patients from the study which resulted in an estimate of 78.6% prevalence. All radiographs were reviewed from patients treated at University of New Mexico Health Sciences Center and found evidence of pleural fluid, even if of minimal amount, in 22 of 23 (95.6%) patients during the course of their illness. In an autopsy review⁵ of HPS, thus representing the sickest of patients, all subjects had large bilateral serous pleural effusions ranging between a total of 210 to 8,420 mL. Histologically, all lungs had varying amounts of intraalveolar and septal edema, and all but one had slight to moderate interstitial infiltrates of mononuclear cells. The respiratory epithelia were intact, capillary endothelial cells were enlarged without evidence of necrosis, and no evidence of vasculitis or thrombosis was detected.

The pleural fluid characteristics have not been previously described but were thought to be exudative on the basis of capillary leak.⁷ In this communication, samples A and D were obtained within 1 day of admission. Sample D clearly was a transudate, while sample A had borderline criteria for an exudate, with an absolute LDH level of 403 IU/L (exudate criteria, two thirds the upper serum limit, 400 IU/L) and is classified a transudate. The presence of a transudate in these two samples could be explained by volume resuscitation and depressed cardiac function. A pulmonary artery catheter was placed in 1 of these subjects (patient D) which revealed a nadir cardiac index of 3.8 L/min/m². Hemodynamic data from other patients have documented very low cardiac output during the acute phase of HPS.⁴ With recovery of acute cardiopulmonary dysfunction and diuresis, the effusion may begin to take on characteristics of an exudate.^{8,9} Two patients (B and C) had profound cardiopulmonary dysfunction with a predicted mortality of 100% (lactate level, greater than 4 mmol/L),4 yet they survived because ECMO was instituted. Sample B, obtained 7 days after admission and successful treatment with ECMO, was exudative, with pleural fluid protein to serum protein ratio greater than 0.5. The initial thoracentesis done on day 7 for patient C narrowly met criteria for an exudate by the protein ratio and LDH level while on day 12 the only criterion for exudate was LDH.

Pleural fluid quantity did not appear to impair respiratory dynamics except for patient B who required insertion of bilateral chest tubes to facilitate weaning from mechanical ventilation.

In conclusion, the vast majority of patients with HPS have evidence of pleural effusion on chest radiographs. The pleural fluid characteristics appear to be transudative during the initial phase of the illness, coincident with the period of maximal cardiopulmonary dysfunction. As cardiac function normalizes during recovery, the pleural fluid characteristics may change to those of an exudate but may remain transudative. It is important to note that ECMO therapy could have influenced the pleural fluid characteristics and could have contributed to the transformation of the transudate into an exudate. On a cautionary note, it is possible that the small number of patient samples obtained may not reflect the true nature of the effusions in HPS, and clearly, as new cases occur, acquisition of more pleural fluid samples will be important to describe better the pleural fluid characteristic.

References

- 1 Levy H. Hantavirus pulmonary syndrome: an outbreak of novel infection. Int Med 1996; 17:47-53
- 2 Levy H, Simpson SQ. Hantavirus pulmonary syndrome. Am J Respir Crit Care Med 1994; 149:1710-13
- 3 Duchin JS, Koster FT, Peters CJ, et al. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. N Engl J Med 1994; 330:949-55
- 4 Hallin GW, Simpson SQ, Crowell RE, et al. Cardiopulmonary manifestations of hantavirus pulmonary syndrome. Crit Care Med 1996; 24:252-58
- 5 Nolte KB, Feddersen RM, Foucar K, et al. Hantavirus pulmonary syndrome in the United States: a pathologic description of a disease caused by a new agent. Hum Pathol 1995; 26:110-20
- 6 Jenison S, Yamada T, Morris C, et al. Characterization of human antibody responses to Four Corners hantavirus infections among patients with hantavirus pulmonary syndrome. J Virol 1994; 68:3000-06
- 7 Light RW. Thoracentesis (diagnostic and therapeutic) and pleural biopsy. In: Light RW. Pleural diseases. 3rd ed. Baltimore: Williams & Wilkins, 1995; 311-18, 77, 184
- 8 Pillay VKG. Total proteins in serous fluids in cardiac failure. S Afr Med J 1965; 39:142-43
- 9 Chakko SC, Caldwell SH, Sforza PP. Treatment of congestive heart failure: its effect on pleural fluid chemistry. Chest 1989; 95:798-802

Bronchoscopic Balloon Dilatation in the Combined Management of Postintubation Stenosis of the Trachea in Adults*

Marc Noppen, MD, PhD, FCCP; Marc Schlesser, MD; Marc Meysman, MD; Jan D'Haese, MD; Rudi Peche, MD; and Walter Vincken, MD, PhD, FCCP

Bronchoscopic balloon dilatation (BBD) using angioplasty balloon catheters has been employed successfully in the treatment of tracheobronchial stenoses in children and has worked with variable success in adults with bronchial stenosis. In adults with tracheal stenosis, BBD only has been reported anecdotally. In this study, experience with BBD using a valvuloplasty balloon catheter in the combined treatment (with Nd-YAG laser photoresection and stenting) of severe benign postintubation tracheal stenoses in

^{*}From the Respiratory Division (Drs. Noppen, Schlesser, Meysman, and Vincken) and Anaesthesiology Department (Dr. D'Haese), Academic Hospital AZ-VUB, Brussels, Belgium; and the Respiratory Division (Dr. Peche), Hôpital Vésale, Montignyle-Tilleul, Belgium.

Manuscript received September 24, 1996; revision accepted February 14, 1997.

Reprint requests: Marc Noppen, MD, PhD, FCCP, Respiratory Division, Academic Hospital, University of Brussels (AZ-VUB), Laarbeeklaan 101, 1090 Brussels, Belgium

three adults is delineated. BBD was particularly successful in establishing tracheal patency when laser photoresection was contraindicated or was too dangerous; BBD allowed easy insertion of tracheal stents and the "opening" of folded silicone stents. BBD is a simple, inexpensive, safe, and efficient adjunct in the combined treatment of severe postintubation rigid tracheal stenosis in selected adults. (CHEST 1997; 112:1136-40)

Key words: airway stents; bronchoscopy; Nd-YAG laser; tracheal stenosis; valvuloplasty balloon catheter

Abbreviation: BBD=bronchoscopic balloon dilatation

 ${f B}$ ronchoscopic balloon dilatation (BBD) has been used successfully in the treatment of congenital and acquired tracheal and bronchial stenoses in children since 1984¹⁻¹⁴ although discouraging results from dilatation of low or long tracheal strictures also have been reported.^{15,16} In adults, mainly bronchial (and not tracheal) stenoses have been treated with BBD: in the majority of the reports, bronchial stenoses were secondary to reanastomosis after sleeve lobectomy or lung transplantation.¹⁷⁻²² Other causes of bronchial stenosis in adults successfully treated with BBD include bronchial artery embolization,²³ granuloma formation after inhalation of a foreign body,²⁴ bronchial cancer,²⁴ and tuberculosis.²⁵ Heretofore, there have been, as best as can be determined, only anecdotal reports on the use of BBD in the management of tracheal postintubation²⁶ and neoplastic²⁷ stenosis in adults. This study details experience with BBD in the combined treatment of tracheal postintubation stenosis in adult patients.

CASE REPORTS

Three patients were treated with BBD from June to August 1996.

Case 1

A 19-year-old man had been treated with mechanical ventilation, delivered via tracheostomy, for 3 months after a car accident. After complete neurologic and orthopedic recovery, the cannula was removed. Three months later, a severe tracheal posttracheostomy stenosis had developed. Because surgery was refused, Nd-YAG laser photoresection followed by insertion of a silicone stent (Dumon), 14×40 mm, was performed,²⁸ resulting in complete restoration of airway patency. Four months later stridor recurred: bronchoscopy revealed distal migration of the silicone stent and recurrence of severe tracheal stenosis (Fig 1). Because laser photoresection was considered too dangerous because of the presence of a silicone stent, and because the stent could not be removed through the proximal stenosis, BBD of the stenosis was successfully performed. After BBD, the proximal end of the stent became visible; using an alligator forceps, the stent could be grasped, twisted, and recovered through the stenosis. Opening of the twisted stent by forceps manipulation was not possible because of the presence of the stenosis (Fig 2). Instead of replacing the stent with one of a smaller diameter, the present stent could be unfolded using the BBD technique through the stent (see "Methods" section [Fig 3]). After the procedure, there was complete restoration of airway patency (Fig 4).

Case 2

A 36-year-old man had been ventilated via a tracheostomy cannula for 6 months after cardiopulmonary resuscitation for cardiac arrest secondary to a myocardial infarction.

After two sessions of Nd-YAG laser phototherapy for granulomatous lesions in the vicinity of the cannula, the latter could be removed. Six weeks later, a severe concentric cicatricial tracheal stenosis developed, which was complicated by retro-obstructive infection. Because of the uncertain and distorted tracheal anatomy distal to the stenosis (due to the long-standing tracheostomy and former laser treatments), only a limited laser resection of the stenosis was considered safe. In the same session, the residual stenosis, however, could easily be dilated using gentle BBD. A 14×40 -mm Dumon silicone stent was inserted for maintenance. Later, displacement and migration necessitated reinsertion procedures on two occasions.

Case 3

A 41-year-old man had developed severe tracheal stenosis and tracheomalacia after prolonged mechanical ventilation for posttraumatic coma. After Nd-YAG laser photoresection of the concentric cicatricial tracheal stenosis, a 16×50-mm Dumon silicone stent tracheal prosthesis was inserted into the stenoticmalacia region, completely restoring airway patency. Six months later, Nd-YAG laser photoresection of a granuloma distal to the tracheal stenosis was performed. The same procedure had to be repeated twice, 18 and 21 months after stenting. At 24 months, the patient was readmitted for severe stridor and retro-obstructive pneumonia. At bronchoscopy, the stent had moved distally, and a severe combined endotracheal-tracheomalacial stenosis had recurred. The stenosis was dilated with 2 BBD attempts. Thereafter, the stent could successfully be grasped with an alligator forceps and withdrawn after folding through the stenosis. Unfolding, however, was impossible with the forceps. Instead of replacing the prosthesis with a smaller sized model, the folded stent easily could be opened using BBD. Thereafter, airway patency was completely restored.

METHODS

BBD is performed with the patient under general anesthesia (intravenous propofol, alfentanil hydrochloride, atracurium besylate) and after intubation with a rigid bronchoscope (Efer; La Ciotat; France; or Storz; Karl Storz GMBH; Tuttlingen, Germany) with its distal end proximal to the tracheal stenosis. Ventilation and oxygenation are ensured using high-frequency jet ventilation (Acutronic; Acutronic Medical Systems; Jona, Switserland) delivered through a side port of the bronchoscope. FIO₂ varies between 0.21 and 1.0.

Dilatation of Postintubation/Post-tracheostomy Stenosis

If possible, radial "incisions" using Nd-YAG laser photoresection are made in the stenotic web.^{29,30} BBD, however, is also possible and successful without previous photoresection. A deflated mitral valve valvuloplasty balloon (Mansfield Scientific; Mansfield, Mass) with a maximal diameter of 15 mm and a length of 30 mm, mounted at the tip of a 9F, 1,200-mm long catheter is inserted through the stenosis (Fig 5). Preoxygenation with 100% oxygen is performed for 2 min. Thereafter, the balloon is gently inflated with saline via a three-way valve, under close balloon pressure monitoring. During this procedure, mechanical ventilation is interrupted. A balloon pressure of 2 atmospheres is produced during the first dilation attempt for 1 min. Then the balloon is deflated and withdrawn, and mechanical ventilation is resumed. If necessary, a second and further attempts are made using up to 3 atmospheres balloon pressure for 1 min.³⁰⁻³³



FIGURE 1. Bronchoscopic view of recurrent severe concentric cicatricial postintubation stenosis of the trachea. The stent is invisible distal to the stenosis.



FIGURE 3. The balloon catheter is passed through the unfolded stent and inflated.



FIGURE 2. The stent is withdrawn through the stenosis but cannot be opened by forceps manipulation.

Opening of a Folded Dumon Stent

The alligator forceps is passed through the rigid bronchoscope and is used to "open" the proximal end of the folded stent. The lubricated tip of the (deflated) balloon catheter then is introduced into the stent and gently pushed until the deflated balloon completely "enters" the stent. After discontinuation of mechanical ventilation, the balloon is gently inflated to 1 atmosphere. Unfolding of the stent can be monitored through the telescope.



FIGURE 4. After the procedure, the tracheal lumen is restored and the stent is completely reopened.

Most often, pressures up to 1 atmosphere suffice for complete stent unfolding. This technique follows the principle of the balloon-expandable Palmaz Stent, which was originally designed for the treatment of vascular obstructions but has been used successfully in tracheal stenosis in children.⁷

DISCUSSION

In this study, experience with BBD of postintubation tracheal stenotic lesions in adults is presented. The BBD



FIGURE 5. The valvuloplasty balloon catheter equipped with a balloon pressure monitoring system.

enabled us to create tracheal patency in three patients with severe postintubation stenoses in whom Nd-YAG laser photoresection was considered too dangerous because of the presence of (dislocated and migrated) silicone stents (patients 1 and 2) or because of an uncertain tracheal anatomy (patients 2 and 3), or both. In this manner, the migrated stents easily could be retrieved using an alligator forceps through the dilated stenosis, and replacement or insertion of the stent became much easier. A second interesting feature of BBD consisted of its ability to "reopen" a folded silicone prosthesis completely in a few seconds, obviating the often difficult and sometimes unsuccessful "twisting and turning" with the forceps.

Migration of the Dumon-type tracheal stents is not uncommon, occurring in 16 to 22% of cases, 34,35 because of an imperfect fit and adherence to the tracheal wall, especially in the case of short and conical stenoses as was the case in our patients. Theoretically, tracheal stent immigration can be limited or even avoided using stent fixation techniques for the Dumon stent³⁶ or by using alternative stent types (eg, the bifurcated Rüsch stent,³⁷ the screw-thread stent,³⁸ or the Montgomery stent in case of a present tracheostomy). Percutaneous balloon dilatation catheters, originally designed for transluminal angioplasty, also have been used for the dilatation of other structures, eg, biliary strictures, ureteral strictures, and gastroenterostomy strictures. Because of their stiffness and capability of exerting and withstanding pressures of several atmospheres, they have also been used in the treatment of tracheobronchial stenoses in children.¹⁻¹⁶ In adults, curiously, there have been very few reports on BBD of tracheal stenoses. However, gentle mechanical dilation of the trachea using the rigid bronchoscope (usually following previous laser photoresection) has been performed successfully in the past without ventilatory or oxygenation problems,^{29,39} and in this study there were no problems using BBD for tracheal stenosis.

In this study, a contrast medium was not used to inflate the balloon, and insufflation procedures were performed without fluoroscopic control because balloon positioning easily could be controlled visually with the bronchoscope and there was no risk for inappropriate placement of the distal catheter tip in a small (sub)segmental bronchus, as is the case for bronchial BBD. However, should the technique given herein be used for distal tracheal lesions, fluoroscopic control seems advisable for safety reasons.

Other potential complications of this technique may be bleeding, rupture (partial or complete) of tracheal rings with resulting pneumomediastinum, pneumothorax and mediastinitis, and balloon rupture. No preoperative or postoperative procedure-related complications were encountered in this study.

BBD dilates the stenotic region, probably by stretching and expanding the tracheal wall,²⁵ perhaps up to creating a longitudinal posterior tracheal wall split,8 somewhat comparable to the mechanism of balloon angioplasty.40 Although this method, therefore, may be considered appropriate for the treatment of cicatricial annular strictures,²⁵ its long-term effects are unknown. In children, BBD of congenital or acquired tracheobronchial lesions has yielded persistent airway patency for periods varying from 2 months1 to 3 years,5 whereas in adults mechanical dilation of bronchial stenosis using mechanical bougie dilatation may be successful for up to 9 years.^{31,41} However, if dilation is performed for stenoses secondary to "active" disorders (eg, sarcoidosis, bronchial posttransplant anastomotic stenosis), subsequent procedures (eg, monthly) usually are necessary to maintain airway patency,19,20,22,25,31 or stents should be inserted in order to maintain airway patency.

The systematic use of corticosteroids or antibiotics as suggested by some authors^{29,30,39} probably is not necessary, although no definitive data are available.³⁹ In this series, antibiotics were given to patients 2 and 3 but only because there was a documented retro-obstructive infection.

CONCLUSION

A variety of endoscopic techniques are available for the treatment of rigid tracheal stenosis in adults in whom surgical resection and end-to-end anastomosis are contraindicated, not feasible, or refused by the patient.^{35,36} Of these, Nd-YAG laser photoresection and stenting probably are used most often. BBD may represent an inexpensive, simple, safe, and efficient adjunct to laser and stent therapy in the following situations: distally migrated silicone stents with recurrent proximal tracheal stenosis (when laser therapy is too dangerous); "pre-stenting" dilatation; uncertain tracheal anatomy; and stents that are difficult or impossible to "unfold" by forceps manipulation.

ACKNOWLEDGMENTS: The authors would like to thank Carine Michiels, Brigitte Terrijn, and Bea Van Elewijck for their assistance during the endoscopic procedures and Hilde De Smedt for secretarial assistance.

References

- 1 Cohen MD, Weber TR, Rao CC. Balloon dilatation of tracheal and bronchial stenosis. AJR Am J Roentgenol 1984; 142:477-78
- 2 Groff DB, Allen JK. Gruentzig balloon catheter dilation for acquired bronchial stenosis in an infant. Ann Thorac Surg 1985; 39:379-81

- 3 Brown SB, Hedlund GL, Glasier CM, et al. Tracheobronchial stenosis in infants: successful balloon dilation therapy. Radiology 1987; 164:475-78
- 4 Philippart AI, Long JA, Greenholz SK. Balloon dilatation of postoperative tracheal stenosis. J Pediatr Surg 1988; 23: 1178-79
- 5 Bagwell CE, Talbert L, Tepas JJ. Balloon dilatation of long-segment tracheal stenosis. J Pediatr Surg 1991; 26: 153-59
- 6 Salama DJ, Body SC. Management of a term parturient with tracheal stenosis. Br J Anaesth 1994; 72:354-57
- 7 Filler RM, Forte V, Carlos Fraga J, et al. The use of expandable metallic airways stents for tracheobronchial obstruction in children. J Pediatr Surg 1995; 30:1050-56
- 8 Messineo A, Forte V, Silver MM, et al. The balloon posterior tracheal split: a technique for managing tracheal stenosis in the premature infant. J Pediatr Surg 1992; 27:1142-44
- 9 Hebra A, Powell DD, Smith CD, et al. Balloon tracheoplasty in children: results of a 15-year experience. J Pediatr Surg 1991; 26:957-61
- 10 Weber TR, Connors RH, Tracy TF. Acquired tracheal stenosis in infants and children. J Thorac Cardiovasc Surg 1991; 102:29-35
- 11 Bétrémieux P, Tréguier C, Pladys P, et al. Tracheobronchography and balloon dilatation in acquired neonatal tracheal stenosis. Arch Dis Child 1995; 72:F3-F7
- 12 Elkerbout SC, vanLingen RA, Gerritsen, J, et al. Endoscopic balloon dilatation of acquired airway stenosis in newborn infants: a promising treatment. Arch Dis Child 1993; 68: 37–40
- 13 Dab I, Malfroot A, Goosens A. Therapeutic bronchoscopy in ventilated neonates. Arch Dis Child 1993; 69:533-37
- 14 Lenoir P, Bougatef A, Ramet J, et al. Nonsurgical intervention in the resolution of acquired neonatal bronchial stenosis. Am J Perinatol 1990; 7:290-29
- 15 Louhimo I, Leijala M. The treatment of low retrosternal tracheal stenosis in the neonate and small children. Thorax Cardiovasc Surg 1995; 33:98-102
- 16 Rowbottom SJ, Sudhaman DA. Anaesthesia in the management of congenital tracheal stenosis. Anaesth Intensive Care 1989; 17:93-96
- 17 Krell WS, Prakash UBS. Therapeutic bronchoscopy. In: Prakash UBS, ed. Bronchoscopy. New York: Mayo Foundation, Raven Press, 1994; 207-26
- 18 Fowler CL, Aaland MO, Harris FL. Dilatation of bronchial stenosis with Gruentzig balloon. J Thorac Cardiovasc Surg 1987; 93:308-09
- 19 Bolman RM, Shumway SJ, Estrin JA, et al. Lung and heart transplantation. Ann Surg 1991; 214:456-70
- 20 Keller C, Frost A. Fiberoptic bronchoplasty: description of a single adjunct technique for the management of bronchial stenosis following lung transplantation. Chest 1992; 102: 995-98
- 21 Starnes VA, Lewiston NJ, Linkart H, et al. Current trends in lung transplantation. J Thorax Cardiovasc Surg 1992; 104: 1060-66
- 22 Carré P, Rousseau H, Lombart L, et al. Balloon dilatation and self-expanding metal Wallstent insertion: for management of bronchostenosis following lung transplantation. Chest 1994; 105:343–48
- 23 Girard P, Baldeyrou P, Lemoine G, et al. Left main-stem bronchial stenosis complicating bronchial artery embolization. Chest 1990; 97:1246-48
- 24 Carlin BW, Harrell JW, Moser KM. The treatment of endobronchial stenosis using balloon catheter dilatation. Chest 1988; 93:1148-51
- 25 Nakamura K, Terada N, Matsushita T, et al. Tuberculous

bronchial stenosis: treatment with balloon bronchoplasty. AJR Am J Roentgenol 1991; 157:1187-88

- 26 Santhosh J, Mandalan KR, Rao VRK, et al. Self-expandable stents for tracheal stenosis: experience in two patients. Australas Radiol 1994; 38:78-81
- 27 Storck M, Berger H, Liewald F, et al. Endotracheal balloon dilatation and self-expanding stent (Wallstent) for inoperable tracheomalacia. J Thorac Cardiovasc Surg 1994; 107:957-59
- 28 Noppen M, Dhondt E, Meysman M, et al. A simplified insertion technique for tracheobronchial endoprosthesis. Chest 1994; 106:520-23
- 29 Shapshay S, Hybels RL, Beamis JF, et al. Endoscopic treatment of subglottic and tracheal stenosis by radial laser incision and dilation. Ann Otol Rhinol Laryngol 1987; 96: 661-64
- 30 Koufman JA, Thompson JN, Kohut RI. Endoscopic management of subglottic stenosis with $\rm CO_2$ surgical laser. Otolaryngol Head Neck Surg 1981; 89:215-20
- 31 Ball JB, Delaney JC, Evans CC, et al. Endoscopic bougie and balloon dilatation of multiple bronchial stenoses: 10 year follow-up. Thorax 1991; 46:933-35
- 32 Petrou M, Goldstraw P. The management of tracheobronchial obstruction: a review of endoscopic techniques. Eur J Cardiothorac Surg 1994; 8:436-41
- 33 Hetzel MR, Smith SGT. Endoscopic palliation of tracheobronchial malignancies. Thorax 1991; 46:325-33
- 34 Bolliger CT, Probst R, Tschopp K, et al. Silicone stents in the management of inoperable tracheobronchial stenoses. Chest 1993; 104:1653-59
- 35 Diaz-Jimenez JP, Farrero Munoz E, Martinez Ballarin JL, et al. Silicone stents in the management of obstructive tracheobronchial lesions: 2 year experience. J Bronchol 1994; 1:15-18
- 36 Colt HG, Harrell J, Newman TR, et al. External fixation of subglottic tracheal stents. Chest 1994; 105:1653-57
- 37 Freitag L, Tekolf E, Linz B, et al. A new dynamic airway stent [abstract]. Chest 1993; 104:44S
- 38 Noppen M, D'Haese J, Meysman M, et al. A new screwthread tracheal endoprosthesis. J Bronchol 1996; 3:22-26
- 39 Mehta AC, Lee FY, Cordasco EM, et al. Concentric tracheal and subglottic stenosis: management using the Nd:YAG laser for mucosal sparing followed by gentle dilatation. Chest 1993; 104:673-77
- 40 Castaneda-Zuniga WR, Formanek A, Taduvarthy M, et al. The mechanism of balloon angioplasty. Radiology 1980; 135:565-71
- 41 Iles PB. Multiple bronchial stenoses: treatment by mechanical dilatation. Thorax 1981; 36:784-86

Bilateral Sequential Lung Transplantation for Pulmonary Alveolar Microlithiasis*

Jeffrey D. Edelman, MD; Joseph Bavaria, MD; Larry R. Kaiser, MD, FCCP; Leslie A. Litzky, MD; Harold I. Palevsky, MD, FCCP; and Robert M. Kotloff, MD, FCCP

Pulmonary alveolar microlithiasis (PAM) is characterized by deposition of calcium phosphate within the alveolar airspaces. There is currently no effective medical therapy and affected individuals may