Pediatr Nephrol (2004) 19:6–12
DOI 10.1007/s00467-003-1291-1

REVIEW

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Can a congenital dysfunctional bladder be diagnosed from a smile? The Ochoa syndrome updated

Received: 20 January 2003 / Revised: 24 July 2003 / Accepted: 28 July 2003 / Published online: 25 November 2003

Abstract During the last 40 years over 100 patients have been reported with a dysfunctional lower urinary tract associated with a peculiar distortion of the facial expression. This most unusual disorder was initially considered a local observation. Time, however, has proven otherwise, since patients with this syndrome have now been reported from various countries throughout the world. This association of lower urinary tract and bowel dysfunction with an abnormal facial expression was named the urofacial (Ochoa) syndrome. Genetic studies have demonstrated that this condition is inherited as an autosomal recessive trait, and a potential gene has been mapped to chromosome 10q23-q24. There is also enough evidence to suggest that patients with this syndrome as well as those with subclinical neurological bladder, occult neuropathic bladder, non-neurogenic neurogenic bladder or Hinman syndrome, dysfunctional voiding, or dysfunctional elimination may be affected by the same congenital disorder of neurological origin.

Keywords Bladder dysfunction · Voiding dysfunction · Elimination dysfunction · Facial expression · Constipation · Congenital diseases · Non-neurogenic neurogenic bladder

Introduction

During the early 1960s we followed a group of children with the characteristic symptomatology of a neurogenic bladder (urinary infection, incontinence, constipation), with no apparent neurological or obstructive pathology. Within this group of patients were two children with a history of repeated episodes of urinary tract infection (UTI), dysuria, frequency, enuresis, constipation, bladder trabeculation, and reflux. In addition, they showed a peculiar distortion of the face, grimacing as if in pain or sadness when they tried to smile or laugh (Fig. 1). At that time there were no descriptions of this association in the medical literature. Shortly thereafter, two new patients were seen at our children's hospital with these same manifestations. In addition, this peculiar facial expression reminded us of that of a patient nephrectomized 10 years previously. These cases prompted us to search for more patients, with the goal of confirming this rare association and conducting a thorough urological and neurological evaluation. The first genetic evaluation of seven patients from three families was performed by Dr. Rafael Elejalde [1] who coined the term "Ochoa syndrome" and suggested a recessive inheritance, a finding that was later confirmed by Ochoa and Gorlin [2]. A collaborative study with the University of Florida was established in 1993, and a candidate gene has been mapped to 10q23-q24. Several reports have recently been published throughout the world on the genetics and clinical aspects of this disorder.

The original studies and observations made in patients with the urofacial characteristics of the urofacial (Ochoa) syndrome (UFOS) have provided new information that may shed new light on the etiology of the dysfunction observed in the lower urinary and gastrointestinal tracts of so many children. Feng and Churchill [3] suggested that "dysfunctions in these two systems represent a broad spectrum of functional disturbances... best described as elimination dysfunction (ED). Urinary and gastrointestinal tracts share the same embryologic origin (endoderm), the same anatomic space (pelvis), and the same innervation (sacral pelvis plexus)...Conditions that affect one significantly affect the other." In this review, dysfunctional elimination (DE) and dysfunctional voiding (DV) are used as synonyms.

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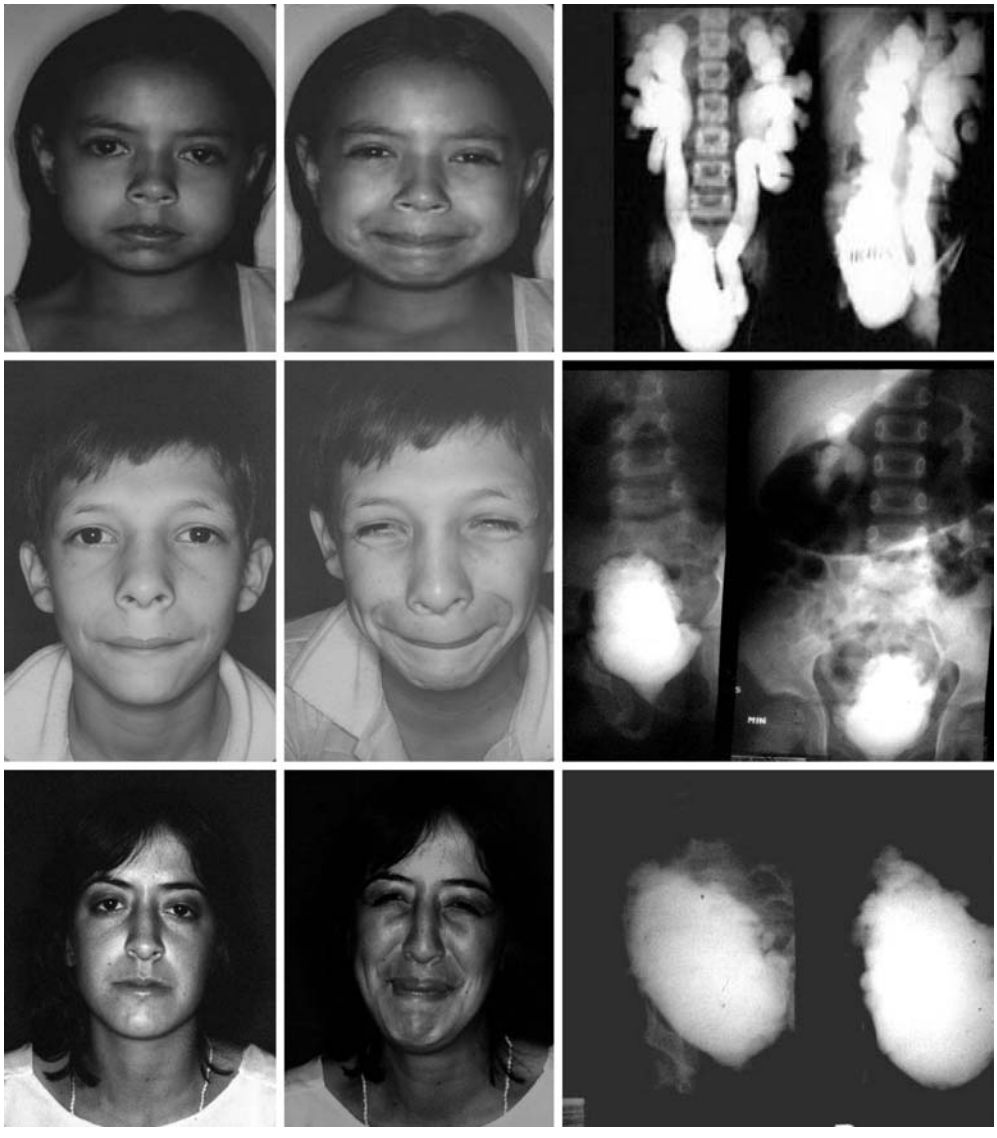

Fig. 1 Three children with the peculiar facial expression associated with a dysfunctional lower urinary tract characteristic of the urofacial (Ochoa) syndrome (UFOS)

Characteristics of the UFOS

During the early years of our work, most patients with the UFOS were found among those consulting for urinary infection and enuresis. Almost two-thirds also had constipation and 33% had encopresis. However, as our colleagues became familiar with the facial component of this syndrome, additional younger patients with the urinary dysfunction were identified. In addition, several "unknown" patients were discovered during the investigation of family pedigrees. The pedigree presented in Fig. 2 is characteristic. The proband was a 4-year-old male with a history of recurrent UTI, enuresis, and constipation. Imaging revealed a badly damaged bladder with reflux and scarred kidneys. The face showed the characteristic inversion of the facial expression. During the investigation of the family pedigree we became aware that more family members were affected and some had

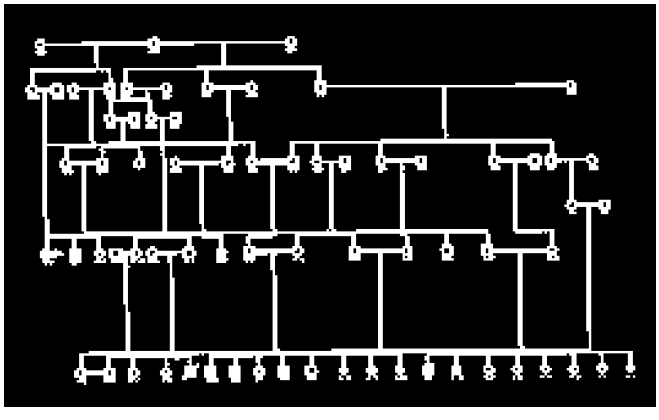

Fig. 2 Characteristic pedigree of a family with UFOS

even died with kidney failure. We then decided to visit three different towns to study other members of the related families, and found 10 additional affected individuals, including 2 adults, 1 on dialysis and the other with a transplant, and 2 children who had died of kidney failure at an early age. Another interesting case was discovered during the collaborative study with the University of Florida. During a visit to the home of 1 of our pediatric patients in the town of Amaga (Colombia) we were told of 4 other siblings with the same facial distortion who had died over the preceding years. This was a family with 8 children, five with the syndrome. Most families in our series have had at least 2 affected members. The age of our group of patients ranges from 50 days to 38 years; 13 patients were less than 2 years old at the time of diagnosis. A review of the clinical charts in our first 50 patients [4] revealed that boys and girls are equally affected. Of 5 patients, 3 are constipated and 1 showed some degree of soiling. Thirty-two patients had reflux, which was bilateral in 18. Some degree of kidney scarring was seen in 39 of 50 patients, with 8 being hypertensive and 12 in chronic renal failure, 9 of whom progressed to end-stage renal disease, 3 were transplanted (1 child and 2 adults).

Morbidity

DV or DE with or without the facial component is an aggressive disease. Patients diagnosed at school age or later generally exhibit a greater degree of kidney damage. Younger patients, however, can also have serious renal deterioration. Yang and Mayo [5] followed 27 patients with DV for 49 months at the end of which 40% had severe morbidity, 30% were cured without surgery, and 30% had unresolved symptoms. Hinman [6] reported patients who "ranged from those boys having symptoms of incontinence with minimal radiographic changes to those with severe upper tract damage." All nine cases reported by Varlam and Dippell [7] had severe scarring of at least one kidney, five were in chronic renal failure, and one in end-stage renal disease. Koff et al. [8] found 66 children with DE among 143 thought to have primary vesicoureteral reflux (VUR). Of the 70 patients that had a breakthrough infection while under control, 77% also had DE. Jayanthi et al. [9] reported seven newborns and infants with DE. Three of seven had a prenatal diagnosis of hydronephrosis, two were admitted with urosepsis, and two had failure to thrive. Bauer et al. [10] reported two newborns with urinary retention, one of whom had urinary ascites from a ruptured bladder, and two infants with severe UTI. The four had a pathophysiology characteristic of DV. Therefore, DV is a very aggressive condition, demanding a prompt diagnosis and treatment. It is not uncommon that children with primary VUR have unrecognized DE that adversely affects the results of reimplantation, and represents a risk for recurrent UTI after reflux resolves.

Geographical distribution

Patients with UFOS were initially considered a local or regional phenomenon, related perhaps to the high inbreeding seen in some of the families in the rural areas of this Colombian region. However, Teebi et al. [11, 12] reported two children from the Middle East in 1989 and 1991. Furthermore, during the last l5 years patients with the UFOS have been reported in different cities in Colombia (O. Salazar personal communication, R.E. Astudillo personal communication), the United States [13], Spain [14, 15], France [16], South Arabia [12, 17], and Japan (Masuno).

The three components of the syndrome

Understanding the three complementary but different components of the UFOS is essential for the correct diagnosis and management of these children. The three components are the genetic background, the dysfunction of the facial expression, and the dysfunctional emptying of urine and feces.

The genetic component

The initial genetic studies were performed by R. Elejalde [1] on seven patients from three unrelated families (REFS). In 1987 more families and patients were studied and pedigrees of four generations were established. Parents were normal and consanguinity existed in 22% of the families. Using the proband method, the corrected ratio clearly reflected an autosomal recessive inheritance [2].A joint research effort between the University of Florida and the University of Antioquia was started in 1993 with the aim of localizing and cloning the gene(s) responsible for this syndrome. A genome screen using a combination of homozygosity mapping and DNA pooling strategies was performed. All patients analyzed were found to be homozygous for two closely linked markers compared with only 12% of the unaffected relatives. These results provided an initial potential location of the responsible gene at 10q23-q24 [19]. To facilitate the cloning and identification of the UFOS gene, haplotype analysis has also been performed and has resulted in the location of the gene within two overlapping BAC clones in a region of <360 kilobases [20]. Chauvé et al. [16] also reported the haplotype analysis of a French family with the symptomatic complex of the Ochoa syndrome. This study showed the same localization of the critical region, favoring the hypothesis of genetic homogeneity.

Two additional patients from the United States with the clinical and radiological characteristics of the syndrome were also found to have the same clinical and genetic background. Both descended from Irish ancestors, indicating the multiracial character of the syndrome [13]. Two other patients of Irish descent were also reported by García-Minaur et al. [15] in Spain.

The dysfunctional facial expression

"The face is not only an index of the mind but also an index of intrauterine stress and strain, congenital malformations, and illness." (Jash Paul) [22]. In 1946 Edith Potter [23] described the association between congenital flat ears and kidney agenesis. Many papers have been written since associating facial congenital deformities, especially ear deformities, and structural damage of the urinary system. Wang et al. [24] found that 29% of their patients with ear deformities also had renal structural defects. There are many other congenital anomalies involving the face and the urinary system, including the branchio-oto-renal syndrome [25], CHARGE syndrome [26], Townes Brock syndrome [27], and the oculo-auricular vertebral spectrum [28], among others.

However, the inversion of the facial expression that characterizes the UFOS is not a structural facial defect, but one of dysfunctional expression. Facial expression and facial identity denote different situations. The facial identity is given by the facial features that characterize the subject at rest, and include the color of eyes, form of forehead, nose, chin, and mouth, implantation and form of the ears, and the visual image of the facial features at rest. In contrast, facial expression refers to the changes imposed by the expression of the emotions and feelings while trying to communicate with others and interact with our environment. The facial identity in patients with the UFOS is similar to normal individuals, but not the facial expression. When UFOS patients laugh, they grimace as if expressing sadness, discomfort, or pain instead of the characteristic expression of joy and happiness seen in normal individuals. However, the facial expression of these patients at rest is similar to any normal individual. When they are sad or suffer pain or when they cry the facial expression is normal. They look like normal persons crying or suffering pain. Therefore, the facial alterations in UFOS patients constitute a real dysfunctional facial expression. Concurrent with these observations, neurological and electromyographic studies performed in some of our patients fail to demonstrate any neuromuscular alterations.

Is there a possible pathophysiological explanation for this dysfunctional facial characteristic at a higher neurological level? Parvizi at al. [29] published a report on "pathological laughing and crying (PLC), a condition defined by relatively uncontrollable episodes of laughter, crying, or both. They suggested that the so-called laughing and crying center must be located above the facial and respiratory nuclei, somewhere in the upper pons or midbrain. PLC can also occur in some patients with central nervous system (CNS) malignancies and cerebro-vascular lesions involving the cerebral peduncles and the pontine basis, strongly suggesting a CNS control of the facial expression at brain stem level. The center for micturition, the nuclei of the facial nerves, and the reticular formation, share the same topographic brainstem location. It is therefore reasonable to assume that changes at this site in the CNS may result in DV and dysfunctional facial expression.

The DE component

Bladder dysfunction syndrome, voiding dysfunction syndrome, elimination dysfunction syndrome, non-neurogenic neurogenic bladder, and urofacial syndrome all have the characteristic spectrum of symptoms and signs of the neurogenic or obstructive bladder, without apparent neurological or obstructive disease. Children with repeated bouts of UTI, frequency, dysuria, day and night wetting, and VUR, without an apparent neurological or obstructive cause have caused great concern to many specialists in the field of pediatrics, and pediatric urology, and have been the subject of extensive research for close to a century. In 1915, Edwin Beer [30] described "a number of children with difficulty in urination, pain, straining, retention of urine and a mass palpable in the hypogastrium that became tender when infection was present. Neurological examination of these patients failed to show any abnormality." Reasoning by analogy, he said, "one feels compelled to view these cases, as due to neurologic disturbances, providing no local physical obstruction is present" and "the condition is frequently one of spasm (or perhaps better disharmony between the detrusor and sphincter muscles or relative hypertonicity of the sphincter." In 1942, Laidley from Australia, reported the cure of patients with chronic pyelitis by "dilating with the cystoscope and ureteric catheters those sphincter muscles which were not acting in a coordinated manner" and added, "in the absence of stricture, bladder neck obstruction or urethral deformity, obstruction still can be present." "That invisible obstruction is apparently due to failure of coordination of the neuromuscular mechanism of one sphincter or another, which we chose to call achalasia" [31]. These insightful explanations were unfortunately disregarded at that time in favor of other competing hypotheses.

Two years before Laidley's observation, Marion, working in Paris, suggested that the bladder neck was responsible for the dysuria, frequency, and enuresis seen in children. In his "Traité d'Urologie" Marion, cited by Bodian [32] wrote: "the designation of bladder neck obstruction should be applied to the dysuric disturbances similar to those due to hypertrophy of the prostate but caused by alterations of the bladder neck without any gross lesion, and not attributable to nervous disorders" [33]. Marion's disease was also called "congenital idiopathic bladder neck obstruction" implying the poorly understood nature of the obstructive process. During postmortem examination of eight children that died with Marion disease, Bodian [32] found "notorious elongation of the prostatic gland" and "prominence of fibro-elastic elements." From then onwards, some workers considered fibro-elastosis the responsible lesion for this poorly understood obstructive process. During the meeting of the American Urologic Association in West Harwich,

Mass., all the surgeons (Spence, Murphy, McGovern, Hendren) felt that "most cases of infection or reflux were caused by vesical neck obstruction" [34]. Spence et al. [35] and DeLuca et al. [36] attributed the chronic episodes of UTI associated with dysuria, enuresis, and reflux to the supposed congenital bladder neck hypertrophy. Surgical procedures were then devised to widen the bladder neck and facilitate the elimination of urine, the best known of which was the Y-V plasty described by Andreassen in 1953 [37]. This operation was frequently accompanied by resection of a portion of the posterior lip of the bladder neck associated with ureteral reimplantation [38, 39, 40, 41]. The diagnosis of congenital hypertrophy of the bladder neck was based on the prominent image of the bladder neck seen in oblique and lateral projections of the cystographic studies [42]. Lich et al. [43] and Murphy et al. [44] advocated that "many revisions of the bladder neck were performed with the unique evidence of this roentgenographic finding." Unfortunately only years later we learned that such a radiological image was perfectly normal and that the symptomatic complex seen in these children had to have a different explanation. Radiologists meeting in Washington, D.C. [34] concluded "they could not make an unequivocal diagnosis of vesical neck obstruction on cystography." The poor results of cystography were clearly expressed by Headstream [34], among others, when he addressed the American Urological Association Meeting in Miami in 1968, and said, "during the first five years I revised too many bladder necks and cured few patients; during the second five years I was taking care of the complications from the previous period, and in the last five years, I did not revise any bladder necks and cured more patients."

Attention was then diverted from the bladder neck to the mid and distal urethra during the late 1960s and early 1970s, based mainly on the studies published by Lyon and Smith [45] and Lyon and Tanagho [46, 47], who postulated that the obstructive symptoms in these patients were caused by "involuntary spasm of the periurethral striated muscle" or by the obstructive ring formed in the distal urethra in girls. In 1966, a group from the Massachusetts General Hospital cited by Smith concluded that distal urethral stenosis is the true culprit in these children and that bladder neck stenosis was rare. Spence et al. [35] stated that "the swing away from the bladder neck in children started with the recognition that the diagnosis and treatment of distal urethral stenosis in young girls affords a satisfactory cure rate for enuresis and cystitis." Consequently, urethra dilatation procedures, including internal urethrotomy, started to be widely used, especially in girls. Our experience with internal urethrotomy in 42 girls [48] showed that the repeated episodes of UTI and enuresis disappeared in most of the 42 girls treated with internal urethrotomy. The reflux was cured in 25%. These were indeed encouraging results; however, not much time passed before we recognized that the improvement observed in our patients was most likely the result of a consistent management program of frequent emptying of the bladder, antibiotics, and cleaning of the rectum. The procedure was abandoned.

In the mid 1960s attention was focused on the etiology of the dysfunction. Lapides et al. [49], at the University of Michigan, was one of the first to discuss "patients with covert partial involvement of the lower motor neurons who strain to void, suffer recurrent urinary tract infections, and whose condition is difficult to diagnose." Several reports followed in the medical literature using terms such as subclinical neurogenic bladder [50], isolated neurogenic dysfunction [51], occult neurological bladder [52], or occult neuropathic bladder [53, 54], all implying the presence of a non-apparent lesion of the neurological system as the cause of the dysfunctional bladder. However, Hinman and Bauman proposed that such dysfunction was secondary to a "failure personality" and addressed the psychological changes observed in their patients with psychological assistance, including "hypnosis" [55, 56]. This theory was widely accepted.

Meanwhile new techniques and devices were developed to register the normal/abnormal changes occurring in the bladder and urethra during the act of micturition. Allen and Bright [57] first studied the urodynamic characteristics of children with DV problems and demonstrated the detrusor sphincter disharmony suggested by Beer in 1915 and Laidley in 1942, referring to it as achalasia, meaning "failure of coordination of the neuromuscular mechanism of one sphincter or another." Dyssynergia, a lack of coordination, disharmony, and achalasia all refer to the lack of harmony between detrusor and external sphincter muscles during the act of voiding.

Possible etiology of DE with and without dysfunctional facial expression

All patients with DE, given different names in the medical literature (subclinical neurological, isolated neurological, occult neuropathic, non-neurogenic neurogenic bladder, urofacial syndrome) fall into the same broad spectrum of clinical, radiological, and urodynamic characteristics. It is already known that DV in patients with UFOS is a congenital condition inherited as a recessive trait [1, 2, 13, 16, 20], caused by a genetic abnormality located at chromosome 10q23-q24. No genetic studies have been performed for patients with DE without a facial component (non-neurogenic or occult neuropathic bladder). There are, however, a number of reasons to suppose they also have a genetic component. Firstly, DV in patients with or without a facial component has exactly the same clinical, radiological, and urodynamic characteristics. Secondly, genetic studies demonstrate that DV in patients with the UFOS, which follows the same pattern as DV seen in patients without a facial component, have an autosomal recessive inheritance trait. Thirdly, enuresis, a basic component of DV, has a strong genetic character [58]. Arnell et al. [59] evaluated the genetic factors and the pattern of inheritance for primary nocturnal enuresis

in 392 families, "indicating the involvement of major genes." Fourthly, the reports of newborns and infants, and even a few unborn children, with non-neurogenic dysfunction [4, 9, 10] seem to be a very strong reason to rule out psychological disorders.Therefore, the available evidence indicates that DE, with or without a facial component, is a congenital disorder.

The controversy surrounding the neurogenic versus non-neurogenic etiology of DE also favors a neurological disorder, as proposed during the early 1970s [49, 50, 51, 52, 53, 54]. Blaivas [60] demonstrated that "micturition is a brain stem reflex centered in the reticular formation. Neurophysiological measurements carried out by Fidas et al. [61] in Edinburgh in 180 patients with a history of lower urinary tract dysfunction showed that "the majority of patients had significantly abnormal responses." According to Colombo [62] "the pontine micturition center plays a central role in regulating the micturition reflex, although the neural mechanisms are unclear." Moll et al. [63] reported that enuresis is "a dysfunction of central nervous regulatory mechanisms: mesopontine reticular neuronal systems, arousal, and circadian rhythm of vasopressin secretion." Von Gontard et al. [64] assessed a group of enuretic children to evaluate the involvement of the CNS and found "a general developmental (neuromotor) delay, in addition to specific dysfunction of the brain stem." In the case of the UFOS where two widely separated neuromuscular systems are simultaneously affected, one controlling facial expression, the other responsible for the emptying of the bladder and rectum, the only plausible explanation is a lesion at the brain stem level, where centers regulating micturition and facial expression are located. If it is a structural lesion, it has to be subtle enough not to cause other neurological manifestations. We have plenty of information to suggest that the lesion responsible for DE with or without a dysfunctional facial expression is in the nervous system. Magnetic resonance imaging brain studies, positron emission tomography scanning, and other techniques should be applied to demonstrate possible changes in the CNS of patients with DE. More-advanced techniques will surely be available in the near future to demonstrate the nature of this neurological disorder. Cultural and religious prejudices have unfortunately prevented the performance of postmortem examination in the few patients that died in our institution. Additional studies will help clone the faulty gene (s) and design more-precise diagnostic tools.

The psychological disturbances observed in some children with DE (with or without dysfunctional facial expression) of school age or older are the consequence of a lifetime of being teased and rejected by schoolmates, neighbors, and even their own siblings, because of being wet and soiled. We have learned that these children recover their normal behavior and self-esteem when they can appropriately empty their bladder and rectum. Most do not require psychological assistance. Williams et al. [53] reported a similar experience, while half of the patients reported by Allen and Bright [57] failed to show any recognizable social and psychological stress.

Conclusions

The UFOS is a congenital condition caused by a genetic alteration potentially located in chromosome 10q23-q24. The abnormal voiding of urine and feces and the abnormal facial expression may be explained by a brain stem lesion whose nature should be investigated. The initial hypothesis that this was a local condition has been changed during the intervening years by reports of cases from different countries around the world. Sound reasons exist today to believe that patients with UFOS may represent a subset of patients within the group of individuals diagnosed with DE. Genetic studies of other groups might provide new insights into this condition. Meanwhile the genetic characteristics of our patients with the UFOS, and the fact that enuresis has also proved to be a genetic disorder, plus the known existence of newborns, infants, and even unborn babies with DE, leave no doubts about the congenital nature of the disorder. More babies with DE will be diagnosed early in life if newborns with prenatal diagnosis of dilatation of the urinary system are carefully evaluated after delivery, and if more attention is given to the voiding habits of newborns and infants. Early diagnosis and opportune treatment will improve the chances of having a relatively normal life. Meanwhile, a few young patients will be entitled to an early diagnosis and treatment because they enter this world with a different smile.

Acknowledgements I would like to thank Dr. Alan Robson and Dr. Augusto C. Ochoa for their critical contributions to this manuscript.

References

1. Elejalde BR (1979) Genetic and diagnostic considerations in three families with abnormalities of facial expression and congenital urinary obstruction: "the Ochoa syndrome". Am J Med Genet 3:97–108
2. Ochoa B, Gorlin R (1987) Urofacial (Ochoa) syndrome. Am J Med Genet 27:661–667
3. Feng WC, Churchill BM (2001) Dysfunction elimination syndrome in children without obvious spinal cord diseases. Pediatr Clin North Am 48:1489–1504
4. Ochoa B (1992) The urofacial (Ochoa) syndrome revisited. J Urol 148:580–583
5. Yang CC, Mayo M (1997) Morbidity of dysfunctional voiding syndrome. Urology 49:445–448
6. Hinman F Jr (1974) Urinary tract damage in children who wet. Pediatrics 54:143–150
7. Varlam DE, Dippell J (1995) Non-neurogenic bladder and chronic renal insufficiency in childhood. Pediatr Nephrol 9:1–5
8. Koff SA, Wagner TT, Jayanthi VR (1998) The relationship among dysfunctional elimination syndromes, primary vesicoureteral reflux and urinary tract infections in children. J Urol 160:1019–1022
9. Jayanthi VR, Khoury AE, McLorie GA, Agarwal SK (1997) The non-neurogenic neurogenic bladder of early infancy. J Urol 158:1281–1285
10. Bauer SB, Dyro FM, Krarup C, Colodny A, Mandel J, Retik AB (1989) The unrecognized neuropathic bladder of infancy. J Urol 142:589–591
11. Teebi AS, Farag TI, El Khalifa MY, Besisso MS, Ansari (1989) Urofacial syndrome. Am J Med Genet 34:608

12. Teebi AS, Hassoon MM (1991) Urofacial syndrome associated to hydrocephalus due to aqueduct stenosis. Am J Med Genet 40:199–200
13. Wang C-Y, Huang J-Q, She J-D, Marron MP, Ruan Q-G, Hawkins-Lee B, Ochoa B, She P-X (1999) Genetic homogeneity, high resolution mapping, and mutation analysis of the urofacial (Ochoa) syndrome and exclusion of the glutamate oxaloacetate transaminase gene (*GOT1*) in the critical region as the disease gene. Am J Med Genet 84:454–459
14. Galan E, Garcia JM, Hidalgo E, Moran JM, Sanjuan S, Gonzales E, Cardes JJ (1997) Sindrome de Ochoa. V Annual Meeting of the Genetics and Dysmorphology Section, Spanish Pediatric Association, Zaragoza
15. García-Minaur S, Oliver F, Yañes JM, Rodriguez S J, Quinn F, Reardon W (2001) Three new European cases of urofacial (Ochoa) syndrome. Clin Dysmorphol 10:165–170
16. Chauve X, Misiriam C, Malzac P, Giraldo L, Guys JM, Louis C, Philip N, Voelckel M (2000) Genetic homogeneity of the urofacial (Ochoa) syndrome confirmed in a new French family. Am J Med Genet 95:10–12
17. Teebi AS, Farag TI, El Khalifa MY, Besisso MS, Ansari AG (1989) Urofacial syndrome. Am J Med Genet 34:608
18. (Deleted)
19. Wang C-Y, Hawkins-Lee, Ochoa B, Walker DR, She J-X (1997) Homozygosity and linkage disequilibrium mapping of the urofacial (Ochoa) syndrome gene to a 1-cM interval on chromosome 10q23-q24. Am J Human Genet 60:1461–1467
20. Wang C-Y, Shi J-D, Huang Y-Q, Cruz PE, Ochoa B, Howkins-Lee B, Davoodi-Semiromi A, She J-X (1999) Construction of a physical and transcript map for a 1-Mb genomic region containing the urofacial (Ochoa) syndrome gene on 10q-23q24 and localization of the disease gene within two overlaping BAC clones (<360 kb). Genomics 60:12–19
21. (Deleted)
22. Paul Y (1972) Face of the child as an index of disease. Indian J Pediatr 39:76–83
23. Potter EL (1946) Bilateral renal agenesis. J Pediatr 29:68–76
24. Wang RY, Earl DL, Ruder RO, Graham J (2001) Syndromic ear anomalies and renal ultrasounds. Pediatrics 108:E32
25. Allanson J (1995) Genetic hearing loss associated with external ear anomalies. In: Gorlin RJ, Toriello H, Cohen MM (eds) Hereditary hearing loss and its syndromes. Oxford University Press, New York
26. Blake KD, Davenport SLH, Hall BD (1998) CHARGE association: un update and review for the primary pediatrician. Clin Pediatr 37:159–173
27. Powell C, Michaelis RC (1999) Townes Brocks syndrome. Am J Genet 36:89–93
28. Rollnick BR, Kaye CL, Nagatoshi K, Hauck W, Martin A (1987) Oculoauriculovertebral dysplasia and variants: phenotypic characteristics of 294 patients. Am J Med Genet 26:361–375
29. Parvizi J, Anderson SW, Martin CO, Damasio H, Damasio AR (2001) Pathological laughing and crying. Brain 124:1708–1719
30. Beer E (1915) Chronic retention of urine in children. JAMA 65:1709–1712
31. Laidley JWS (1942) Achalasia of the urinary tract in children. Med J Aust 2:475–477
32. Bodian M (1957) Some observations on the pathology of congenital idiopathic bladder neck obstruction (Marion's disease). Br J Urol 393–398
33. Marion G (1940) Traité d'urologie, 4th edn. Masson et Cie, Paris
34. Smith DR (1969) Critique on the concept of vesical neck obstruction in children. JAMA 207:1686–1692
35. Spence HM, Murphy JJ, McGovern JH, Hendren WH, Pryles CV (1964) Urinary tract infections in infants and children. J Urol 91:623–638
36. DeLuca FG, Fisher JH, Swenson O (1963) Review of recurrent urinary infections in infancy and early childhood. N Engl J Med 268:75–77
37. Andreassen M (1953) Vesical neck obstruction in children. Acta Chir Scand 105:398–406
38. Leadbetter GW Jr, Leadbetter WF (1961) Ureteral reimplantation and bladder neck reconstruction. JAMA 175:349–353
39. Gross RE, Randolf J, Wise HM Jr (1963) Surgical correction of bladder neck obstruction in children. N Engl J Med 258:5–14
40. Hendren WH (1965) Vesicoureteral reflux and pyelonephritis in children. Postgrad Med 37:529–538
41. Straffon RA, Angel WJ (1960) Diagnosis and treatment of urinary tract infection in children. A group of 74 children with recurrent infections were studied to aid in planning a therapeutic program. JAMA 174:1377–1381
42. Burrows EH, Allen PR (1964) Urethral lesions in infancy and childhood studied by micturition cysto-urethrography. Br J Radiol 37:187–199
43. Lich R Jr, Howerton L, Davis LA (1961) Vesicourethrography. J Urol 85:396–397
44. Murphy JJ, Tristan TA, Shoenberg HW (1964) Studies on the pathogenesis and prevention of pyelonephritis. Surgery 56:760–768
45. Lyon RP, Smith DR (1963) Distal urethral stenosis. J Urol 89:414–421
46. Lyon RP, Tanagho EA (1965) Distal urethral stenosis in little girls. J Urol 93:379–388
47. Tanagho EA, Miller ER, Lyon RP, Fisher R (1971) Spastic external striated sphincter and urinary tract infection in girls. Br J Urol 43:69–82
48. Ochoa B, Piedrahita W, Marulanda A (1969) Internal urethrotomy in girls with chronic urinary infection and reflux. Proceedings of the Colombian Congress of Urology, Popayan
49. Lapides J, Anderson EC, Petrone AF (1966) Urinary tract infection in children. JAMA 195:248–253
50. Dorfman L, Bailey J, Smith JP (1969) Subclinical neurogenic bladder in children. J Urol 101:48–54
51. Kamhi B, Horowitz MI, Kovetz A (1971) Isolated neurogenic dysfunction of the bladder in children with urinary tract infection. J Urol 106:151–153
52. Martin DC, Datta NS, Shweitz B (1971) The occult neurological bladder. J Urol 105:733–738
53. Williams DI, Hirst G, Doyle D (1974) The occult neuropathic bladder. J Pediatr Surg 9:35–41
54. Mix L (1977) Occult neuropathic bladder. Urology 10:1–9
55. Hinman F, Baumann FW (1973) Vesical and ureteral damage from voiding dysfunction in boys without neurological or obstructive disease. J Urol 109:727–732
56. Hinman F Jr (1986) Nonneurogenic neurogenic bladder (the Hinman syndrome) 15 years later. J Urol 136:769–777
57. Allen TD, Bright TC III (1978) Urodynamic patterns in children with dysfunctional voiding problems. J Urol 119:247–249
58. Von Gontard A, Eiberg H, Hollman E, Ritting S, Lemkul G (1998) Molecular genetics of nocturnal enuresis: clinical and genetic heterogeneity. Acta Pediatrica 87:571–578
59. Arnell H, Hjalmas K, Jagerwall M, Lackgren G, Stenberg A, Bengtsson B, Wassen C, Emahazion T, Anneren G, Petterson U, Sundwall M, Dahl N (1997) The genetic of primary nocturnal enuresis: inheritance and suggestion of a second major gene on chromosome 12q. J Med Genet 34:360–365
60. Blaivas JG (1982) The neurophysiology of micturition: a clinical study of 550 patients. J Urol 127:958–963
61. Fidas A, Elton RA, McInnes A, Chisholm GD (1987) Neurophysiological measurement of the voiding reflex arcs in patients with functional disorders of the lower urinary tract. Br J Urol 60:205–211
62. Colombo T (2000) Central nervous system control of micturition in patients with bladder dysfunctions in comparison with healthy control probands (abstract). Urologie 39:160
63. Moll GH, Wicker M, Rothenberger A (1999) Central nervous regulatory mechanisms in nocturnal enuresis (abstract). Monatsschr Kinderheilkd 147:90
64. Von Gontard A, Schmelzer D, Seifen S, Pukrop R (2001) Central nervous system involvement in nocturnal enuresis: evidence of general neuromotor delay and specific brainstem dysfunction. J Urol 166:2448–2451