	21144.0	679.0	31912.0	859.0	19914.0	613.0	78.0	25.0	101617.0
30.00	17618.0	530.0	14506.0	614.0	6199.0	540.0	40732.0	587.0	45.0	25.0	95856.0
48.00	0.0	0.0	3502.0	839.0	5335.0	680.0	19942.0	944.0	28.0	25.0	40463.0

POSTERIOR COUNTS

HRS + T0	ASC CTS	PIXELS	TRANS CTS	PIXELS	DESC CTS	PIXELS	REC/SIG CTS	PIXELS	BGD CTS	PIXELS	TOTAL CTS
6.00	37870.0	665.0	0.0	0.0	0.0	0.0	0.0	0.0	62.0	25.0	71680.0
24.00	11774.0	600.0	12260.0	679.0	22168.0	859.0	12478.0	613.0	67.0	25.0	74110.0
30.00	11855.0	530.0	7632.0	614.0	4571.0	540.0	25480.0	587.0	41.0	25.0	67455.0
48.00	0.0	0.0	2764.0	839.0	4246.0	680.0	12532.0	944.0	41.0	25.0	31749.0

ANTERIOR PIXEL CORRECTION

HRS + T0	ASC	TRANS	DESC	REC/SIG	BGD	TOT CTS
6.00	142.0	0	0	0	2.2	8.0
24.00	27.3	31.1	37.2	32.5	3.1	6.2
30.00	33.2	23.6	11.5	69.4	1.8	5.9
48.00	0	4.2	7.8	21.1	1.1	2.5

POSTERIOR PIXEL CORRECTION

HRS + T0	ASC	TRANS	DESC	REC/SIG	BGD	TOT CTS
6.00	56.9	0	0	0	2.5	4.4
24.00	19.6	18.1	25.8	20.4	2.7	4.5
30.00	22.4	12.4	8.5	43.4	1.6	4.1
48.00	0	3.3	6.2	13.3	1.6	1.9

ANTERIOR BGD CORRECTION

HRS + T0	ASC	TRANS	DESC	REC/SIG	TOT CTS	EXP CTS
6.00	93020.6	0.0	0.0	0.0	131189.0	138349.5
24.00	14521.0	19025.5	29231.9	18001.4	101617.0	
30.00	16664.0	13400.8	5227.0	39675.4	95856.0	
48.00	0.0	2562.3	4573.4	18884.7	40463.0	

POSTERIOR BGD CORRECTION

HRS + T0	ASC	TRANS	DESC	REC/SIG	TOT CTS	EXP CTS
6.00	36220.8	0.0	0.0	0.0	71680.0	75592.4
24.00	10166.0	10440.3	19865.9	10835.2	74110.0	
30.00	10985.8	6625.0	3685.4	24517.3	67455.0	
48.00	0.0	1388.0	3130.8	10983.8	31749.0	

B

GEOMETRIC MEAN CALCULATION

HRS + T0	ASC	TRANS	DESC	REC/SIG	TOT CTS	EXP CTS
6.00	58045.5	0.0	0.0	0.0	96972.3	102719.1
24.00	12149.9	14093.7	24098.1	13966.0	86780.4	
30.00	13530.2	9422.4	4389.0	31188.7	80411.2	
48.00	0.0	1885.9	3784.0	14402.3	35842.2	

C

DECAY CORRECTION

HRS + T0	ASC	TRANS	DESC	REC/SIG	TOT CTS	EXC CTS	EXP CTS
6.00	61213.7	0.0	0.0	0.0	102265.2	41505.4	102719.1
24.00	15027.8	17431.9	29806.0	17274.0	107335.3	0.0	
30.00	17648.5	12290.3	5724.9	40681.6	104886.1	0.0	
48.00	0.0	2885.1	5788.8	22033.0	54832.2	47886.9	

D

HRS	SMALL BOWEL	ASC	TRANS	DESC	REC/SIG	EXCRETED	CHECK
6.00	40%	60%	0%	0%	0%	0%	100%
24.00	0%	19%	22%	37%	22%	0%	100%
30.00	0%	23%	16%	7%	53%	0%	100%
48.00	0%	0%	4%	7%	28%	61%	100%

E

HRS + T0	GEOMETRIC CENTRE CALCULATION
6.00	1.60
24.00	3.62
30.00	3.91
48.00	5.46

INDEX = 14.59

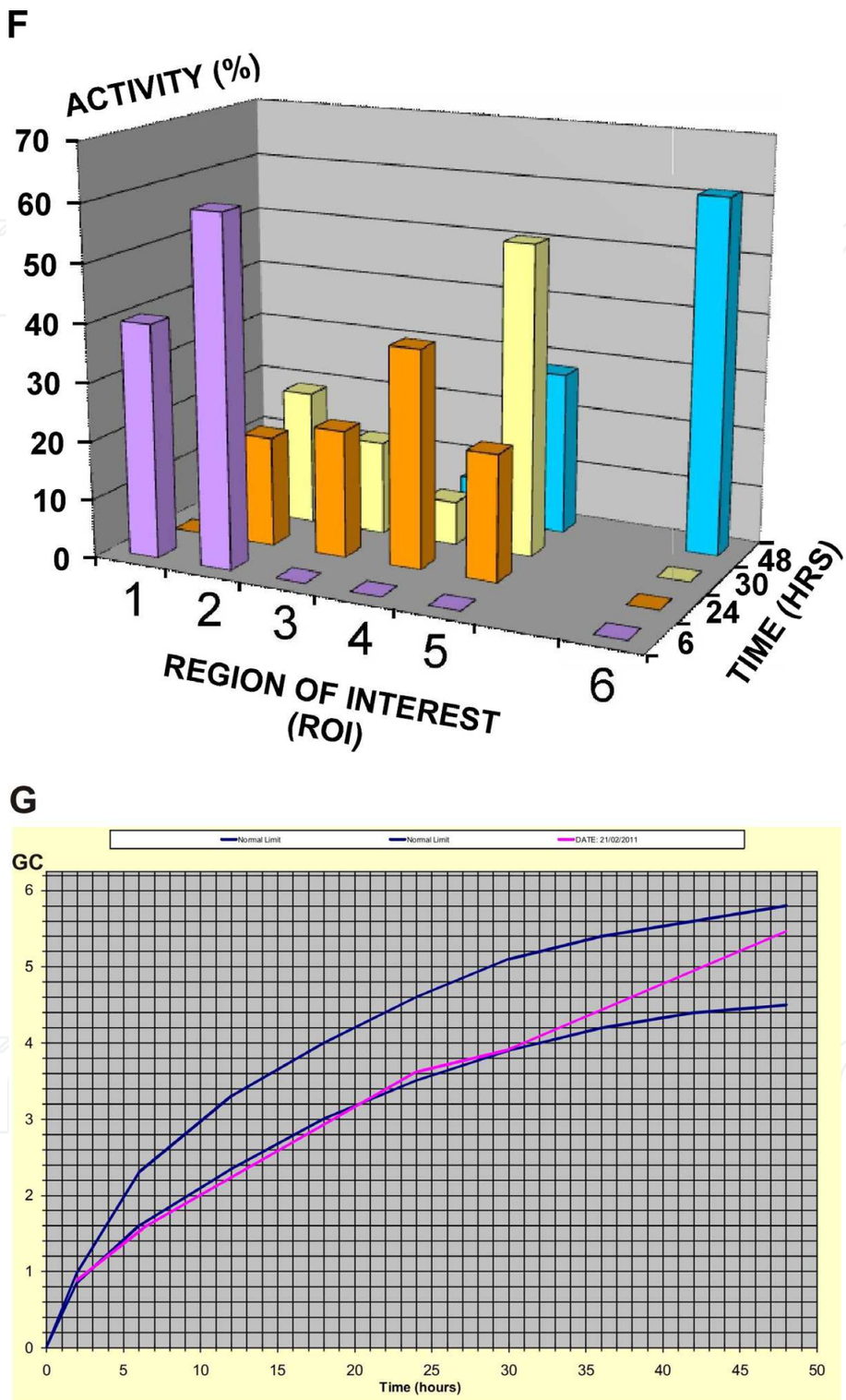

Fig. 4. Example of GC calculation steps - based on ROI at each time interval.

A - Background correction is applied, based on counts/pixel for each ROI
B - Geometric mean calculated from background corrected counts for both anterior and posterior
C - Geometric mean counts corrected for time (decay corrected)
D - Counts expressed as a % of total counts for each time point
E - Geometric centre (GC) calculation for each time point [e.g. GC calculation at 24 hour = (0.00x1)+(0.19x2)+(0.22x3)+(0.37x4)+(0.22x5)+(0.00x6) = 0.38+0.66+1.48+1.10 = 3.62] and the GC Index is the sum of all GC's
F - Histograms displaying the percentage of the ingested meal present in the pre-colonic, each colonic segment and excreted at each time of imaging
G - Patient's GC data plotted vs time (with normal range referenced)

4. Groups identified

Since 1998, 770 NTS have been undertaken in 626 children, investigating the underlying colonic dysmotility contributing to their chronic constipation. Four (4) main groups were identified based on rates of segmental colonic transit:

1. Normal colonic transit (>40% excretion at 48 hour) with no evidence of colonic dysmotility (Figure 5A) (Southwell et al. 2009; Sutcliffe et al. 2009)
2. Anorectal retention (AR, Figure 5B) (Southwell et al. 2009; Sutcliffe et al. 2009)
3. Rapid proximal colonic transit (rapid transit through proximal colon at 6 and 24 hr, Figure 5C) (Yik et al. in press)
4. Slow proximal colonic transit (Sutcliffe et al. 2009)
    a. Slow proximal colonic transit (slow-transit constipation, STC, Figure 5D)
    b. Focal hold-up (Figure 5E)
    c. STC with AR (Figure 5F, common in adults, may need additional imaging at 72 hr for confirmation in paediatrics)

Gastric emptying can be normal or delayed (NGE or DGE). Normal gastric emptying time is defined as $T_{50\%} \leq 50$ mins and % retention at 2 hr < 15% (Yik et al. 2011).
Likewise, small bowel transit can be normal (NSBT) or slow (SSBT). Normally the small bowel is empty by 4 hours and slow small bowel transit is defined as > 25% of radiopharmaceutical remaining within the small bowel at 6 hr (Yik et al. 2011).
The subgroup of children with rapid proximal colonic transit are identifiable at 6 hour and 24 hr with > 25% of the ingested meal having passed beyond hepatic flexure and distal descending colon respectively (Figure 5C) (Yik et al. in press).

5. Clinical importance

Treatment strategies differ for different causes of colonic dysmotility. Anorectal retention usually responds to a toilet training program, behavioural therapy and laxative therapy. For children with rapid proximal colonic transit and associated anorectal retention, dietary exclusion is worth considering with a reasonable probability of success (Yik et al. in press). However, this may take time (usually months and not weeks) before improvement becomes apparent because the rectum is chronically distended. The time may be needed to recover receptor function to sense filling with faecal matter. The most difficult to manage is the group with slow-transit constipation (STC). STC does not respond to multiple laxative therapies, and a high-fibre diet is not an appropriate option as it may aggravate symptoms

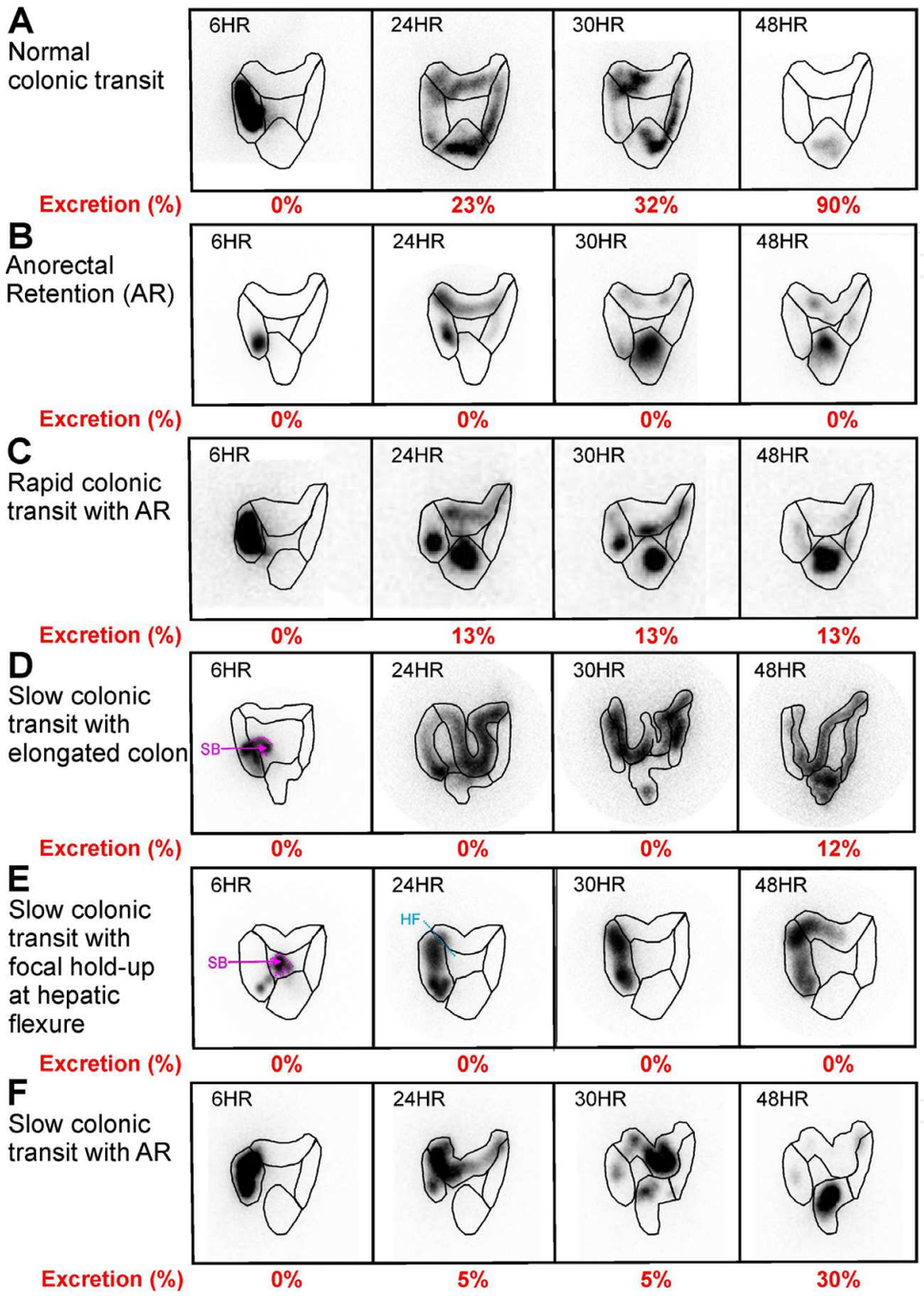

Fig. 5. Colonic transit patterns in children:
A – Normal colonic transit with normal excretion;
B – Anorectal retention (AR) with retention of activity in the rectum at 48 hr;
C – Rapid proximal colonic transit with anorectal retention at 48 hr;
D – Slow colonic transit [with an unusually elongated colon (Southwell 2010)];
E – Slow colonic transit with focal hold-up at hepatic flexure, and
F – Slow colonic transit with AR (may be difficult to identify as this may required imaging at 72 hr to diagnose in adults). [HF = Hepatic flexure; SB = small bowel]

(Voderholzer et al. 1997; Knowles & Martin 2000; Wald 2002; Hutson et al. 2009). Invasive surgical interventions may have complications with associated morbidities and mortality. High rates of symptom recurrence have been reported in this group (Kamm et al. 1988; Yoshioka & Keighley 1989; de Graaf et al. 1996; Lubowski et al. 1996; Mollen et al. 2001; Sample et al. 2005). A less invasive surgical option - antegrade continence enema (ACE) - was introduced in 1990 (Malone et al. 1990). This has helped many children with faecal incontinence and/or impaction. We have employed appendix stoma/ACE in STC children since 1997 (Stanton et al. 2002; King et al. 2005). Since 2006, we have used transcutaneous electrical stimulation (TES) therapy to treat this special group of children and have shown promising results (Chase et al. 2005; Clarke et al. 2009; Clarke et al. 2009; Ismail et al. 2009). TES has not only improved colonic transit in these children (Clarke et al. 2009) but also alleviated their soiling, feelings of chronic fullness and abdominal discomfort which has improved their quality of life (Clarke et al. 2009; Ismail et al. 2009). The use of TES therapy has significantly reduced the need for appendix stoma formation in STC children in our institute (unpublished).

The success of therapy largely depends on accurate identification of the underlying colonic dsymotility, which is aided by the use of NTS at our institute. The NTS helps triage patients into aetiological groups where appropriate treatment strategies can be instituted. The positive psycho-social impact on families previously labelled "dysfunctional", when an explanation for their child's problem is suggested, cannot be overestimated.

Significantly, identifying the hold-up site may guide the site for biopsies to look for underlying pathology (King et al. 2005), as opposed to the standard practice of investigating children with chronic constipation by performing rectal mucosal biopsy to exclude Hirschsprung disease. Colonic seromuscular biopsies (collected laparoscopically) may be more useful for children with dysmotility proximal to the anorectum. However, rectal mucosal biopsy can be useful for the diagnosis of food intolerance/allergy if eosinophilia and mast cells are demonstrated (Carroccio et al. 2000; Daher et al. 2001; Carroccio & Iacono 2006; Scaillon & Cadranel 2006).

Some centres advocate the identification of "the site of slowing in the colon" to decide on the part/segment of the colon to be resected in patients with intractable symptoms, desperate for a cure (Youssef et al. 2004). This has important implications because patients with pancolonic slow transit will not benefit from a segmental resection as the risk of relapse of symptoms is much higher. In this situation, NTS may have a crucial role in surgical planning (CB et al. 2001).

6. Limitations

We are currently performing NTS using a 48-hour protocol which does not encompass the total colonic transit time in some children with a severe form of STC. However, we feel that by 48 hours, we are able to characterise most colonic dysmotility permitting us to treat associated symptoms with appropriate strategies. However, using the 48-hour protocol, we will miss AR if it occurs in these patients.

Another limitation is the need for the child (and parent) to attend the hospital Nuclear Medicine Department over 2 ½ days while the serial images are acquired. It is perhaps a

telling indication of the social disruption that results from chronic constipation, that in our series, we have not encountered a single family unwilling to attend for this investigation, despite the time involved and the inconvenience.

7. Future directions

A standardised/nationwide protocol for NTS in children and standardised diagnostic criteria would allow more appropriate treatment strategies to help all children with this debilitating condition.

8. Conclusion

NTS is a useful diagnostic tool for the investigation of colonic dysmotility in children with intractable chronic constipation, and provides objective, reproducible and quantifiable data, to monitor the progression of the condition, and allow clinicians to decide on the "best treatment" strategy and response to therapy.

9. Acknowledgment

We would like to extend our sincere thanks to Mrs. Mita Pedersen and Ms. Pam Grant for all their assistance in tracing the patients' data. Most importantly, we would like to thank all the children with intractable chronic constipation and their parents for encouraging us to work harder to seek the answers for their long-standing, previously untreatable condition and to become well again.

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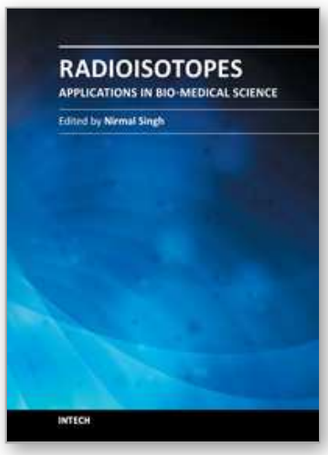

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The book Radioisotopes - Applications in Bio-Medical Science contains two sections: Radioisotopes and Radiations in Bioscience and Radioisotopes and Radiology in Medical Science. Section I includes chapters on medical radioisotope production, radio-labeled nano-particles, radioisotopes and nano-medicine, use of radiations in insects, drug research, medical radioisotopes and use of radioisotopes in interdisciplinary fields etc. In Section II, chapters related to production of metal PET (positron emission tomography) radioisotopes, 3-dimensional and CT (computed tomography) scan, SS nuclear medicine in imaging, cancer diagnose and treatments have been included. The subject matter will by highly useful to the medical and paramedical staff in hospitals, as well as researchers and scholars in the field of nuclear medicine medical physics and nuclear bio-chemistry etc.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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